REFERENCE CODE GDHC113PIDR | PUBLICATION DATE SEPTEMBER 2015

GlobalData
PharmaPoint

ALLERGIC RHINITIS – GLOBAL DRUG FORECAST AND MARKET ANALYSIS TO 2024

Executive Summary

Allergic Rhinitis: Key Metrics in the Seven Major Markets, 2014–2024	
2014 Prevalent AR Cases	
Number of cases of AR	155,237,386
Drug-treated population	35,877,112
2014 Market Sales	
US	$2.8bn
5EU	$2.5bn
Japan	$1.89bn
Total	**$7.18bn**
Pipeline Assessment (Non-Allergen Immunotherapies)	
Number of drugs in Phase IIb–III	2
Number of first-in-class drugs	2
Key Events (2014–2024)	**Level of Impact**
Nasonex patent expiry in 2014	↓↓↓
Patanase patent expiry in 2014	↓
Astepro patent expiry in 2014	↓
Singulair patent expiry in Japan in 2016	↓↓↓
Veramyst generic entry in 2016	↓
HP-3060 drug launch in 2017	↑
S-555739 launch in the US and Japan in 2017	↑
2024 Prevalent AR Cases	
Number of cases of AR	157,426,939
Drug-treated population	36,430,171
2024 Market Sales	
US	$2.74bn
5EU	$2.57bn
Japan	$1.96bn
Total	**$7.27bn**

Source: GlobalData
5EU = France, Germany, Italy, Spain, and UK

The table above presents the key metrics for allergic rhinitis (AR) in the seven major pharmaceutical markets (7MM) (US, France, Germany, Italy, Spain, UK, and Japan) during the forecast period from 2014–2024.

Allergic Rhinitis Market Will Grow to $7.3 Billion by 2024

GlobalData estimated the sales for AR (prescription drugs only) in 2014, the base year of the forecast period, at approximately $7.20 billion across the seven markets covered in this report. The US contributed 38% of these sales, generating an estimated $2.8 billion. This was mainly due to the much higher prices of AR medications in the US, and the lack of over-the-counter (OTC) intranasal corticosteroids (INCS) for AR in this market in the base year.

By the end of the forecast period in 2024, AR sales in the 7MM are forecast to remain stagnant to $7.27 billion at a Compound Annual Growth Rate (CAGR) of 0.1% over the 10-year period. The second-generation H1 receptor antagonists and INCS are the leading drug classes in terms of market value. The INCS currently capture almost half the total AR market; however, their market share will shrink to 34% as allergen immunotherapies (AITs) for the treatment of moderate-to-severe AR enter the market over the forecast period and start dominating this space, growing from 14% to 26% of the total AR sales. The uptake of these novel drugs will be a major driver of AR market growth, and will offset the dip

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in sales caused by Nasonex's (mometasone furoate) 2014 patent expiry. The US market size will shrink slightly compared to the other markets — at a negative CAGR of 0.1% — due to the expected surge in generic and OTC competition in this market, driven by the first approvals of OTC INCS. In 2024, the US will retain its AR market share, representing 38% of the total market.

The major drivers of the growth of the AR market over the forecast period include:

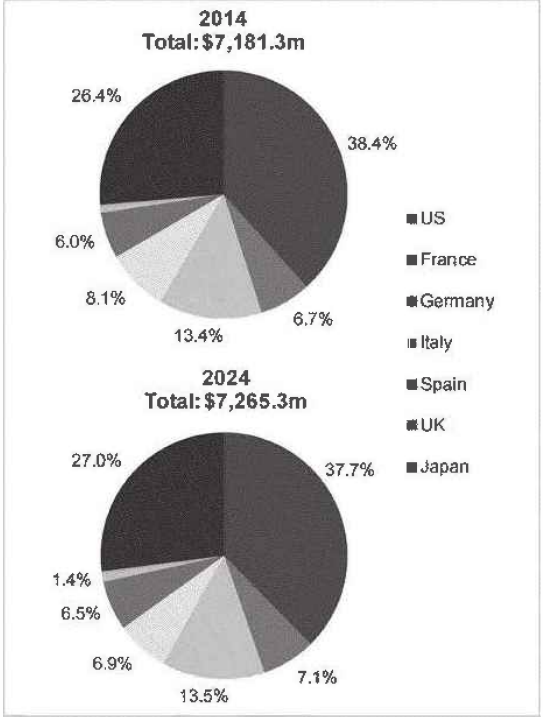
- The introduction of several AIT tablets: Merck's Grastek (grass), Ragwitek (ragweed), and Mitizax (house dust mite [HDM]) tablets, as well as Greer's Oralair (grass) in the US. These new products overcome the inconvenience of conventional subcutaneous immunotherapies (SCITs).
- The increasing global prevalence of AR.

The major barriers to the growth of the AR market include:

- Generic erosion of the leading brands for AR treatment, such as Nasonex, Astepro (azelastine hydrochloride), and Singulair (montelukast sodium) in (Japan).
- The increasing push for patients to self-medicate using OTC drugs will decrease the prescription AR drug market size.
- Increasing pressure for cost-effectiveness across all markets, which will limit the pricing of new products, and in some cases, prevent their reimbursement.

The figure below illustrates the sales for AR in the US, 5EU, and Japan during the forecast period.

Sales for AR by Region, 2014–2024



Source: GlobalData

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Companies are Diverting Their AR Portfolios to the OTC Market

Historically, the AR market has been very large, with several companies launching drugs that gained blockbuster status. In particular, Merck & Co. has had a very strong presence, leading the AR market with its three franchises, Nasonex, Singulair, and Clarinex (desloratadine). Other players defining the AR market include GlaxoSmithKline (GSK), Sanofi, and Teva. However, over the past decade, almost all the key drugs for the treatment of AR symptoms have lost patent protection, including Sanofi's Allegra (fexofenadine hydrochloride), Pfizer/UCB Pharma's Zyrtec (cetirizine hydrochloride) and two of Merck's blockbuster drugs, Singulair and Nasonex. As a result, AR, which was once a blockbuster-status therapy area, is now highly saturated and genericized, with companies seeing large declines in the sales of their respiratory portfolios due to generic erosion.

In an attempt to retain a revenue stream from branded generics, companies have sought a successful strategy to convert their AR prescription drugs to OTC status, known as the Rx-to-OTC switch, transferring these products to their respective consumer care units. The most recent examples of this are the Food and Drug Administration's (FDA's) approval of OTC status for Sanofi's Nasacort Allergy 24HR (triamcinolone intranasal) and GSK's Flonase (fluticasone propionate), the first INCS to be available OTC in the US. This is set to have a large impact on the prescription drug treatment rate, as patients are incentivized to self-diagnose and self-medicate using the growing number of OTC options. Direct-to-consumer (DTC) advertising, increased co-payments on prescription AR drugs, and stretched healthcare resources, as well as the increasingly competitive cost of OTC-equivalent options, will all further the progressively increasing trend for AR patients to seek treatment independently.

GlobalData expects the large pharmaceutical companies with a previously strong foothold in the AR market, such as GSK, to be increasingly less focused on AR drugs. Instead, the major players are investing in research and development (R&D) for respiratory indications, but for asthma and chronic obstructive pulmonary disease (COPD), rather than for AR.

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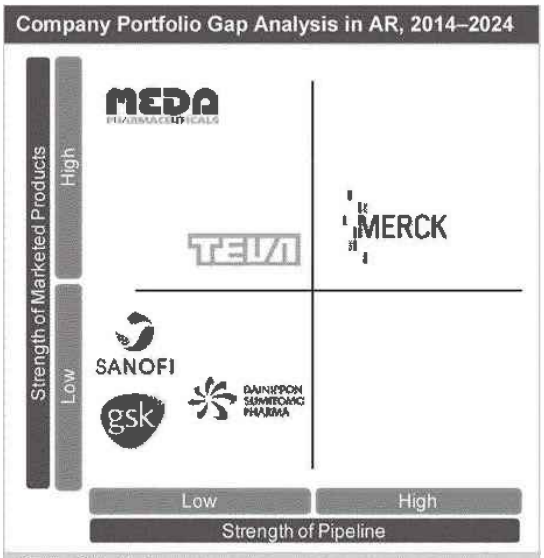
The figure below provides an analysis of the company portfolio gap in AR during the forecast period.



Source: GlobalData

There is a Growing Prevalence of AR Patients

AR is becoming an increasingly prevalent condition, with the most common form being moderate to severe in nature (Baena-Cagnani et al., 2015). According to the European Academy of Allergy and Clinical Immunology (EAACI), 50% of Europeans will suffer from an allergy by 2027 (Papadopoulos et al., 2012). A GlobalData epidemiological study estimated that about one in seven people in the US have been diagnosed with AR at some point in their life, or about 43 million people. This rate appears to be on the rise, and is expected to reach over 46 million by 2024.

Japanese pollen counts have grown five fold over the past three decades. A primary cause of the rising pollen levels is the afforestation policy of cedar, cypress, and birch trees, which was introduced during the post-World War II era (1949–1954) to provide a steady supply of domestic lumber. Today, there are an estimated 4.5 billion cedar trees in Japan. In addition to the increasingly prevalent Japanese tree pollen, Asian dust events occur, where smog laden with fine particles less than 2.5 micrometers in diameter, known as PM2.5, enters Japan through from inland China — for example, from the Gobi Desert, where the yellow dust picks up dirt and pollen and carries it to South Korea and Japan via the westerly winds. Increasing pollution from this region is contributing to the AR problem in Japan.

Furthermore, studies have shown that pollen levels are rising in tandem with global warming. Global climate change is evidenced by the increasing average earth temperature, increasing anthropogenic (caused by humans) greenhouse gas levels, and elevated pollen levels. Pollutants of interest include carbon dioxide (CO_2), ozone (O_3), and nitrous oxide (NO_2), because they can enhance the allergic response and lead to increased symptoms of allergic respiratory diseases. Heightened CO_2 levels stimulate pollen production via photosynthesis and increased growth in multiple investigated plant species (Lin and Zacharek, 2012). Allergen patterns are also changing in response to climate change, and air

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pollution can modify the allergenic potential of pollens, especially under specific weather conditions. The prevalence of asthma and allergic diseases has increased dramatically during the past few decades (D'Amato et al., 2013). This notion is supported by the change in the prevalence of AR in the US population, from 10% in 1970 to 30% in 2000. It has been postulated that the changing environment, particularly the trend of global warming, may lead to increased pollen exposure and expanded environments for the growth of numerous plant species. An increase in the growing season, with earlier flowering and possibly increased airborne pollen counts, could be the consequences of the projected rise in the earth's temperature.

Pollen seasons are set to last longer and to become increasingly more intense. If pollen seasons are going to overlap more frequently, the severity of symptoms experienced by polysensitized patients is set to increase. This increase in the AR prevalence will be a strong driver of the growth of this market, as the AR patient pool will increase, leading to higher consumption of medications used to treat the disease.

There is a Large Unmet Need for the Treatment of Severe, Persistent AR That is Refractory to the Standard Therapies

AR symptoms can be controlled in the majority of patients using the current standard therapies, which are based mainly on combinations of antihistamines (AHs), INCS, and orai leukotriene receptor antagonists (LRAs), which are also known as leukotriene inhibitors and antileukotrienes. INCS and AHs are the gold-standard, first-line therapies for AR patients. However, despite receiving maximum doses of evidence-based therapy as directed by the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines, a significant percentage (approximately 20%) of patients with AR, particularly moderate to severe AR, have inadequately controlled symptoms (Bousquet et al., 2010). Refractory patients are often diagnosed with severe chronic upper airway disease (SCUAD), and represent a therapeutic challenge clinically. Furthermore, AR is often undiagnosed; in Europe, as many as 25–60% of patients with AR are not diagnosed (Bauchau and Durham, 2004). Therefore, there are considerably high unmet needs within the indication, which are both clinical and environmental in nature. Overall, these needs mainly reflect the primary care culture, which often dismisses AR as a minor condition, despite the huge socioeconomic and morbidity costs associated with the disease. This leads to poor diagnosis, lack of patient compliance with the standard therapies, and inadequate symptom-related treatment.

The level of environmental unmet need in AR is high. Patients and primary care physicians (PCPs) alike have a low awareness of the impact of AR. This directly impacts the drug treatment rate, with many AR patients not taking any therapy.

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Physicians also often show an underappreciation for the prevalence of mixed rhinitis, which consists of a combination of allergic and non-allergic rhinitis (NAR), and the challenges involved in its diagnosis and treatment. Multiple patient-derived factors, combined with inadequate treatment options, means that the majority of AR patients continue to experience symptoms, even though they have received treatment directed by the ARIA guidelines. Patients are often highly dissatisfied with their treatment options, are non-compliant, and often alternate their prescription medications with OTC products due to a lack of adequate efficacy or a perceived reduction in efficacy over time. Patients often try several medications, with approximately 75% of patients taking more than one symptomatic therapy simultaneously in search of a medication that actually "works" (Demoly et al., 2002).

Novel Symptomatic Products Will Struggle to Enter This Large Genericized Market

The AR treatment paradigm is well-defined, and the AR market is mature and highly genericized, with numerous drug classes that target a number of nasal symptoms associated with AR. Following the high-profile patent expiries of several blockbuster drugs marketed by the leading manufacturers in this area, a wealth of inexpensive generic options became available, both by prescription and OTC. As the market is very saturated, the average daily cost of therapy is exceedingly low for all the drug classes.

There is little room for new entrants, as the market is well-served by a wealth of symptomatic therapies. Since the competition is increasing, the market for AR therapies is becoming increasingly less lucrative. Also, there are currently no breakthrough symptomatic therapy products in clinical development. The remaining clinical unmet needs in this market include the requirement for more efficacious products, and the underserved area of causative therapies, such as immunotherapies, which target the underlying cause of the disease.

Clinical trials evaluating novel AR treatments are complicated by several factors, including variable allergy testing methods, fluctuations in pollen counts, and the timing and intensity of additional seasonal allergens. This is further complicated when assessing immunotherapies, as the treatment must be initiated prior to the onset of the following pollen season. Therefore, subjects are enrolled into trials based on their symptoms during the previous pollen season, which may vary over consecutive years and pollen seasons. Variable weather patterns, and hence fluctuating pollen counts, have thwarted the efforts of several drug manufacturers that are developing new treatments for AR.

Environmental exposure chambers (EECs) create stable and reproducible allergen exposure under highly standardized environmental conditions, and have been used to assess several AR drugs, including AHs such as Allegra and Claritin

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(loratadine). However, this method has been criticized, as it doesn't reflect the "real-world" experience of patients with AR. Further validation of this study method will be required before it gains acceptance by the European Medicines Agency (EMA) and the FDA as a sufficient method to assess AR drug efficacy and safety.

The challenges involved in evaluating novel AT pipeline agents using the current gold-standard clinical practices will affect the launch of new AR drugs, which could ultimately discourage drug companies from pursuing the development of pipeline candidates in this space.

The Market Entry of Approved Immunotherapies Will Improve the Treatment Landscape for the Difficult-to-Treat AR Population

One of the few remaining unmet needs in the AR market is for a causative therapy that is capable of providing long-term relief of symptoms. The allergen-specific immunotherapy (SIT) market is the clinical development of a new generation of tablet formulations, moving away from the standard SCIT injections and sublingual immunotherapy (SLIT) drops. Tablet formulations that have been evaluated according to a standardized stepwise algorithm in dose-finding studies and double-blind, placebo-controlled efficacy trials have gained marketing authorization (MA) via the traditional routes. These products will continue to add legitimacy to immunotherapy as an important treatment option for patients with AR. ALK-Abello and Stallergenes will lead the way by introducing their relevant allergens in tablet form into the Japanese and US markets through licensing partners. Japan, a market previously not widely treated with SIT, is set to see a new range of standardized, clinically-evaluated products containing the two most prevalent allergens: HDM and Japanese cedar pollen. These treatment options will include AIT formulations that were previously unavailable in the market. Advancements in SIT, particularly the advent of tablet formulations, will increase the use of immunotherapy among the pediatric population. The introduction of AITs will drive growth in the AR market, due to their high cost relative to the standard subcutaneous (SC) allergen extracts, thereby decreasing the negative impact of the growing genericized market.

What Do Physicians Think?

The key opinion leaders (KOLs) interviewed by GlobalData for this report highlighted the need for an increase in awareness of the evidence-based AR treatment guidelines among healthcare professionals, pharmacists, and patients, which would ideally lead to an increase in the number of patients with adequate symptomatic control. The current standard medications, such as AH and INCS therapies, tackle only the symptoms; KOLs said they do not expect that novel drugs in these classes will fulfill this need. The immunotherapies in development will address these issues to some

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degree, but only in a very small proportion of AR sufferers, and they will be very costly.

"There are quite a lot unmet needs [in AR]. First of all, if you look at — actually, the quality of life of these patients — there's still a debate. In reality, optimal quality of life is reached by no more than one third of [AR] patients. No more than one third of our patients. This means that two third[s] — they don't have the optimal quality of life. There is still room for improvement. And they recently did a survey of many societies, and in reality, the patients, independently of the prescription of the GP [general practitioner] or whatever, the vast majority are using two or three different treatments [at the same time] for the allergic rhinitis. This means that there is a lot to investigate, and a lot of [room for] improvement for treatment."

EU Key Opinion Leader

"One of the ways in which we can help patients with rhinitis is to promulgate the guidelines. We're just re-doing the evidence-based guidelines. I think the promulgation — getting them down to patients, to GPs, [and] to practice nurses in a way that they can use them will be very helpful to patients."

EU Key Opinion Leader

"I think [the US-based practice parameters, and also the ARIA guidelines] are pretty comprehensive, and I think they are largely, heavily evidence-based, which makes it very useful for me. I [have] found them [to be] very good; I think they are useful. I don't think they are widely distributed. But personally, when I teach about allergic rhinitis or research, or give patient care, I refer to them and use them."

US Key Opinion Leader

"In the United States, the primary care doctors…see many, many patients in a day. They have very little time to get educated on [the] guidelines for [the] multitudes of diseases that they manage. And for a disease like allergic rhinitis, the chances are [that] they are not up on [the] guidelines or the guideline-driven care for it, so overall, in my opinion, they do a bad job at [managing] it."

US Key Opinion Leader

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"Well, [in] the [AR] patient population, in general, there's a very significant [percentage] — perhaps 40% of patients seen will have mixed rhinitis. That is, they will have positive allergy skin tests, some of which are clinically significant, but the pathology underlying their disease is not limited to allergy. Although we classify them as having allergic rhinitis, they're really mixed. So, [this means] that they'll have underlying triggers which are irritants, such as cigarette smoke, paint fumes, [and] weather conditions, as well. These are the [treatment-] resistant population; it's not the purely seasonal allergic rhinitis. A person who comes into this office with tree and grass pollen allergy limited to the springtime is really a piece of cake. They're very easy to treat. They respond almost universally to therapy, and they're not resistant. [However,] it's a patient who comes into the office that has positive skin tests, and they also have seasonal allergic rhinitis, but they have an underlying pathology related to non-allergic triggers as well; they're the resistant ones."

US Key Opinion Leader

"Of course, it is easier to spend money on antihistamines and nasal steroids. But the problem is [that] in the future, if [the number of] this kind of patient with severe allergic rhinitis increases, it is possible that this kind of treatment is not sufficient and cannot satisfy the patient. For this reason, immunotherapy and the use of immunotherapy can, in a way, increase."

EU Key Opinion Leader

"We know that about over half the patients with nasal allergies never go see a physician; [instead,] they treat it [using products sold] over the counter."

US Key Opinion Leader

As I mentioned, the [AR patient] flow is, they usually go first to pharmacists, the second step is the GP, and the third step is the specialist. Usually, when they come [to the specialist], [it's because] there's a special reasons [sic], or [it's] because they have already got the disease. And, of course, [it's] because with the usual treatments, they don't get the sufficient benefit, or because they specifically want to have immunotherapy, for instance, and this is the [turning] point for them.

EU Key Opinion Leader

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"Clearly, if family doctors cured [AR] patients enough, [allergy] specialists would not exist. [Yet] we exist still. This fact suggests they're [family doctors] incompetent when prescribing [allergy] treatments, [and] are not following any guidelines."

Japanese Key Opinion Leader

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2 Introduction

2.1 Catalyst

The allergic rhinitis (AR) market has declined very slowly over the past decade, as has it become saturated with relatively efficacious standard therapies, such as antihistamines (AHs), intranasal corticosteroids (INCS), and leukotriene receptor antagonists (LRAs), and has also been facing increasing generic competition. Despite the rising prevalence of AR, and a large patient population that is dissatisfied with the current treatment options, the market size for symptomatic therapies alone is set to shrink, as the remaining branded products lose patent protection. There is an increasing shift in the transfer of prescription AR products to over-the-counter (OTC) status, which is driving patients to pharmacies rather than to physicians, further diluting the prescription AR market. In the US, the first INCS, Nasacort (triamcinolone acetonide), was launched OTC in 2014, with the second INCS product, Flonase (fluticasone propionate), launching early 2015. In Japan, two key factors will drive a reduction in the prescription AR market size over the forecast period: the patent expiry of Singulair (montelukast sodium) in Japan, and pricing reforms leading to the increasing the use of generics and OTC AR drugs.

The immense, crowded generic AR market has been largely unappealing to drug manufacturers. Consequently, only two symptomatic therapies are expected to launch before 2024. These are Shionogi's, prostaglandin D2 (PGD2) receptor antagonist, S-555739, and Hisamitsu Pharmaceutical's transdermal patch formulation of an undisclosed existing AR drug, HP-3060, which is being developed only for the Japanese market.

Key opinion leaders (KOLs) interviewed by GlobalData stated that the greatest clinical unmet need in AR is for novel immunotherapies that can alter the cause of AR and offer long-term relief of symptoms, along with convenient administration.

Key opinion leaders (KOLs) interviewed by GlobalData stated that the greatest clinical unmet need in AR is for novel immunotherapies that can alter the cause of AR and offer long-term relief of symptoms, along with convenient administration. The launch of allergen-specific immunotherapies (SITs) delivered by the next-generation tablet formulations will be a strong driver of growth in the AR market over the next 10 years. These immunotherapy agents will not only reshape the growth of the market, but will also mark the beginning of a new era in the causative, personalized approach to AR treatment.

Introduction

2.2 Related Reports

- GlobalData (2014). PharmaPoint: Atopic Dermatitis – Global Drug Forecast and Market Analysis to 2022, November, 2013, GDHC66PIDR
- GlobalData (2014). OpportunityAnalyzer: Allergic Rhinitis: Allergen-Specific Immunotherapy – Opportunity Analysis and Forecast to 2018. September 2014, GDHC023POA
- GlobalData (2014). Asthma – Global Drug Forecast and Market Analysis to 2023. August 2014, GDHC83PIDR
- GlobalData (2014). Allergic Conjunctivitis – Global Drug Forecast and Market Analysis to 2023. September 2014, GDHC030PIDR

2.3 Upcoming Related Reports

- GlobalData (2015). PharmaPoint: Chronic Obstructive Pulmonary Disease – Global Drug Forecast and Market Analysis to 2023

3 Disease Overview

3.1 Etiology and Pathophysiology

Allergic rhinitis (AR) is a common immunoglobulin E (IgE)-mediated inflammatory disorder of the nasal mucosa. It is characterized by symptoms of nasal congestion, pruritus, rhinorrhea, and sneezing, which occur upon exposure to an airborne allergen(s) in a sensitized individual. Table 1 lists examples of airborne allergens that cause AR, which include pollen, house dust mite (HDM) fecal particles, animal dander, cockroach residues, and mold (Esch et al., 2001; Greiner et al., 2011). AR is strongly linked to asthma and allergic conjunctivitis, and has a significant impact on a patient's quality of life (QoL), affecting both sleep patterns and work performance (Small and Kim, 2011; Bousquet et al., 2012).

Table 1: Airborne Allergens That Cause AR

Type of AR	Allergen	Origin/Specific Example of Allergen
Seasonal	Tree pollen	Pine (Pinus), birch (Betula), alder (Alnus), cedar (Cedrus), hazel (Corylus), hornbeam (Carpinus), horse chestnut (Aesculus), willow (Salix), poplar (Populus), plane (Platanus), linden/lime (Tilia), and olive (Olea)
	Grass pollen	Subfamilies Pooideae, Chloridoideae, and Panicoideae. The temperate zones are dominated by grasses belonging to the subfamily Pooideae. The cool-season turf-grasses, bluegrass (Poa), bentgrass (Agrostis), fescues (Festuca), and ryegrass (Lolium) represent the major allergenic genera, along with orchard grass (Dactylis glomerata), timothy grass (Phleum pratense), and vernal grass (Anthoxanthum odoratum), which are common in meadows, pastures, and waste places. This subfamily also includes the important cereals, wheat (Triticum), rye (Secale), and barley (Hordeum). Subfamily Chloridoideae includes Bermuda grass (Cynodon dactylon). Subfamily Panicoideae includes Bahiagrass (Paspalum notatum).
	Weed pollen	Ragweed (Ambrosia), plantain (Plantago), nettle (Parietaria/Urticaceae), mugwort (Artemisia vulgaris), fat hen (Chenopodium), and sorrel/dock (Rumex)
Perennial	HDM	Allergen in the fecal pellets of HDMs and storage mites, including Dermatophagoides pteronyssinus, Dermatophagoides farina, Euroglyphus maynei, and Alternaria alternarta
	Animal dander	Cats (Felis domestica), dogs (Canis familiaris), horses (Equus caballus), mice (Mus musculus), and rats (Rattus norvegicus)
	Insects (cockroaches)	Periplaplaneta americana, Blatella germanica, and Blatta orientalis
Seasonal and perennial symptoms	Fungi (molds)	Cladosporium herbarum and Aspergillus fumigatus

Source: GlobalData; Esch et al., 2001

Disease Overview

AR occurs when an individual reacts to an otherwise innocuous and ubiquitous inhaled substance in the environment, either indoors or outdoors. In predisposed individuals, initial exposure to an allergen(s) can cause a cascade of events leading to allergen sensitization, a condition known as atopy. As shown in Figure 1, allergens are recognized by antigen-presenting cells (APCs), resulting in the activation of allergen-specific T-helper 2 (T_H2) cells, which leads to the synthesis of IgE, an antibody that plays a major role in allergic diseases, by plasma B cells. Individuals with AR have IgE antibodies for specific allergen(s) that are bound to tetrameric (alpha, beta, gamma2), high-affinity IgE receptors (FcεRIs) on the surface of mast cells and basophils, rendering them "sensitized" (Sin and Togias, 2012). Upon subsequent exposure to the allergen, numerous inflammatory cells, including eosinophils, CD4-positive T cells, B cells, and macrophages, are recruited and infiltrate the nasal lining, resulting in activation and the release of chemical mediators of inflammation (Small and Kim, 2011). Consequently, early-phase (acute) and late-phase allergic (hypersensitivity) responses occur.

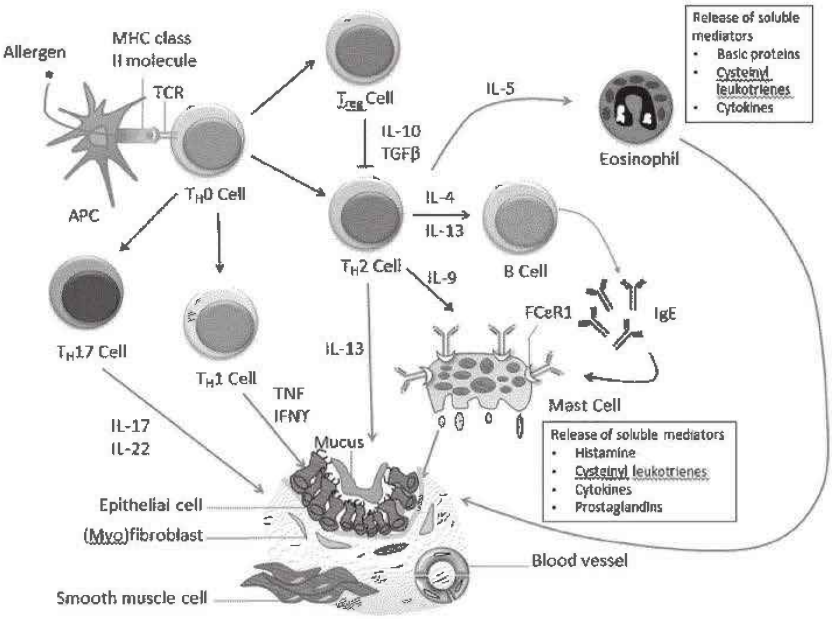
In the early-phase allergic response, within minutes of re-exposure to the allergen(s), cross-linking of adjacent IgE molecules occurs, and the mast cells degranulate and rupture, releasing both preformed and newly-synthesized chemical mediators, including histamine, cysteinyl leukotrienes, prostaglandins, and cytokines (specifically, interleukins [ILs]-3, -4, -5, and -13) (Broide, 2010). This promotes increased vascular permeability, smooth muscle contraction, and mucus production (Dykewicz and Hamilos, 2010). Early-phase allergic responses are associated with immediate rhinitis symptoms, such as sneezing, rhinorrhea, itching, and nasal congestion.

In addition, patients can also experience a late-phase allergic response. The late-phase response occurs over the four to eight hours following subsequent exposure to the allergen. It is induced by chemokines secreted from mast cells and other immune cell types during the early-phase immune response, and is characterized by the recruitment and influx of eosinophils and T_H2 cells. This induces the release of eosinophilic inflammatory mediators, including cysteinyl leukotrienes and basic proteins, similar to those seen in asthma. This leads to chronic rhinitis and recurrent symptoms, including nasal blockage and nasal hyper-reactivity (Scadding et al., 2008).

Disease Overview

Figure 1 illustrates the immunological mechanisms involved in the early- and late-phase response to an inhaled allergen in a sensitized individual.

Figure 1: Immunological Mechanisms Involved in the Early- and Late-Phase Allergic Response



Source: GlobalData, adapted from Holgate and Polosa, 2008

APC = antigen-presenting cell; FCεRI = high-affinity IgE receptor; IFNγ = interferon-gamma; IgE = immunoglobulin E, IL = interleukin, MHC = major histocompatibility complex; TCR = T-cell receptor; TGF-β = transforming growth factor-β; T_H = T helper cell; TNF = tumor necrosis factor, T_{Reg} = regulatory T cell

The immunomodulatory effects of allergen immunotherapy (AIT) are complex and not fully understood. Successful immunotherapy has been linked to a shift from T-helper 2 (T_H2) immune responses, which are associated with the development of atopic conditions, to T-helper 1 cell (T_H1) immune responses (Moote and Kim, 2011). Other associated effects include the production of regulatory T cells (T_{Regs}) that secrete several anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta (TGF-β). This inhibits T_H2-mediated synthesis of IgE-mediated antibodies, while increasing the levels of immunoglobulin G (IgG) antibodies. IgE-blocking antibodies have been shown to be involved in secondary immune responses, and reduce the

release of pro-inflammatory cytokines from mast cells, eosinophils, and T cells. Allergen-specific immunotherapy (SIT) has been shown to decrease the recruitment of mast cells, basophils, and eosinophils to the skin, nose, eye, and bronchial mucosa after exposure to allergens, and reduces the release of mediators, such as histamine, from basophils and mast cells. Research is ongoing to determine the mechanism of action of immunotherapy and how it exerts a therapeutic effect in individuals with allergic diseases (Moote and Kim, 2011).

3.2 Symptoms

Table 2 lists the symptoms most commonly associated with AR.

Table 2: Common Symptoms of AR

Symptoms	Description
Nasal congestion	Excessive clear, watery mucus is common in patients with AR. Persistent nasal congestion can result in chronic mouth breathing. The long-term effects associated with mouth breathing include the development of a high, arched palate, an elevated upper lip, and an overbite. Teenagers with AR might end up needing braces.
Nasal/palate itch	Nasal/palate itch can lead to a transverse nasal crease, known as the "allergic salute." As patients, particularly children, rub their nose in an upward direction to relieve nasal congestion or itching, a line can form across the bridge of the nose.
Rhinorrhea	This condition occurs when a substantial volume of mucous fluid fills the nasal cavity. Often termed a "runny nose," the condition occurs frequently and can often be present in conjunction with nasal congestion.
Postnasal drainage	Postnasal drip is particularly prominent in children who experience allergic mucous build-up in the nasal cavity, which is then discharged into the throat, leading to repeated sore throats. The long-term effects of chronic postnasal drip include a loss of the sensations of taste and smell.
Repetitive sneezing	AR sufferers often experience paroxysmal sneezing, which is accompanied by itchiness in the nose.
Headache caused by nasal congestion	Patients with AR often have sinusitis. Symptoms can include tender sinuses, headache, dizziness, or a feeling of fullness in the head.
Non-medical symptoms	Disturbed sleep, tiredness, and listlessness

Source: GlobalData; Storms, 2008

3.3 Classification

3.3.1 Seasonal and Perennial AR

AR has traditionally been classified as either seasonal or perennial. Seasonal allergic rhinitis (SAR) occurs during a specific season, lasts for a period of a few months, and is caused by cyclic allergens, such as pollens (Greiner et al., 2011). Alternatively, AR can be caused by allergens that are present perennially, such as HDM, animal dander, and molds; therefore, patients with perennial allergic rhinitis (PAR) can experience symptoms that last all year.

The classification of AR as either seasonal or perennial is overly simplistic, and does not provide a finite rule for all allergens. For example, SAR only exists in countries that have seasons, and patients can still experience pollinosis (hay fever), such as when the allergen persists on fabrics after the pollen season has officially ended (Greiner et al., 2011). Affected individuals may be sensitized to a single allergen (monosensitization), to several allergens (polysensitization), or to both seasonal and perennial allergens. Furthermore, "seasonal" allergens, such as pollen, may be perennial in some countries, depending on the climate (Small and Kim, 2011). Finally, the severity of the allergic inflammation of the nasal airways can vary between individuals.

Affected individuals may be sensitized to a single allergen (monosensitization), to several allergens (polysensitization), or to both seasonal and perennial allergens.

3.3.2 ARIA Classification of AR

The organization known as Allergic Rhinitis and its Impact on Asthma (ARIA) has developed classification and treatment guidelines for AR (Bousquet et al., 2008a). These guidelines classify AR in terms of the duration of the presence of symptoms as either intermittent or persistent, rather than as either seasonal or perennial. AR is defined as intermittent if the duration of the symptoms is less than four weeks, and as persistent when the symptoms continue throughout the year. In addition, the ARIA guidelines classify the disease by severity as either "mild" or "moderate to severe." AR symptoms are categorized as mild when individuals are able to perform their normal activities at work or school and sleep normally, and are typically intermittent. The symptoms are classified as moderate to severe when they significantly affect daily activities and sleep. This classification is important when selecting patient treatment strategies.

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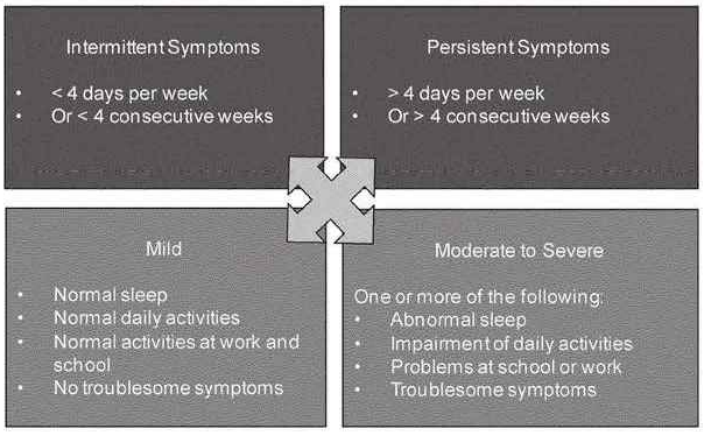
Figure 2 presents the ARIA classification of AR by the duration of symptoms and severity.

Figure 2: ARIA Classification of AR by Duration of Symptoms and Severity



Source: GlobalData, adapted from Bousquet et al., 2001

3.4 Diagnosis

AR is typically a chronic condition that is frequently trivialized, despite the fact that it is widespread and has a serious negative impact on the QoL of many affected individuals (Holgate and Polosa, 2008). It is believed to be underdiagnosed, particularly in the primary care setting, as patients often do not seek medical attention, but instead self-medicate with over-the-counter (OTC) therapies (Small and Kim, 2011). AR is also associated with multiple comorbidities, including other allergic diseases, such as asthma and atopic dermatitis (Zheng et al., 2011). In particular, it is estimated that 95% of asthmatic individuals also have rhinitis. Therefore, it is recommended that all asthmatics be screened for rhinitis (Leynaert et al., 1999).

AR is typically diagnosed based on the patient's symptoms and medical history. A positive diagnosis is typically made if two or more AR symptoms — watery rhinorrhea, sneezing, nasal obstruction, or nasal pruritus — are present for at least one hour on several days within a given week (Min, 2010). The severity of AR should be determined using the ARIA guidelines outlined in Figure 2. A physical examination of outward signs that are indicative of AR should be conducted, including persistent mouth breathing, a transverse nasal crease (or general rubbing of the nose), frequent sniffling or throat clearing, and "allergic shiners," which are dark circles under the eyes

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resulting from nasal congestion. The physicians should also perform an endoscopic examination of the intranasal cavity for structural abnormalities or nasal polyps, which are fleshy swellings that grow from the lining of the nose or sinuses, and are caused by the inflammation that occurs as a result of AR (Small and Kim, 2011).

To determine the exact underlying cause of AR, two common diagnostic allergy tests may be performed. A blood test can be performed to quantify a patient's serum-specific IgE level. For example, a radioallergosorbent test (RAST) or multiple allergen simultaneous test (MAST), such as the ImmunoCAP Phadiatop assay (ThermoScientific, UK), can be used to determine a patient's specific IgE levels against a particular allergen *in vitro* (Min, 2010). The ARIA guidelines recommend that this test be conducted in a primary care setting. If a patient has a positive result, they are likely to be allergic (Bousquet et al., 2008a).

If more information is required, the patient can be referred to an allergy specialist, who can confirm a diagnosis of AR using a skin prick test (immediate hypersensitivity test) for IgE. The skin prick test involves putting a small drop of a commercial allergen extract (one that is likely to be the cause of the patient's allergy, such as animal dander or pollen) on the patient's back or forearm, and then pricking the skin through the drop to bring the extract into contact with the epidermis (Haahtela et al., 2014). If the test is positive, and the patient is allergic to the extract, a wheal and flare response — an irregular blanched wheal surrounded by an area of redness — will appear within 15 to 20 minutes (Small and Kim, 2011). Skin prick tests not only provide a result within a short timeframe, but are also considered to be more sensitive and cost-effective than allergen-specific IgE tests (Heinzerling et al., 2013). However, as they must be performed by an allergy specialist, not all patients are able to receive these tests to determine the exact cause of their AR. Furthermore, IgE-specific tests, such as MAST, are costly and require samples to be sent away for testing, which is another barrier to establishing a correct diagnosis of AR.

3.5 Quality of Life

AR is a highly prevalent condition affecting millions of adults and children worldwide. Although AR is often dismissed as being nothing more than a unimportant nuisance, there are considerable health-related and economic costs associated with the condition. Several studies have demonstrated that if AR is poorly managed, and the symptoms are poorly controlled, it can contribute to a decreased health-related quality of life (HRQoL). Poor disease management can also result in daytime fatigue, reduced sleep quality, impaired learning, impaired cognitive functioning, and decreased long-term productivity. AR is also directly linked to the exacerbation of other inflammatory airway diseases, such as asthma and rhinosinusitis, which has additional health implications (Meltzer, Eli O., Gross, Gary N., Katial, Rohit, Storms, 2012).

Although AR is often dismissed as being nothing more than a unimportant nuisance, there are considerable health-related and economic costs associated with the condition.

4 Epidemiology

4.1 Disease Background

Allergic rhinitis (AR) is a chronic respiratory disease characterized by inflammation of the nasal cavity, and affects people of all ages. The main symptoms of AR are sneezing, nasal itching, a blocked or runny nose, and a sore throat (NHS, 2012; WHO, 2013). Research suggests that a combination of genetic factors, such as a family history of AR, and environmental factors, such as exposure to allergens, including smoke, dust, pollen, insects, molds, and animal dander, may increase the risk for developing AR (NHS, 2012; WHO, 2013). Different individuals are sensitive to different allergens; therefore, the individual's serum-specific immunoglobulin E (IgE) levels are used to determine their sensitivity to specific allergens (NHS, 2012; WHO, 2013).

In the seven major markets (7MM) (US, France, Germany, Italy, Spain, UK, and Japan), the prevalence of self-reported AR ranges from 13.7% in men and 14.3% in women in the US, to 35.1% in men and 39.3% in women in Japan (Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997; Ozdoganoglu and Songu, 2012). According to the World Health Organization (WHO), an estimated 400 million people worldwide were affected by AR during 1996–2006. The mild form of AR is not a life-threatening condition. However, severe AR has a significant socioeconomic impact due to the fact that it affects people of all ages and is associated with low performance at school and loss of productivity at work, which lead to a deterioration in the quality of life (QoL) (Bousquet et al., 2008a; WHO, 2007). Research also suggests that many individuals with AR experience comorbidities such as asthma, atopic dermatitis, depression, and sinusitis, which place an additional burden on patients and their families, as well as on healthcare systems, making AR a major public health burden worldwide (Bousquet et al., 2008a; Canonica et al., 2007; Min et al., 2001; WHO, 2007).

This report provides an overview of the risk factors, comorbidities, and the global and historical trends for AR in the 7MM. It also includes a 10-year epidemiological forecast for the total prevalent cases of AR in these markets, segmented by sex and age (age≥18 years). To forecast the total prevalent cases of AR in the 7MM, GlobalData epidemiologists selected nationally-representative studies that provided the total prevalence of AR using uniform diagnostic criteria based on the self-reported prevalence of AR. Additionally, GlobalData epidemiologists provide the total prevalent cases of AR segmented by etiological type (seasonal, perennial, and both), as well as by severity

(mild or moderate to severe). In addition, GlobalData epidemiologists provide the total prevalent cases of AR in the 7MM (except for the US) that are sensitized to specific allergens.

Table 3 describes the classification of AR based on the etiological type and severity.

Table 3: Classification of AR Based on Etiological Type and Severity

Classification Based on Etiological Type	Characteristics
SAR or hay fever	Symptoms are present during a particular season, such as spring and early summer, and are mostly triggered by outdoor allergens, such as pollen, dust, grass, or mold.
PAR	Symptoms are present all year, and are mostly triggered by indoor allergens, such as HDM, pets, dust, and mold.
Classification Based on Severity	**Characteristics**
Mild AR	No sleep disturbance No impairment of daily activities, leisure, and/or sports No impairment of school or work performance Symptoms present, but not troublesome
Moderate to severe AR	Sleep disturbance Impairment of daily activities, leisure, and/or sports Impairment of school or work performance Troublesome symptoms

Source: GlobalData; ARIA, 2007; Bousquet and Cauwenberge, 2002; Bousquet et al., 2008a; WHO, 2013

4.2 Risk Factors and Comorbidities

AR is a chronic respiratory disease that is largely preventable. The risk factors for AR include a family history of AR, exposure to allergens in the environment, and living in an urban environment. People with AR also suffer from a host of comorbidities, such as asthma, atopic dermatitis, and depression.

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Table 4 lists the most common risk factors and comorbidities associated with AR.

Table 4: Common Risk Factors and Comorbidities for AR	
Risk Factors	**Description**
Family history	A family history of AR is a strong predictor for AR in children and adults.
Allergens in the environment	Exposure to allergens in the environment increases the risk for AR.
Urban living	Urban living elevates the risk for AR.
Comorbidities	
Asthma, atopic dermatitis, anxiety, depression, pharyngitis, sinusitis, and allergic conjunctivitis	Asthma, atopic dermatitis, anxiety, depression, pharyngitis, sinusitis, and allergic conjunctivitis are common comorbidities in people with AR.

Source: GlobalData; Batlles-Garrido et al., 2010; Canonica et al., 2007; Eriksson et al., 2010; Keil et al., 2010; Lam et al., 2011; Lee and Kim, 2011; Lee et al., 2004; Min et al., 2001; Mullol, 2009; Pherwani et al., 2009; Scadding and Williams, 2008; Schatz, 2007

4.2.1 A family history of AR is a strong predictor for AR in children and adults

A family history of AR in parents is a strong predictor for AR in their offspring. Batlles-Garrido and colleagues conducted a cross-sectional study in the city of Almeria in southeast Spain as part of the International Study of Asthma and Allergies in Childhood (ISAAC) project. The researchers aimed to assess the risk factors associated with AR in children ages 10–11 years during the spring and autumn in 2001 (Batlles-Garrido et al., 2010). In the multivariable analysis, the researchers found that children with past symptoms of AR were nearly two times more likely to have parents who had a history of AR (adjusted Odds Ratio [OR] = 1.8; 95% Confidence Interval [CI] = 1.31–2.59) when compared with children without any past symptoms of AR (Batlles-Garrido et al., 2010).

The familial risk for AR was examined in another cross-sectional study conducted in a housing estate in Singapore in 2002. The researchers administered questionnaires to 257 Chinese families residing in the housing estate to obtain the prevalence of AR among the family members (Lee et al., 2004). Based on the analysis, parents who had a history of AR were 2.5 times more likely to have a first child with AR (Prevalence Rate Ratio [PRR] = 2.5; 95% CI = 1.31–2.59) when compared with parents who did not have a history of AR. The researchers also reported that the risk for developing AR in a second child increased dramatically when the parents had a history of AR. Parents who had a history of AR were 3.7 times more likely to have a second child with AR (PRR = 3.7; 95% CI = 1.6–8.3) when compared with parents who did not have a history of AR. Additionally, the researchers found that families where both the parents and the eldest child had a history of AR were 6.9 times more likely to have a next child with AR (PRR = 6.9; 95% CI = 3.5–

13.9) than families without a history of AR (Lee et al., 2004). Because family history is a strong predictor for the risk of developing AR, the disease can be prevented if exposure to environmental allergens that may trigger the disease is limited.

4.2.2 Exposure to allergens in the environment increases the risk for AR

Allergens in the environment, such as smoke, dust, pollen, insects, molds, and animal dander, are risk factors for AR. Different individuals are sensitive to different allergens present in the environment. Exposure to allergens present in the indoor or outdoor environment might lead to allergic sensitization in an individual, thereby increasing the risk for developing AR.

A population-based cohort study analyzed the data for 467 German children who were recruited for the study in 1990 and followed for 13 years, and showed that exposure to environmental allergens was significantly associated with the development of AR. The researchers assessed the sensitization of the children to five indoor and outdoor aeroallergens — mite, cat, dog, timothy grass pollen, and birch — at different time points. In the multivariable analysis, the researchers found that the children who were sensitive to the aeroallergens were 18.85 times more likely to develop AR (adjusted OR = 18.85; 95% CI = 9.38–38.39) than the children who were not sensitive to any of the aeroallergens (Keil et al., 2010).

Furthermore, a cross-sectional study conducted in Hanoi, Vietnam in adults age 21–70 years from August 2007 to January 2008 also showed that exposure to allergens such as gas, dust, or fumes in the indoors or the outdoors increases the risk of developing AR. In the multivariable analysis, the researchers found that individuals who were exposed to allergens such as dust, smoke, or fumes, either in the indoor or outdoor environment, were 1.57 times more likely to develop AR (adjusted OR = 1.57; 95% CI = 1.34–1.84) than individuals who were not exposed to these allergens (Lam et al., 2011).

4.2.3 Urban living elevates the risk for AR

Several epidemiological studies have shown that people living in urban localities are more prone to developing AR than people living in semi-urban or rural localities.

Several epidemiological studies have shown that people living in urban localities are more prone to developing AR than people living in semi-urban or rural localities. The cross-sectional study conducted in Hanoi, Vietnam, which included both an urban and a rural locality, showed that people living in the urban region were more likely to have AR than their rural counterparts (Lam et al., 2011). In the multivariable analysis, the researchers found that people from urban Vietnam

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were almost four times more likely to develop AR (adjusted OR = 3.94; 95% CI = 3.40–4.50) than people from rural Vietnam (Lam et al., 2011).

In another cross-sectional study, the researchers collected data during 2008 on the self-reported prevalence of AR in 29,218 individuals age 16–75 years who resided in the city of Gothenburg, Sweden, and the adjoining towns and rural areas. The multivariable analysis showed that the risk of developing AR increased with increasing urbanization. The residents of Gothenburg were 1.29 times more likely to develop AR (adjusted OR =1.29; 95% CI = 1.15–1.44) than the residents of the rural areas (Eriksson et al., 2010). The higher risk of developing AR in the residents of the urban areas can be attributed to the extremely high levels of pollutants, such as smoke, fumes, and dust, in the cities and towns, which increase the risk for developing AR.

4.2.4 Comorbidities

Table 5 presents the prevalence of the most frequently occurring comorbidities in people with AR by age group. According to several epidemiological studies, asthma, atopic dermatitis, anxiety, depression, pharyngitis, sinusitis, and allergic conjunctivitis are the most frequently occurring comorbidities in people with AR. These comorbidities impose an additional burden on the healthcare system as well as on AR patients and their families, leading to a diminished QoL for millions of affected individuals (Bousquet et al., 2008a; WHO, 2007).

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Table 5: Prevalence of the Most Frequently Occurring Comorbidities in People with AR

Comorbidity	Age Group	Prevalence (%) of Comorbidities in People with AR	Source
Asthma	≤8 years	7.29	Lee and Kim, 2011
	≥12 years	28.4	Schatz, 2007
	≥12 years	38.7	Scadding and Williams, 2008
	<6 years	73.9	Pherwani et al., 2009
	6–14 years	76.2	Pherwani et al., 2009
	Adults	52.6	Pherwani et al., 2009
	All ages	10.1	Min et al., 2001
	≥12 years	34.1	Mullol, 2009
	≥12 years	31.5	Canonica et al., 2007
Atopic dermatitis	≤18 years	24.24	Lee and Kim, 2011
	All ages	20.9	Min et al., 2001
	<6 years	17.39	Pherwani et al., 2009
Allergic conjunctivitis	6–14 years	35.7	Pherwani et al., 2009
	Adults	47.4	Pherwani et al., 2009
	≥12 years	21.6	Mullol, 2009
Anxiety	≥12 years	9.4	Schatz, 2007
	≥12 years	9.7	Scadding and Williams, 2008
	≥12 years	11.6	Canonica et al., 2007
Depression	≥12 years	9.4	Schatz, 2007
	≥12 years	4.7	Canonica et al., 2007
Pharyngitis	≥12 years	5.7	Mullol, 2009
	≥12 years	3.4	Mullol, 2009
Sinusitis	≥12 years	6.5	Scadding and Williams, 2008
	≥12 years	6.1	Canonica et al., 2007
	≥12 years	12.5	Schatz, 2007

Source: GlobalData (various sources listed above)

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4.3 Global and Historical Trends

According to the WHO, AR is a common chronic respiratory disease that occurs globally, with an estimated 400 million people worldwide affected with the condition during 1996–2006 (Bousquet et al., 2008a; Bousquet et al., 2008b; WHO, 2007). The prevalence of AR varies from study to study and across populations. In the 7MM, the prevalence of self-reported AR ranges from 13.7% in men and 14.3% in women in the US to 35.1% in men and 39.3% in women in Japan (Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997; Ozdoganoglu and Songu, 2012). Additionally, Phase III of the ISAAC study, which was conducted during 2001–2002, found a wide geographical variation in the prevalence of AR in children age 6–7 years and 13–14 years. In children age 6–7 years, the prevalence of AR varied from 11.1% in the state of Georgia, the US, to 46.4% in Taiwan (Björkstén et al., 2008). Meanwhile, the prevalence of AR in children age 13–14 years varied from 19.2% in Georgia to 60.7% in Japan (Björkstén et al., 2008). GlobalData epidemiologists believe that the wide range in the prevalence of AR in children from different regions of the world may be due to variations in the environmental and genetic risk factors for AR across these regions.

4.3.1 US

In the US, epidemiological data on the trends in the prevalence of AR are limited, with most studies providing data on the prevalence of hay fever, a subtype of AR. The Centers for Disease Control and Prevention (CDC) provided data on the prevalence of hay fever in civilian non-institutionalized children and adults in the US through the National Health Interview Survey (NHIS) conducted in 2011 (CDC, 2012a; CDC, 2012b). The NHIS data provided information on the total (self-reported) hay fever prevalence in children less than 18 years of age, and the diagnosed (reported by a physician) hay fever prevalence in adults above 18 years of age. The NHIS data showed that the total prevalence of hay fever in 74,518 children age <18 years was 9.0%, and that the diagnosed prevalence of hay fever in 231,376 adults age ≥18 years was approximately 7.3%.

Table 6 provides the age-specific prevalence of hay fever in both children and adults from the 2011 NHIS survey (CDC, 2012a; CDC, 2012b). The total prevalence of hay fever in the US ranged from 4.8% in children age 0–4 years to 12.6% in children age 12–17 years. Additionally, the prevalence of hay fever in the US was much lower than the prevalence of AR in the 5EU (France, Germany, Italy, Spain, and the UK) markets and Japan because hay fever is a subtype of AR.

Table 6: Age-Specific Prevalence of Hay Fever from the 2011 NHIS Survey			
Source	Prevalence Type	Age Group	Prevalence (%)
		≤18 years	9.0
CDC, 2012a	Total prevalence	0–4 years	4.8
		5–11 years	9.1
		12–17 years	12.6
		≥18 years	7.3
		18–44 years	5.5
CDC, 2012b	Diagnosed prevalence	45–64 years	9.9
		65–74 years	7.7
		≥75 years	5.9

Source: GlobalData (various sources listed above)

4.3.2 5EU

The 5EU markets lack data needed to assess the historical trends in the prevalence of AR. However, one study, the European Community Respiratory Health Survey (ECHRS), evaluated the geographical trends in the self-reported total prevalence of AR in Europe during the 1990s. The researchers randomly selected individuals age 20–44 years from 35 different geographical areas spread across 15 European countries to answer a questionnaire assessing the self-reported total prevalence of AR.

Table 7 presents the self-reported total prevalence of AR in the 5EU markets in people age 20–44 years from the ECHRS. The self-reported total prevalence of AR in the 5EU markets ranged from 18.1% in Spain to 36.0% in France, showing a wide geographical variation across the 5EU markets (Bousquet et al., 2008b).

Table 7: Self-Reported Total Prevalence (%) of AR in the 5EU, Age 20–44 Years					
5EU	France	Germany	Italy	Spain	UK
Total AR prevalence (%)	36.0	20.0	18.6	18.1	28.9

Source: GlobalData; Bousquet et al., 2008b
5EU = France, Germany, Italy, Spain, and UK

In a more recent study, the ISAAC study, the researchers randomly selected students enrolled in schools in over 50 countries during 2001–2002, and examined the total prevalence of AR in children age 6–7 years and age 13–14 years using questionnaire surveys (Björkstén et al., 2008).

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Unfortunately, of the 5EU markets covered in this report, France was the only one that did not have any data because it was not a participant country in the ISAAC study.

Table 8 shows the reported total prevalence of AR in children age 6–7 years and age 13–14 years in the EU markets (Germany, Italy, Spain, and the UK) from the ISAAC study (Björkstén et al., 2008). GlobalData epidemiologists observed that the reported total prevalence of AR in children age 6–7 years was much lower than the total prevalence of AR in children age 13–14 years in the respective markets.

Table 8: Total Prevalence (%) of AR in the EU, Age 6–14 Years

Markets	Total AR Prevalence, Age 6–7 Years (%)	Total AR Prevalence, Age 13–14 Years (%)
Germany	19.5	41.0
Italy	25.1	41.4
Spain	20.5	39.2
UK	23.9	38.8

Source: GlobalData; Björkstén et al., 2008

4.3.3 Japan

A series of questionnaire surveys conducted in schoolchildren in Japan provided evidence of an increasing trend in the prevalence of AR in Japanese children.

Similar to the US and the 5EU markets, AR is a major public health problem in Japan. A series of questionnaire surveys conducted in schoolchildren in Japan provided evidence of an increasing trend in the prevalence of AR in Japanese children. Yura and colleagues analyzed the results of questionnaire surveys conducted annually in elementary schoolchildren age 7–15 years in Osaka, Japan from 1983–2006, and reported that the total prevalence of AR in Japanese children increased from 12.3% to 16.7% during 1983–1991. The total prevalence of AR in Japanese children further increased to 25.4% by 2003, and then stabilized at 24.7% by 2006 (Yura et al., 2011).

Another questionnaire survey by Kusunoki and colleagues evaluated the trends in the total prevalence of AR in schoolchildren age 7–15 years during 1996 and 2006 in Kyoto, Japan. The researchers surveyed 16,176 schoolchildren in 1996 and 13,215 schoolchildren in 2006, and reported that the total prevalence of AR increased from 20.3% in 1996 to 27.4% in 2006 (Kusunoki et al., 2009). GlobalData epidemiologists observed that the total prevalence of AR in schoolchildren age 7–15 years in the cities of Osaka and Kyoto was similar to the total prevalence of AR in children age 6–7 years in the four EU markets (Germany, Italy, Spain, and the UK) in the ISAAC

study, but was lower than the total prevalence of AR in children age 13–14 years in the four EU markets in the ISAAC study (Björkstén et al., 2008; Kusunoki et al., 2009; Yura et al., 2011).

AR prevalence data for adults were available from a nationally-representative, cross-sectional study that reported the prevalence of AR in Japanese adults age 20–79 years during 2006–2007 using the ECHRS questionnaire. The researchers reported that the age-adjusted total prevalence of AR in Japanese adults age 20–79 years was 35.1% in men and 39.3% in women, which was similar to the age- and sex-adjusted prevalence of AR in adults in France reported in the ECHRS study, the 5EU country with the highest total AR prevalence in adults (Bousquet et al., 2008b; Konno et al., 2012). Although the total prevalence of AR in Japanese children showed an increasing trend, the temporal data for adults were limited, and therefore, further studies are warranted in the Japanese adult population.

4.4 Forecast Methodology

To forecast the total prevalent cases of AR in the 7MM from 2013–2023, GlobalData epidemiologists selected only nationally-representative studies that provided the total prevalence of AR using uniform diagnostic criteria based on the self-reported prevalence of AR. GlobalData epidemiologists provide the total prevalent cases of AR segmented by age, sex, etiological type (seasonal, perennial, and both), and severity (mild, moderate, and severe). In addition, GlobalData epidemiologists provide the total prevalent cases of AR in the 7MM (except for the US) sensitized to specific allergens.

Table 9 presents a summary of all the sources that were used to build the epidemiological forecast for the total prevalent cases of AR in the 7MM over the forecast period, segmented by age, sex, etiological type (seasonal, perennial, and both), severity (mild or moderate to severe), and sensitization to specific allergens.

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Table 9: 7MM, Sources of Data Used to Forecast the Total Prevalent Cases of AR					
Country	**Source**	**Estimated Total Prevalence (%) of AR for 2013 (Men and Women)**	**Location**	**Study Period**	**Ages**
US	Nathan et al., 1997	15.20	US	1993	≥18 years
France Germany Italy Spain UK	Bauchau and Durham, 2004	France = 18.20 Germany = 20.50 Italy = 16.10 Spain = 15.10 UK = 21.80	Western Europe	2001	≥18 years
Japan	Konno et al., 2012	35.98	Japan	2006–2007	20–79 years
Segmentation by AR Severity					
Country	**Source**	**Severity of AR (%), (Men and Women)**	**Location**	**Study Period**	**Age**
US	Schatz, 2007	Mild: 37.40 Moderate: 55.20 Severe: 7.40	US	2006	>12 years
5EU	Canonica et al., 2007	Mild: 32.80 Moderate: 59.50 Severe: 7.70	France, Germany Italy, Spain and the UK	2006	>12 years
Japan	Gotoh et al., 2013	Mild: 9.00 Moderate/severe: 91.00	Japan	2011	All ages
Segmentation by AR Etiological Type					
Country	**Source**	**Types of AR (%), (Men and Women)**	**Location**	**Study Period**	**Age**
US	Schatz, 2007	Seasonal: 34.50 Perennial: 46.30 Seasonal and perennial: 19.20	US	2006	>12 years
5EU	Canonica et al., 2007	Seasonal: 69.60 Perennial: 26.50 Seasonal and perennial: 3.90	France, Germany Italy, Spain, and the UK	2006	>12 years
Japan	Baba et al., 2009	Seasonal: 76.60	Japan	2008	–
Japan	Okubo et al., 2011	Perennial: 23.40	Japan	2008	–
Segmentation by Sensitization to Specific Allergens					
Country	**Source**	**Types of AR Due to Specific Allergens (%), (Men and Women)**	**Location**	**Study Period**	**Age**
US	Paucity of data for the US				
5EU	Bauchau and Durham, 2004	Grass pollen: 52.20 Tree pollen: 33.41	Western Europe	2001	≥18 years

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		Weed pollen: 27.07 Mold: 10.00 Animal: 25.61 Dust mites: 48.78			
Spain	Sala-Cunill et al., 2013	Parietaria judaica pollen: 42.78	Spain	2009–2010	18–65 years
Japan	Sakashita et al., 2010	Cryptomeria japonica: 56.00 Other aero-allergens (Dermatophagoides pteronyssinus, Dermatophagoides farinae, Dactylis glomerata, Ambrosia artemisiifolia, Candida albicans, Aspergillus fumigatus): 41.00	Eiheiji-cho,Fukui, and Echizen in Fukui prefecture, in the central Hokuriku area of Japan	May and June in 2006 and 2007	20–40 years

Source: GlobalData (various sources listed above)
5EU = France, Germany, Italy, Spain, UK; 7MM = US, 5EU, and Japan

4.4.1 Sources Used

4.4.1.1 7MM

GlobalData epidemiologists obtained the most up-to-date, country-specific total population data from the US Census Bureau's (USCB's) International Data Base for each country covered in the forecast. The USCB was chosen as the source for population data because the population estimates are calculated using census and survey data, vital statistics, country-specific administrative statistics, and information from multinational organizations that collect and publish data for these countries. Additionally, the USCB uses a cohort-component projection method that incorporates fertility, mortality, and migration into the forecast population estimates (USCB, 2012).

4.4.1.2 US

GlobalData epidemiologists obtained the age-specific total prevalence of AR in the US from a nationally-representative study that provided the self-reported prevalence of AR in the US in 1993. The study was divided into two parts. In the first part, the investigators sent a screening questionnaire to 15,000 randomly selected households across the US. The household members were screened for the number of days in the past 12 months during which they experienced symptoms of sneezing, runny nose, stuffy nose, itchy eyes, or watery eyes (Nathan et al., 1997). They were also screened for doctor-diagnosed hay fever, rhinitis, persistent stuffy nose or head, or allergies involving the eyes, nose, or throat in the past 12 months. Around 10,000 households responded to the first part of the study, representing 22,285 people from across the US. In the

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second part of the study, the investigators sent a follow-up questionnaire to a sample of 1,450 persons who responded affirmatively to having symptoms for >7 days within the past year, either singly or consecutively. In the follow-up questionnaire, the participants were asked to select the term that best described their symptoms. If the participants replied affirmatively to the options "seasonal allergy" or "an allergy I have all the time," they were considered to have AR (Nathan et al., 1997).

GlobalData epidemiologists obtained data on the severity and types of AR in the US from a cross-sectional study of 447 clinically-confirmed AR patients age >12 years that was conducted between February and April 2006. The patients were classified as having mild, moderate, or severe AR, based on physician-reported data on the severity of AR. They were also classified as having seasonal, perennial, or both types of AR, based on physician-reported data on the type of AR (Schatz, 2007). For the AR population in the US sensitized to specific allergens, GlobalData epidemiologists were unable to find any sources that provided robust and reliable data.

4.4.1.3 5EU

GlobalData epidemiologists obtained the age- and sex-specific total prevalence of AR in the 5EU from a two-part, cross-sectional, population-based study that was conducted from February to April 2001. In the first part of the study, the researchers chose four to five areas in each of the 5EU countries that were a maximum distance of 50 kilometers from a selected clinical study center. The researchers then randomly conducted telephone interviews with 9,646 people age≥18 years , during which they administered a questionnaire survey to obtain the self-reported total prevalence of AR. The researchers screened the participants for both a history and symptoms of AR, and/or being self-aware of having AR. Participants who responded affirmatively to "being self-aware of having allergic rhinitis" were considered to have AR (Bauchau and Durham, 2004). In the second part of the study, the researchers invited the participants who screened positively for AR in the questionnaire survey to the study clinics to obtain clinical confirmation of the condition. AR was clinically confirmed in 411 of the 725 participants who visited the study clinics. Additionally, the researchers measured the serum IgE levels for specific allergens, such as grass pollen, tree pollen, weed pollen mold, animal dander, and dust mites, in the participants with clinically-confirmed AR to determine the distribution of the AR population sensitized to specific allergens (Bauchau and Durham, 2004).

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To determine the distribution of the severity and types of AR in the 5EU, GlobalData epidemiologists used the results of a cross-sectional study of 1,279 clinically-confirmed AR patients age >12 years conducted between February and April 2006. The patients were classified as having mild, moderate, or severe AR based on physician-reported data on the severity of AR. They were also classified as having seasonal, perennial, or both types of AR, based on physician-reported data on the type of AR (Canonica et al., 2007).

GlobalData epidemiologists obtained data on the AR population in the EU sensitized to specific allergens, such as Parietaria judaica pollen, which is the most common pollen in the four EU markets from a cross-sectional, multicenter study conducted in Spain during 2009–2010 in people ages 18–75 years. The study researchers recorded the demographic and clinical characteristics of all patients with symptomatically-confirmed AR who had a positive skin prick test for Parietaria judaica pollen (Sala-Cunill et al., 2013).

GlobalData epidemiologists obtained data on the AR population in the EU sensitized to specific allergens, such as Parietaria judaica pollen, which is the most common pollen in the four EU markets from a cross-sectional, multicenter study conducted in Spain during 2009–2010 in people ages 18–75 years.

4.4.1.4 Japan

GlobalData epidemiologists obtained the age- and sex-specific total prevalence of AR in Japan from a population-based, cross-sectional study conducted during 2006–2007 in 10 randomly selected areas in Japan. For data collection, the researchers conducted either door-to-door or postal surveys using the translated version of the ECHRS questionnaire to obtain the self-reported prevalence of AR in 22,819 Japanese adults age 20–79 years. The researchers classified the participants as having AR if they responded affirmatively to the question, "Do you have any nasal allergies including hay fever?" (Konno et al., 2012).

GlobalData epidemiologists obtained data on the severity of AR in Japan from a cross-sectional study conducted in May 2011 in 3,382 individuals who had potential symptoms of Japanese cedar pollinosis. The study researchers conducted a survey based on an Internet questionnaire, and classified the patients as having mild intermittent, mild persistent, moderate/severe intermittent, or moderate/severe persistent AR, based on the ARIA criteria in people of all ages and both sexes (Gotoh et al., 2013). GlobalData epidemiologists obtained data on the type of AR (perennial) in Japan from the "Japanese Guideline for Allergic Rhinitis" and the "Practical Guideline for the Management of Allergic Rhinitis in Japan" (Baba et al., 2009; Okubo et al., 2011).

To determine the distribution of the AR population in Japan sensitized to specific allergens, GlobalData epidemiologists used a cross-sectional study that examined 681 AR patients who were determined to be sensitized to specific allergens based on the measurement of IgE levels for seven

aeroallergens: Cryptomeria japonica, Dermatophagoides pteronyssinus, Dermatophagoides farinae, Dactylis glomerata, Ambrosia artemisiifolia, Candida albicans, and Aspergillus fumigatus (Sakashita et al., 2010).

4.4.2 Sources Not Used

To ensure the comparability of the forecast total prevalent cases of AR in the 7MM, GlobalData epidemiologists selected only those studies that provided data on the total prevalence of AR based on the self-reported prevalence of the condition in each of the 7MM for use in the forecast model. GlobalData epidemiologists excluded studies from the forecast model that provided the prevalence of hay fever because hay fever is a subtype of AR, and does not include all AR cases.

Table 10 lists the sources that were excluded from GlobalData's epidemiological forecast. While some of these studies were used to understand the historical and global trends for AR, the data provided were not used directly in the forecast.

Table 10: 7MM, Sources Excluded from the Epidemiological Forecast for the Total Prevalent Cases of AR

Source	Reason for Exclusion	Location	Study Period	Study Population
CDC, 2012b	The study provides data on the diagnosed prevalence of hay fever in people age≤18 years, whereas the forecast used the prevalence of AR.	US	2011	Participants in the NHIS, 2011
Arif et al., 2003	The study provides data on the diagnosed prevalence of hay fever in people age≤20 years, whereas the forecast used the prevalence of AR.	US	1988–1994	Participants in the National Health and Nutrition Examination Survey III (NHANES III) conducted from 1988–1994
Bousquet et al., 2008b	This study was outdated, as it provided data on the total prevalence of AR from the ECHRS study during the 1990s.	35 centers in 15 European countries	Early 1990s (exact time period of the study is unclear)	15,394 adults age 20–44 years from the ECHRS study.

Source: GlobalData (various sources listed above)

4.4.3 Forecast Assumptions and Methods

4.4.3.1 US

To construct the epidemiological forecast for the total prevalent cases of AR in the US, GlobalData epidemiologists used data on the self-reported total prevalence of AR from the 1993 study by Nathan and colleagues, which provides the overall age-specific, self-reported total prevalence of

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AR. Because the study reported no difference in the sex-specific total prevalence of AR, GlobalData epidemiologists applied the overall (both sexes) age-specific total prevalence of AR to both sexes to obtain the age- and sex-specific total prevalence of AR in the US (Nathan et al., 1997). Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (1993) constant throughout the forecast period. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in the US for each year to forecast the total prevalent cases of AR in the US from 2013–2023 (Nathan et al.,1997; USCB, 2012).

To forecast the total prevalent cases of AR in the US segmented by severity and type, GlobalData epidemiologists obtained the proportions of the severity and types of AR in clinically-confirmed AR patients from a study by Schatz and colleagues. GlobalData epidemiologists applied the proportions of the severity and types of AR to the forecast total prevalent cases of AR to obtain the total prevalent cases of AR, segmented by severity and type, from 2013–2023 (Schatz, 2007; USCB, 2012).

GlobalData epidemiologists were unable to find any reliable source for the AR population in the US sensitized to specific allergens, due to the paucity of data, and therefore, the forecast for this segment was not provided for the US.

4.4.3.2 5EU

To construct the epidemiological forecast for the total prevalent cases of AR in the 5EU, GlobalData epidemiologists used data on the overall self-reported total prevalence of AR from a study conducted in each of the 5EU markets (Bauchau and Durham, 2004). Because the study did not provide the age- and sex-specific total prevalence of AR, and due to the lack of historical data needed to develop future trends, GlobalData epidemiologists applied the overall total prevalence of AR obtained for each of the 5EU markets to the age- and sex-specific population estimates in the respective 5EU markets for each year to forecast the age- and sex-specific total prevalent cases of AR in each of the 5EU markets from 2013–2023 (Bauchau and Durham, 2004; USCB, 2012).

To forecast the total prevalent cases of AR in the 5EU segmented by severity and type, GlobalData epidemiologists obtained the proportions of the severity and types of AR for each of the 5EU markets from a study by Canonica and colleagues. GlobalData epidemiologists applied the proportions of the severity and types of AR for each of the 5EU markets to the forecast total

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prevalent cases of AR in the respective 5EU markets to forecast the total prevalent cases of AR segmented by severity and type in each of the 5EU markets from 2013–2023 (Canonica et al., 2007; USCB, 2012).

To forecast the total prevalent cases of the AR population in the 5EU sensitized to specific allergens, GlobalData epidemiologists calculated the proportion of this population based on data on the number of undiagnosed and diagnosed AR patients in the 5EU sensitized to specific allergens (Bauchau and Durham, 2004). GlobalData epidemiologists then applied the calculated proportion of the AR population in the 5EU sensitized to specific allergens to forecast the total prevalent cases of the AR population in each of the 5EU markets sensitized to specific allergens from 2013–2023. Additionally, GlobalData epidemiologists obtained data for the proportion of the AR population in the 5EU sensitized to Parietaria judaica pollen, which is a common pollen in the four EU markets, from a cross-sectional multicenter study conducted in Spain. GlobalData epidemiologists applied the proportion of AR patients sensitized to Parietaria judaica pollen to the total prevalent cases of AR in each of the four EU markets for each year to obtain the total prevalent cases of the AR population sensitized to Parietaria judaica pollen in each of the four EU markets from 2013–2023 (Bauchau and Durham, 2004; Sala-Cunill et al., 2013; USCB, 2012).

4.4.3.3 Japan

To construct the epidemiological forecast for the total prevalent cases of AR in Japan, GlobalData epidemiologists obtained the age- and sex-specific total prevalence of AR from a Japanese study (Konno et al., 2012). Because the study provided the self-reported total prevalence of AR only for individuals age >20 years in both sexes, GlobalData epidemiologists assumed that the total prevalence of AR for individuals age 18–19 years was the same as that for those age 20–29 years in both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2007) constant throughout the forecast period. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Japan for each year to forecast the total prevalent cases of AR in Japan from 2013–2023 (Konno et al., 2012; USCB, 2012).

To forecast the total prevalent cases of AR in Japan by severity, GlobalData epidemiologists obtained data on the severity proportions of AR in Japan from a cross-sectional study conducted in individuals who had potential symptoms of Japanese cedar pollinosis. GlobalData epidemiologists

calculated the proportion for mild AR by adding the proportions for mild intermittent and mild persistent AR, and calculated the proportion for moderate/severe AR by adding the proportions for moderate/severe intermittent and moderate/severe persistent, based on the available data. The severity proportions were then applied to the forecast total prevalent cases of AR in Japan to forecast the total prevalent cases of AR in Japan segmented by severity from 2013–2023 (Gotoh et al., 2013; USCB, 2012).

To forecast the total prevalent cases of AR by type in Japan, GlobalData epidemiologists obtained data on the type of AR (perennial) in Japan from the "Japanese Guideline for Allergic Rhinitis." GlobalData epidemiologists then calculated the proportion of SAR in Japan by assuming that the SAR proportion is equal to 100% minus the proportion of PAR. These proportions for the type of AR were then applied to the forecast total prevalent cases of AR in Japan to forecast the total prevalent cases of AR in Japan segmented by type from 2013–2023 (Baba et al., 2009; Okubo et al., 2011; USCB, 2012).

To forecast the total prevalent cases of the AR population in Japan sensitized to specific allergens, GlobalData epidemiologists used data obtained from a cross-sectional study that examined 681 Japanese AR patients who were determined to be sensitized to specific allergens using IgE test measures. The IgE levels were measured for seven aeroallergens: Cryptomeria japonica, Dermatophagoides pteronyssinus, Dermatophagoides farinae, Dactylis glomerata, Ambrosia artemisiifolia, Candida albicans, and Aspergillus fumigatus (Sakashita et al., 2010). Based on the sensitization proportions from this study, GlobalData epidemiologists calculated the proportion of AR patients in Japan sensitized to these specific allergens. GlobalData epidemiologists then applied the calculated proportions of AR patients sensitized to specific allergens to the total prevalent cases of AR in each year to forecast the AR population sensitized to specific allergens in Japan from 2013–2023 (Sakashita et al., 2010; USCB, 2012).

To forecast the total prevalent cases of the AR population in Japan sensitized to specific allergens, GlobalData epidemiologists used data obtained from a cross-sectional study that examined 681 Japanese AR patients who were determined to be sensitized to specific allergens using IgE test measures.

4.5 Epidemiological Forecast for AR (2013–2023)

4.5.1 Total Prevalent Cases of AR

Table 11 and Figure 3 show the total prevalent cases of AR in the 7MM during the forecast period from 2013–2023. The total prevalent cases of AR in the 7MM will increase from 123,273,876 total prevalent cases in 2013 to 125,427,387 total prevalent cases in 2023, at an Annual Growth Rate (AGR) of 0.17% during the forecast period.

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In 2023, the US will have the highest number of total prevalent cases of AR, with 39,031,365 total prevalent cases, followed by Japan with 36,602,227 total prevalent cases. In 2023, Spain will have the lowest number of total prevalent cases of AR, with 6,329,647 total prevalent cases, followed by Italy with 8,450,941 total prevalent cases, and France with 9,754,538 total prevalent cases.

During the forecast period, Spain will have the highest growth in the total prevalent cases of AR, at an AGR of 0.80%, followed by the US at an AGR of 0.66%, and the UK at an AGR of 0.50%. GlobalData epidemiologists forecast a decline in the total prevalent cases of AR in Japan at a negative AGR of 0.45%, and in Germany at a negative AGR of 0.14%. Because GlobalData epidemiologists held the total prevalence of AR constant throughout the forecast period, population changes in respective markets are driving the increase or decrease in the total prevalent cases of AR in these markets during the forecast period.

Table 11: 7MM, Total Prevalent Cases of AR, Both Sexes, Ages ≥18 Years, N, 2013–2023

Markets	2013	2015	2017	2019	2021	2023	AGR (%)
US	36,605,625	37,074,488	37,547,339	38,042,295	38,523,213	39,031,365	0.66%
France	9,328,875	9,417,688	9,502,437	9,592,001	9,675,327	9,754,538	0.46%
Germany	13,967,710	13,951,538	13,935,018	13,901,076	13,842,487	13,769,620	-0.14%
Italy	8,254,517	8,310,778	8,357,634	8,395,627	8,423,646	8,450,941	0.24%
Spain	5,859,491	5,944,677	6,041,257	6,138,183	6,233,974	6,329,647	0.80%
UK	10,940,062	11,070,132	11,189,864	11,290,986	11,384,590	11,489,049	0.50%
Japan	38,317,596	38,071,276	37,845,756	37,447,368	37,042,042	36,602,227	-0.45%
5EU	**48,350,655**	**48,694,813**	**49,026,210**	**49,317,873**	**49,560,024**	**49,793,795**	**0.30%**
7MM	**123,273,876**	**123,840,577**	**124,419,305**	**124,807,536**	**125,125,279**	**125,427,387**	**0.17%**

Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan
Note: Totals may not sum due to rounding.
AGR = Annual Growth Rate from 2013–2023

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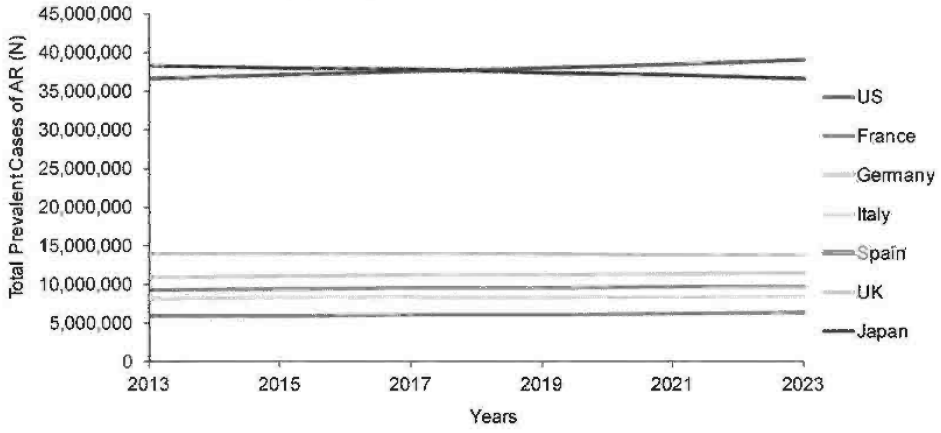
Figure 3: 7MM, Total Prevalent Cases of AR, Both Sexes, Age ≥18 Years, N, 2013–2023



Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

4.5.2 Age-Specific Total Prevalent Cases of AR

Table 12 and Figure 4 show the total prevalent cases of AR in the 7MM in 2013, segmented by 10-year age groups. Adults age 35–44 years comprised the highest number of total prevalent cases of AR, with 23,978,261 total prevalent cases (19.45% of all total prevalent cases), followed closely by adults age 25–34 years with 22,448,682 total prevalent cases (18.21% of all total prevalent cases), and adults age 45–54 years with 22,414,728 total prevalent cases (18.18% of all total prevalent cases). The lowest number of total prevalent cases of AR was in adults age≥75 years , with 10,021,383 total prevalent cases (8.13% of all total prevalent cases), followed by adults age 65–74 years with 11,493,563 total prevalent cases (9.32% of all total prevalent cases). The differences in the number of total prevalent cases of AR across the various age groups in the 7MM can be attributed to differences in the actual age-specific total AR prevalence, combined with the population demographics in these markets.

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Table 12: 7MM, Age-Specific Total Prevalent Cases of AR, Both Sexes, N (Row %), 2013

	Age Group (Years)							
Markets	18–24	25–34	35–44	45–54	55–64	65–74	≥75	Total
US	5,671,673 (15.49)	7,915,931 (21.62)	7,159,794 (19.56)	6,925,075 (18.92)	5,509,193 (15.05)	1,918,768 (5.24)	1,505,191 (4.11)	36,605,625 (100.00)
France	1,002,479 (10.75)	1,476,601 (15.83)	1,579,509 (16.93)	1,610,601 (17.26)	1,512,122 (16.21)	1,051,125 (11.27)	1,096,438 (11.75)	9,328,875 (100.00)
Germany	1,292,196 (9.25)	2,019,147 (14.46)	2,139,372 (15.32)	2,822,706 (20.21)	2,219,038 (15.89)	1,801,211 (12.90)	1,674,040 (11.99)	13,967,710 (100.00)
Italy	703,106 (8.52)	1,174,960 (14.23)	1,563,436 (18.94)	1,536,213 (18.61)	1,221,869 (14.80)	1,029,787 (12.48)	1,025,146 (12.42)	8,254,517 (100.00)
Spain	499,214 (8.52)	980,992 (16.74)	1,256,435 (21.44)	1,068,204 (18.23)	806,225 (13.76)	615,389 (10.50)	633,032 (10.80)	5,859,491 (100.00)
UK	1,287,441 (11.77)	1,856,977 (16.97)	1,812,069 (16.56)	2,011,546 (18.39)	1,584,802 (14.49)	1,291,242 (11.80)	1,095,985 (10.02)	10,940,062 (100.00)
Japan	4,139,566 (10.80)	7,024,074 (18.33)	8,467,646 (22.10)	6,440,383 (16.81)	5,468,335 (14.27)	3,786,041 (9.88)	2,991,551 (7.81)	38,317,596 (100.00)
5EU	**4,784,436 (9.90)**	**7,508,677 (15.53)**	**8,350,821 (17.27)**	**9,049,270 (18.72)**	**7,344,056 (15.19)**	**5,788,754 (11.97)**	**5,524,641 (11.43)**	**48,350,655 (100.00)**
7MM	**14,595,675 (11.84)**	**22,448,682 (18.21)**	**23,978,261 (19.45)**	**22,414,728 (18.18)**	**18,321,584 (14.86)**	**11,493,563 (9.32)**	**10,021,383 (8.13)**	**123,273,876 (100.00)**

Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan
Note: Totals may not sum due to rounding.

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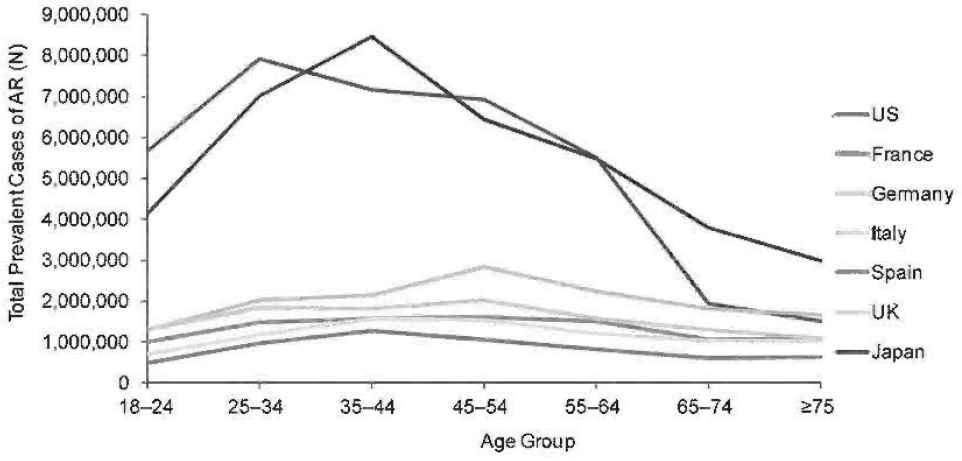
Figure 4: 7MM, Age-Specific Total Prevalent Cases of AR, Both Sexes, N, 2013



Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

4.5.3 Sex-Specific Total Prevalent Cases of AR

Table 13 and Figure 5 show the total prevalent cases of AR in the 7MM in 2013, segmented by sex. The number of total prevalent cases of AR was slightly higher in women than in men, with 64,137,146 total prevalent cases in women (52.03%) and 59,136,730 total prevalent cases in men (47.97%). The proportion of the total prevalent cases of AR was higher in women than in men across all the 7MM covered in this analysis.

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Table 13: 7MM, Sex-Specific Total Prevalent Cases of AR, Ages ≥18 Years, N (Row %), 2013			
Markets	Men	Women	Total
US	18,070,419 (49.37)	18,535,206 (50.63)	36,605,625 (100.00)
France	4,502,952 (48.27)	4,825,923 (51.73)	9,328,875 (100.00)
Germany	6,806,106 (48.73)	7,161,604 (51.27)	13,967,710 (100.00)
Italy	3,936,600 (47.69)	4,317,917 (52.31)	8,254,517 (100.00)
Spain	2,864,771 (48.89)	2,994,720 (51.11)	5,859,491 (100.00)
UK	5,391,001 (49.28)	5,549,061 (50.72)	10,940,062 (100.00)
Japan	17,564,881 (45.84)	20,752,715 (54.16)	38,317,596 (100.00)
5EU	**23,501,430 (48.61)**	**24,849,225 (51.39)**	**48,350,655 (100.00)**
7MM	**59,136,730 (47.97)**	**64,137,146 (52.03)**	**123,273,876 (100.00)**

Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan
Note: Totals may not sum due to rounding.

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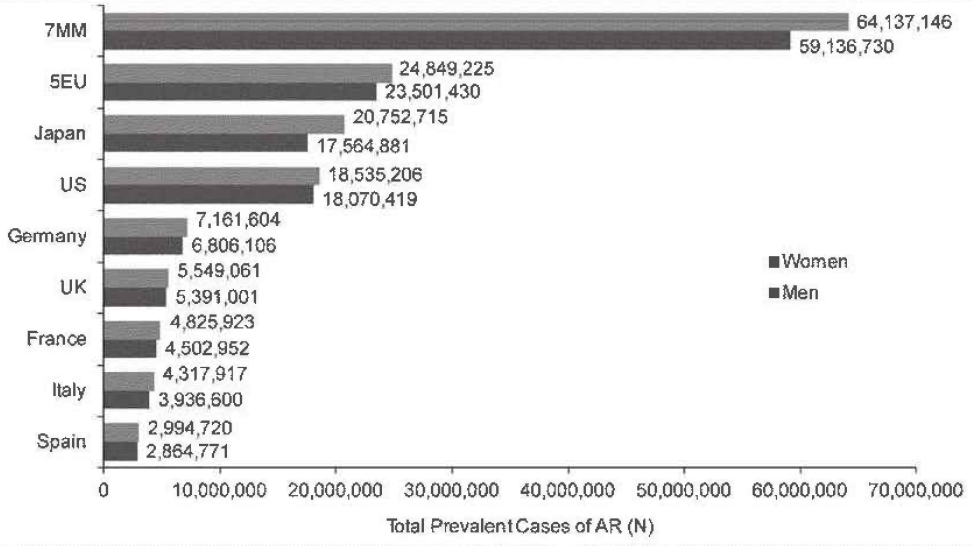
Figure 5: 7MM, Sex-Specific Total Prevalent Cases of AR, Ages ≥18 Years, N, 2013



Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

4.5.4 Age-Standardized Total Prevalence of AR

The age-standardized, or age-adjusted prevalence, of a disease is the weighted average of the age-specific prevalence. The age-specific prevalence proportions are applied to the respective age-specific world standard population weights to obtain the age-standardized prevalence (Segi, 1960). Since the age composition of the population differs between countries, the age-standardized prevalence can be used to compare the prevalence of a disease or condition between countries. However, it is important to note that the age-standardized prevalence is not an actual measure, but rather an artificial one. Therefore, the age-standardized prevalence should only be used to compare the disease prevalence between countries, rather than for forecasting purposes.

After age standardization, Japan had the highest age-standardized total prevalence of AR in both men (40.33%) and women (43.87%), and Spain had the lowest age-standardized total prevalence of AR in both men and women (15.10%).

Using data from 2013, GlobalData epidemiologists calculated the age-standardized total prevalence of AR in the 7MM, as shown in Figure 6. After age standardization, Japan had the highest age-standardized total prevalence of AR in both men (40.33%) and women (43.87%), and Spain had the lowest age-standardized total prevalence of AR in both men and women (15.10%). The identical age-standardized prevalence for men and women in all of the 7MM, except for Japan,

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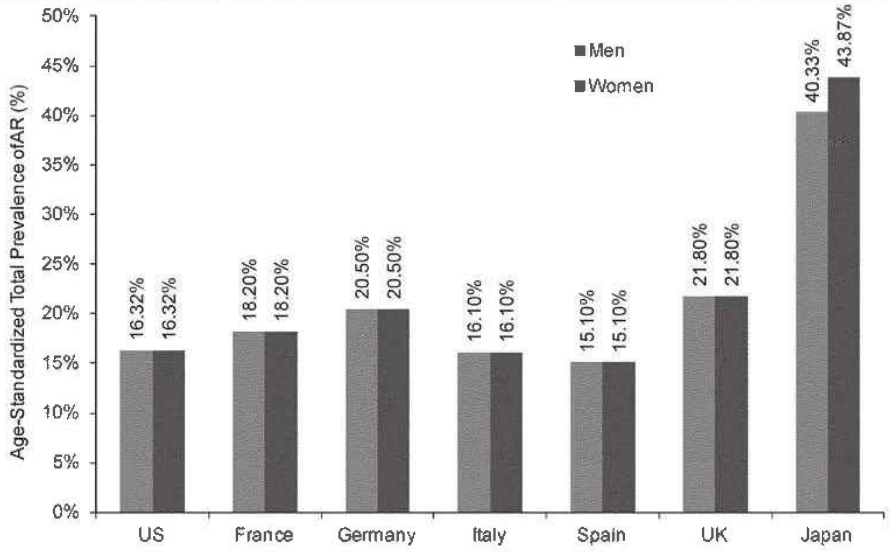
was due to the use of prevalence percentages that were measured for both sexes for the forecast. In Japan, the sex-specific total prevalence was used for the forecast.

Figure 6: 7MM, Age-Standardized Total Prevalence (%) of AR, Ages ≥18 Years, by Sex, 2013



Source: GlobalData; Bauchau and Durham, 2004; Konno et al., 2012; Nathan et al., 1997
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

4.5.5 Distribution of Total Prevalent Cases of AR by Severity

Table 14 shows the distribution of the total prevalent cases of AR in the 7MM in 2013, segmented by severity. Japan had the highest number of moderate/severe AR total prevalent cases (34,869,012 total prevalent cases), followed by the US (22,915,121 total prevalent cases), whereas the mild form of AR total prevalent cases was the highest in the US (13,690,504 total prevalent cases), followed by Germany (4,581,409 total prevalent cases).

Table 14: 7MM, Distribution of Total Prevalent Cases of AR by Severity, Both Sexes, N (Row %), 2013

Markets	Mild	Moderate	Severe	Total
US	13,690,504 (37.40)	20,206,305 (55.20)	2,708,816 (7.40)	36,605,625 (100.00)
France	3,059,871 (32.80)	5,550,681 (59.50)	718,323 (7.70)	9,328,875 (100.00)
Germany	4,581,409 (32.80)	8,310,787 (59.50)	1,075,514 (7.70)	13,967,710 (100.00)
Italy	2,707,482 (32.80)	4,911,438 (59.50)	635,598 (7.70)	8,254,517 (100.00)
Spain	1,921,913 (32.80)	3,486,397 (59.50)	451,181 (7.70)	5,859,491 (100.00)
UK	3,588,340 (32.80)	6,509,337 (59.50)	842,385 (7.70)	10,940,062 (100.00)
Japan	3,448,584 (9.00)	34,869,012* (91.00)*	** **	38,317,596 (100.00)

Source: GlobalData; Canonica et al., 2007; Gotoh et al., 2013; Schatz, 2007
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan
Note: Totals may not sum due to rounding.
*For Japan, the proportion and the total number of prevalent cases represent the moderate/severe segment.
**For Japan, separate data for the "severe" AR segment were unavailable.

4.5.6 Distribution of Total Prevalent Cases of AR by Type

Table 15 shows the distribution of the total prevalent cases of AR by type in the 7MM in 2013. Japan had the highest number of seasonal total prevalent cases of AR (29,351,279 total prevalent cases), followed by the US (12,628,941 total prevalent cases). On the other hand, the perennial total prevalent cases of AR were the highest in the US (16,948,404 total prevalent cases).

Table 15: 7MM, Distribution of Total Prevalent Cases of AR by Type, Both Sexes, N (Row %), 2013

Markets	Seasonal	Perennial	Seasonal and Perennial	Total
US	12,628,941 (34.50)	16,948,404 (46.30)	7,028,280 (19.20)	36,605,625 (100.00)
France	6,492,897 (69.60)	2,472,152 (26.50)	363,826 (3.90)	9,328,875 (100.00)
Germany	9,721,526 (69.60)	3,701,443 (26.50)	544,741 (3.90)	13,967,710 (100.00)
Italy	5,745,144 (69.60)	2,187,447 (26.50)	321,926 (3.90)	8,254,517 (100.00)
Spain	4,078,206 (69.60)	1,552,765 (26.50)	228,520 (3.90)	5,859,491 (100.00)
UK	7,614,283 (69.60)	2,899,116 (26.50)	426,662 (3.90)	10,940,062 (100.00)
Japan	29,351,279 (76.60)	8,966,317 (23.40)	– –	38,317,596 (100.00)

Source: GlobalData; Baba et al., 2009; Canonica et al., 2007; Gotoh et al., 2013; Okubo et al., 2011; Schatz, 2007
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan
Notes: Totals may not sum up due to rounding. For Japan, the data for "seasonal and perennial" were unavailable.

4.5.7 Distribution of Total Prevalent Cases of AR Sensitized to Specific Allergens

Table 16 shows the distribution of the total prevalent cases of AR sensitized to specific allergens in the 7MM in 2013. In Japan, 89.60% of the total prevalent cases of AR were sensitized to the Cryptomeria japonica allergen, followed by other aeroallergens (75.50%). In the 5EU markets, 52.20% of the total prevalent cases of AR were sensitized to grass pollen, followed by dust mites (48.78%).

In Japan, 89.60% of the total prevalent cases of AR were sensitized to the Cryptomeria japonica allergen, followed by other aeroallergens (75.50%).

Table 16: 7MM, Proportion of Total Prevalent AR Cases Sensitized to Specific Allergens, Both Sexes, %, 2013

Markets			
US	France, Germany, Italy, and Spain	UK	Japan
No data were available for the US	Grass pollen (52.20)	Grass pollen (52.20)	Cryptomeria japonica (89.60)
	Tree pollen (33.41)	Tree pollen (33.41)	Other aeroallergens (Dermatophagoides pteronyssinus, Dermatophagoides farinae, Dactylis glomerata, Ambrosia artemisiifolia, Candida albicans, Aspergillus fumigatus) (75.50)
	Weed pollen (27.07)	Weed pollen (27.07)	
	Mold (10.00)	Mold (10.00)	
	Animal dander (25.61)	Animal dander (25.61)	
	Dust mites (48.78)	Dust mites (48.78)	
	Parietaria judaica pollen (42.78)	– –	

Source: GlobalData; Bauchau and Durham, 2004; Sakashita et al., 2010; Sala-Cunill et al., 2013
Note: Total proportions may not sum to 100% due to overlap.

Epidemiology

4.6 Discussion

4.6.1 Epidemiological Forecast Insight

AR is recognized as a major global health problem because of its common occurrence in many countries, its chronic nature, and the comorbidities associated with the disease. AR is a chronic respiratory disease, and epidemiological studies have consistently shown that asthma is the most common comorbidity in patients with AR (Bousquet et al., 2008a). Although mild AR is not a life-threatening condition, severe forms of the disease may lead to disability and even death due to the condition. AR can exacerbate asthma and increase the risk for asthma attacks, which is a significant cause of disability worldwide. Furthermore, because AR affects people of all ages, the condition is also associated with reduced performance at school and loss of productivity at work, which leads to a diminished QoL and has a significantly negative socioeconomic impact.

GlobalData epidemiologists forecast an increase in the total prevalent cases of AR in the 7MM, from 123,273,876 total prevalent cases in 2013 to 125,427,387 total prevalent cases in 2023. AR is equally prevalent in both sexes; however, there is considerable geographical variation in the prevalence of AR due to variations in the populations' exposure to its associated risk factors, especially in the variety of indoor and outdoor aeroallergens. Epidemiologic data on trends in the incidence and prevalence of AR are scarce, and therefore, epidemiological studies that examine the temporal trends in the disease would be vital to deepen our understanding of the etiological risk factors and the natural history of the condition.

4.6.2 Limitations of the Analysis

The epidemiological forecast for the total prevalent cases of AR in the 7MM, except for Japan, is limited by the lack of sex-specific and age-specific data for the total prevalence of AR. To arrive at the forecast for the age- and sex-specific total prevalent cases of AR in the 5EU, GlobalData epidemiologists assumed that the sex- and age-specific total prevalence of AR in each of the 5EU markets would be the same as that of the overall (both sexes) total prevalence of AR in the respective 5EU markets. For the sex- and age-specific total prevalence of AR in the US, GlobalData epidemiologists assumed that the age-specific total prevalence of AR in men and women would be the same as that of the overall (both sexes) age-specific total prevalence of AR in the US. Because AR is equally prevalent in both sexes, and also because there is not much age-specific variation in the total prevalence of AR, GlobalData epidemiologists believe that any

differences between the forecast total prevalent cases and the actual total prevalent cases in each of these markets would be minimal.

Also, historical data needed to forecast future trends in the total prevalence of AR were limited. Therefore, GlobalData epidemiologists used a constant age-and sex-specific total prevalence of AR for the forecast period in each of the 7MM. This approach could potentially overestimate the total prevalent cases of AR if the actual trend in the total prevalence of AR declines in each of the 7MM, and vice versa.

Lastly, although GlobalData epidemiologists provided a comprehensive forecast for the total prevalent cases of AR in the 7MM, segmented by age, sex, severity, and type, and also by the total prevalent cases of AR sensitized to specific allergens, there was a lack of data on AR patients in the US sensitized to specific allergens. Therefore, GlobalData epidemiologists were unable to provide a forecast for the total prevalent cases of AR patients in the US sensitized to specific allergens.

4.6.3 Strengths of the Analysis

GlobalData's epidemiological forecast for the total prevalent cases of AR in the 7MM is supported by peer-reviewed, country-specific, population-based studies that are nationally-representative of the entire population in the respective markets. Moreover, GlobalData epidemiologists selected studies that used uniform diagnostic criteria across the markets — that is, self-reported cases of AR based on questionnaire surveys in all the 7MM markets. The use of studies that provided uniform diagnostic criteria for the total prevalence of AR allowed for a meaningful comparison of the forecast total prevalent cases of AR across the 7MM. Despite the lack of sex- and age-specific prevalence data for AR in the 7MM, except for Japan, GlobalData epidemiologists forecast the age- and sex-specific total prevalent cases of AR in each of these markets. This approach is reasonable because of the fact that AR is equally prevalent in both sexes, and because there is not much age-specific variation in the total prevalence of AR. In addition, GlobalData epidemiologists provide a comprehensive forecast for the total prevalent cases of AR, segmented by severity (mild, moderate, and severe) as well as by type (seasonal, perennial, and both). GlobalData's epidemiological forecast also provides the total prevalent cases of AR, as well as the proportion of the population with AR in the 5EU and Japan sensitized to specific allergens, which are of utmost importance in the management of the condition.

5 Disease Management

5.1 Diagnosis and Treatment Overview

5.1.1 Diagnosis

AR is typically a chronic condition that is frequently trivialized, despite the fact that it is widespread and has a serious negative impact on the QoL of many affected individuals (Holgate and Polosa, 2008). It is believed to be underdiagnosed, particularly in the primary care setting, as patients often do not seek medical attention, but instead self-medicate with OTC therapies (Small and Kim, 2011). AR is also associated with multiple comorbidities, including other allergic diseases, such as asthma and atopic dermatitis (Zheng et al., 2011). In particular, it is estimated that 95% of asthmatic individuals also have rhinitis. Therefore, it is recommended that all asthmatics be screened for rhinitis (Guerra et al., 2002) (Leynaert et al., 1999).

AR is typically a chronic condition that is frequently trivialized, despite the fact that it is widespread and has a serious negative impact on the QoL of many affected individuals.

AR is typically diagnosed based on the patient's symptoms and a medical history, which is taken by a general practitioner (GP) or a primary care physician (PCP). A positive diagnosis is typically made if two or more AR symptoms — watery rhinorrhea, sneezing, nasal obstruction, or nasal pruritus — are present for at least one hour on several days within a given week (Min, 2010). The severity of AR should be determined using the ARIA guidelines outlined in Figure 2. A physical examination of outward signs that are indicative of AR should be conducted, including persistent mouth breathing, a transverse nasal crease (or general rubbing of the nose), frequent sniffling or throat clearing, and "allergic shiners," which are dark circles under the eyes resulting from nasal congestion. The physician should also perform an endoscopic examination of the intranasal cavity for structural abnormalities or nasal polyps, which are fleshy swellings that grow from the lining of the nose or sinuses, and are caused by inflammation that occurs as a result of AR (Small and Kim, 2011).

To determine the exact underlying cause of AR, two common diagnostic allergy tests may be performed. A blood test can be performed to quantify a patient's serum-specific IgE level. For example, a radioallergosorbent test (RAST) or multiple allergen simultaneous test (MAST), such as the ImmunoCAP Phadiatop assay (ThermoScientific, UK), can be used to determine a patient's specific IgE levels against a particular allergen *in vitro* (Min, 2010). The ARIA guidelines recommend that this test be conducted in a primary care setting. If a patient has a positive result, they are likely to be allergic (Bousquet et al., 2008a).

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If more information is required, the patient can be referred to an allergy specialist, who can confirm a diagnosis of AR using a skin prick test (immediate hypersensitivity test) for IgE. The skin prick test involves putting a small drop of a commercial allergen extract (one that is likely to be the cause of the patient's allergy, such as animal dander or pollen) on the patient's back or forearm, and then pricking the skin through the drop to bring the extract into contact with the epidermis (Haahtela et al., 2014). If the test is positive, and the patient is allergic to the extract, a wheal and flare response — an irregular blanched wheal surrounded by an area of redness — will appear within 15 to 20 minutes (Small and Kim, 2011). Skin prick tests not only provide a result within a short time frame, but they are also considered to be more sensitive and cost-effective than allergen-specific IgE tests (Heinzerling et al., 2013). However, as they must be performed by an allergy specialist, not all patients are able to receive these tests to determine the exact cause of their AR. Furthermore, IgE-specific tests, such as MAST, are costly and require samples to be sent away for testing, which is another barrier to establishing a correct diagnosis of AR.

5.1.2 Treatment Guidelines and Leading Prescribed Drugs

Both national and international organizations have published guidelines for the treatment of AR. Table 17 lists the treatment guidelines that are available in each of the countries covered in this report. The most widely-known and widely-adopted international guidelines are those published by ARIA.

Disease Management

Table 17 provides an overview of the treatment guidelines for AR that are used in each of the 7MM.

Table 17: Treatment Guidelines for AR

Country	Guidelines	Publication Date
United States	The diagnosis and management of rhinitis: An updated practice parameter	2008
	Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	2010
	Treatments for Seasonal Allergic Rhinitis	2013
	Allergen immunotherapy: A practice parameter third update	2011
France	Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	2010
Germany	Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	2010
Italy	Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	2010
Spain	Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	2010
United Kingdom	Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	2010
	BSACI guidelines for the management of allergic and non-allergic rhinitis	2011
Japan	Japanese Guideline for Allergic Rhinitis	2011

Source: GlobalData; Brozek et al., 2010; Cox et al., 2011; Glacy et al., 2013; Okubo et al., 2011; Scadding et al., 2008 Wallace et al., 2008
BSACI = British Society for Allergy & Clinical Immunology

Disease Management

Table 18 provides a summary of the most commonly prescribed drugs for AR by class in all the markets covered by this report.

Table 18: Most Commonly Prescribed Drugs for AR in the 7MM by Class, 2014

Country	H1 Oral AHs	INCS	Intranasal Cromone	LRAs	Anticholinergics	Decongestants
United States	Fexofenadine hydrochloride (Allegra), loratadine (Claritin) and cetirizine hydrochloride (Zyrtec)	Mometasone furoate (Nasonex), fluticasone propionate (Flonase), fluticasone furoate (Veramyst) triamcinolone acetonide (Nasacort)	Cromolyn sodium (Nasalcrom)	Montelukast sodium, generic	Ipratropium bromide (Atrovent)	Pseudoephedrine hydrochloride (Sudafed)
France	Bilastine, cetirizine hydrochloride, desloratadine	Mometasone furoate (Nasonex), fluticasone furoate (Avamys)	Cromolyn sodium (Iomusol)	Montelukast sodium, generic	Ipratropium bromide (Atrovent)	
Germany	Cetirizine hydrochloride, loratadine (Lorano), fexofenadine hydrochloride (Telfast)	Mometasone furoate (Nasonex), fluticasone furoate(Veramyst)	Cromolyn sodium	Montelukast sodium, ,generic	Ipratropium bromide (Atrovent)	
Italy	Cetirizine hydrochloride, desloratadine, rupatadine	Mometasone furoate (Nasonex), fluticasone propionate (Flonase), fluticasone furoate (Veramyst)	Cromolyn sodium	Montelukast sodium generic	Ipratropium bromide (Atrovent)	
Spain	Ebastine (now generic), bilastine (Faes Farma's Bilaxten) loratadine, cetirizine hydrochloride,	Mometasone furoate (Nasonex), Fluticasone propionate (Flonase), budesonide	Nedocromile (Sanofi's Tilarin or Mediolanum Kovinal OTC)	Montelukast sodium generic	Ipratropium bromide (Atrovent)	
United Kingdom	Cetirizine hydrochloride (10mg; generic), Loratadine (10mg;	Beclomethasone dipropionate (half generic half as Beconase), fluticasone propionate	Sodium cromoglicate (Rynacrom)	Montelukast sodium, generic	Ipratropium bromide	Xylometazoline hydrochloride (generic)

	generic) fexofenadine hydrochloride (180mg; generic)	(generic), mometasone furoate (Nasonex)				
Japan	Allegra (fexofenadine hydrochloride; Sanofi K.K.), Allelock (olopatadine; Kyowa Hakko Kirin) levocetirizine (GSK's Zaizuru)	Beclomethasone propionate (Rhinocort), fluticasone propionate (Flunase), mometasone furoate hydrate (Nasonex)	Disodium cromoglycate (Intal), tranilast (Rizaben), amlexanox (Solfa), pemirolast potassium (Alegysal, Pemilaston)	Montelukast sodium (Singulair)	Ipratropium bromide (Atrovent)	

Source: GlobalData
GSK = GlaxoSmithKline; INCS = intranasal corticosteroids

5.1.3 Clinical Practice

AR patients commonly do not take any medication for their symptoms, and often underestimate the negative impact of the condition on their QoL. Of those patients who do seek drug treatment, a large majority use OTC symptomatic therapies, such as AHs. The transition of many prescription AR drugs to OTC status has resulted in many patients being able to access previously prescribed treatments from the local pharmacy. Furthermore, patients often pay for these OTC AR drugs out of pocket, decreasing the incentive for them to visit their doctor. For patients who do seek the advice of a physician, a wealth of inexpensive, rapid-onset therapies are available, which can also be prescribed in combination and titrated through several steps in an attempt to control the symptoms before a referral to a specialist is considered. For patients who have SAR, the symptoms may only last for a few weeks during a particular pollen season.

The majority of AR patients use OTC remedies on an as-needed basis. There is such a high level of dissatisfaction and poor symptomatic control with the current prescription and OTC treatments that patients sometimes self-refer to an allergy specialist. Similar to patients, physicians often overlook the distress caused by AR, such as a lack of sleep or missed school days. A diagnosis of AR is typically made by an allergy specialists, who can determine the patient's particular allergen sensitization(s). The prescribing of AIT is restricted to allergy specialists. In countries such as the UK, a referral to an allergy specialist is required for immunotherapy, which can restrict its use to patients with severe, persistent refractory AR, who often are sensitized to multiple allergens.

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In line with the current disease management guidelines, physician prescribing of AR medication is largely determined based on the assessment of an individual's disease severity and response to treatment. The guidelines and clinical practice for the treatment of AR in each of the countries included in this report are broadly similar to those set out in the evidence-based guidelines produced by ARIA in collaboration with the WHO. Ultimately, the successful management of AR depends largely on a patient's ability to control the disease.

The guidelines and clinical practice for the treatment of AR in each of the countries included in this report are broadly similar to those set out in the evidence-based guidelines produced by ARIA in collaboration with the WHO.

Figure 7 provides the step-wise algorithm for the management of AR in adults and children that is used across the seven markets covered in this report. It is adapted from the ARIA guidelines, and GlobalData's primary and second research confirmed its use in the US, 5EU, and Japan. Those patients who demonstrate poor control of their AR symptoms will progress up the treatment steps, receiving more intensive treatment until their disease is controlled. Conversely, patients who respond to treatment may have their treatment reduced to the lowest level at which they are able to maintain adequate control of the disease.

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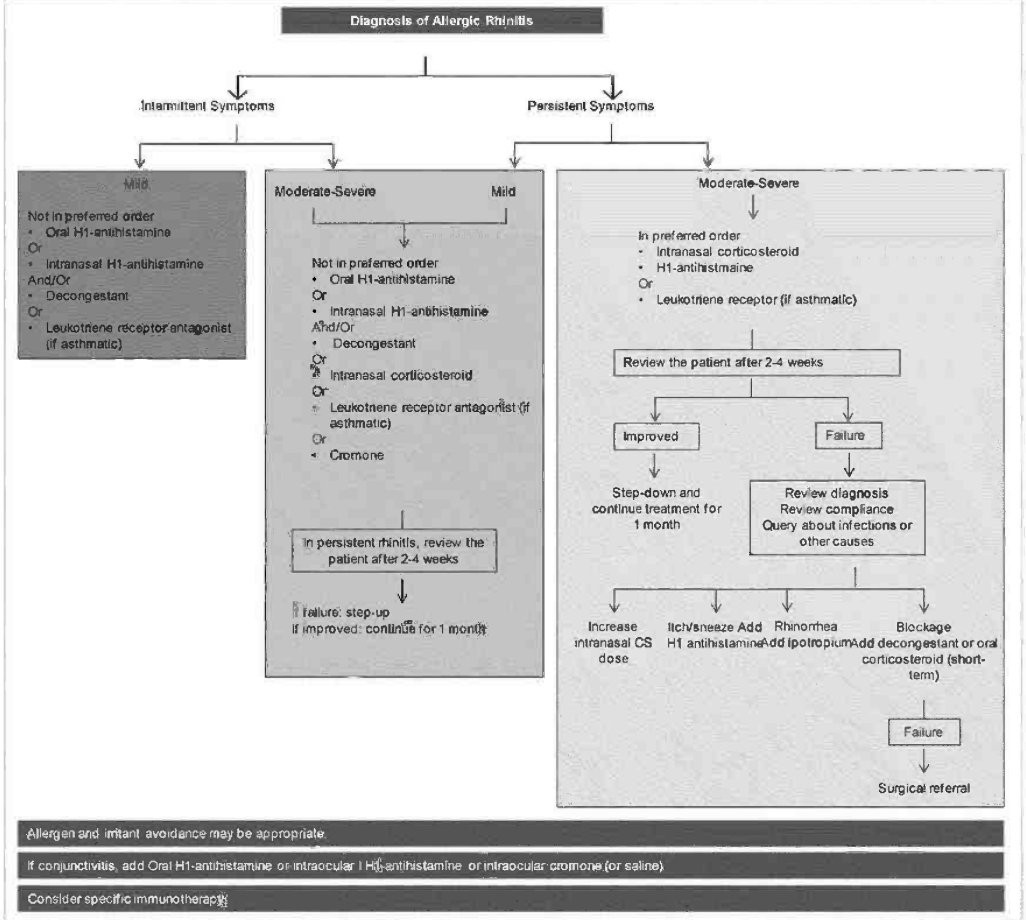
Figure 7: Algorithm Used for the Management of AR in the 7MM*



Source: GlobalData, adapted from Min, 2010

*This algorithm is based on the ARIA guidelines for the management of AR, which GlobalData's primary and secondary research confirmed is used in the US, 5EU, and Japan.

The goal of AR therapy is to relieve the patient's symptoms, which can include a combination of intermittent or persistent nasal conditions, such as a runny, itchy, or blocked nose, with or without sneezing. Symptomatic therapies represent the vast majority of the available treatments for AR, and dominate the well-established and highly-defined treatment algorithm for patients with either seasonal or perennial AR.

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The first treatment recommendation for any individual with AR is allergen avoidance or environmental control of allergens, where possible. Allergen avoidance and environmental control both have several advantages, the greatest being a minimal ongoing cost, although there may be an initial cost to modify the environment. Along with allergen avoidance, where possible, AR sufferers are also advised to perform regular nasal douching, as it is safe, inexpensive, and reduces symptoms in both adults and children with AR.

However, complete allergen avoidance or eradication is not always possible, as it relies on the correct identification of the allergen. Since routine testing of allergen-specific IgE levels is rarely conducted by PCPs, it is difficult for patients to avoid an unknown allergen. Mite eradication techniques, such as chemical barriers (acaricides) and physical barriers (for example, vacuum-cleaning and freezing) often require repeated treatment. For patients with allergies to pollen, avoidance or eradication can be outright impossible. In addition, the majority of patients are sensitized to multiple allergens, making it impractical or even impossible to try to avoid them all.

The first-line treatment strategy for AR focuses on symptom reduction. There is some variation in the pharmacotherapy treatment strategies for AR patients, with the choice of a therapy being dependent on the disease severity (mild or moderate to severe) and on whether the symptoms are intermittent or persistent, according to the ARIA classification of AR (see Figure 2).

Patients with mild, intermittent AR are mostly treated with OTC therapies, including long-acting, non-sedating, second-generation H1 receptor antagonists (antihistamines [AHs]) (also known as H1 antihistamines [H1AHs]) and decongestants, to relieve a runny nose or congestion. Regular therapy with second-generation AHs is more effective than as-needed therapy, and can significantly improve QoL as well as symptoms at non-nasal sites, such as the palate, eyes, skin, and lower airways. Patients can choose between intranasal and oral formulations. First-, second-, and third-generation AHs are widely available, almost all generically, and can be purchased OTC. However, patients are advised against using first-generation AHs, as they are sedating. These key issues are less clear to patients than physicians when choosing AH brands OTC. Also, despite the localized delivery provided by intranasal AHs, patients often prefer to take a tablet AH. Therefore, physicians most commonly prescribe second-generation, oral-tablet, once-daily generic options.

If the patient's AR symptoms are not adequately controlled, and regular preventer therapy is required, or if they have persistent or moderate/severe disease according to the ARIA classification, INCS are recommended. INCS are available as both OTC and prescription

preparations. Nasal corticosteroids are therapeutically superior to AHs; however, they have a slow onset of action and may take two weeks to achieve a maximal effect. For this reason, INCS are often started two weeks prior to beginning of the pollen season for patients with SAR. Individuals who fail to respond to first-line treatment with INCS often have their dose increased, are given instruction on their correct use, and are checked periodically to ensure proper administration technique and compliance.

Disease Management

Table 19 presents the major brands of INCS, along with their usual doses and availability.

Table 19: Major Brands of INCS

Generic Name	Brand Name	Company	Formulation	Usual Daily Adult Dosage	Usual Daily Pediatric Dosage	Indicated Use	Availability
Beclomethasone diproprionate	Beconase AQ	GSK, A&H	Metered-dose pump spray (42mcg/spray)	50mcg/nostril twice daily 1–2 sprays per nostril twice daily	Age ≥6 years: 1–2 sprays per nostril twice daily	For the treatment of seasonal and perennial AR in adults and children age ≥6 years	Generic OTC
Budesonide Aqueous 120	Rhinocort Aqua	AstraZeneca	Metered-dose pump spray (32mcg/spray)	64mcg/nostril once daily 1–4 sprays per nostril once daily	Age 6–11 years: 1–2 sprays per nostril once daily	For the treatment of seasonal and perennial AR in adults and children age ≥6 years	Generic
Fluticasone furoate	Veramyst/ Avamys	GSK	Metered-dose pump spray (27.5mcg/spray)	55mcg/nostril twice daily 2 sprays/ nostril once daily	Age 2–11 years: 1–2 sprays per nostril once daily	For the management of the symptoms associated with seasonal and perennial AR in adults and children age ≥2 years	Generic
Triamcinolone acetonide	Nasacort AQ	Sanofi-Aventis	Metered-dose pump spray (55mcg/spray)	110mcg/nostril twice daily 2 sprays per nostril once daily	Age 2–5 years: 1 spray per nostril once daily Age 6–11 years: 1–2 sprays per nostril once daily	For the management of the symptoms associated with seasonal and perennial AR in adults and children age ≥6 years	OTC
Mometasone furoate	Nasonex	Schering-Plough	Metered-dose pump spray (55mcg/spray)	100mcg/nostril twice daily 2 sprays per nostril once daily	Age 2–11 years: 1–2 sprays per nostril once daily	Management of the symptoms of seasonal and perennial AR in adults and children age ≥2 years Prevention of SAR symptoms in adults and children age ≥12 years, starting at 2–4 weeks before the pollen season begins	Generic
Fluticasone propionate	Flixonase/ Flutiform Nasofan Flonase	Teva A&H GSK	Metered-dose pump spray (50mcg/spray)	50mcg/nostril twice daily 1–2 sprays per nostril once daily or 1 spray per nostril twice daily	Age ≥4 years: 1–2 sprays per nostril once daily	Management of nasal symptoms associated with seasonal and perennial AR, and NAR	Generic OTC

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Ciclesonide	Omnaris	Sunovion Pharmaceuticals (a subsidiary of Sunitomo Dainippon Pharma	Metered-dose pump spray (50mcg/spray)	Two sprays per nostril once daily	Age ≥6 years*: 2 sprays per nostril once daily	Management of nasal symptoms associated with SAR in adults and children ≥6 years, and PAR in adults and children age ≥12 years	On patent in US; not marketed for AR in Japan and the 5EU
Ciclesonide	Zetonna	Sunovion Pharmaceuticals	Metered-dose pump spray (37mcg/spray)	1 spray per nostril once daily	Age ≥12 years: 1 spray per nostril once daily	Seasonal and perennial nasal allergies in adults and children age ≥12 years	On patent in US; not marketed for AR in Japan and the 5EU
Flunisolide	Syntaris		Metered-dose pump spray (25mcg/spray)	2 sprays per nostril 2 or 3 times daily	Age 6–14 years: 1 spray per nostril three times daily or 2 sprays per nostril twice daily	Seasonal and perennial AR in adults and children age ≥6 years	Generic

Source: GlobalData; Beconase AQ package insert, 2005; Flonase package insert, 2015; Flunisolide package insert, 2006; Nasacort AQ package insert, 2013; Nasonex package insert, 2013; Omnaris package insert, 2013; Rhinocort Aqua package insert, 2010; The Medical Letter, 2013; Veramyst package insert, 2012 Zetonna package insert, 2014
*Not approved for the treatment of PAR in children age <12 years.

Patients whose symptoms are poorly controlled by H1-AHs and nasal corticosteroids alone are prescribed these medications in combination as a second-line treatment; however, there is little data to recommend this practice. The combination of an H1AH and an INCS is also the first-line treatment for patients with moderate/severe, persistent AR. If this therapy is still insufficient for controlling symptoms, the dose of inhaled steroids can be increased, and a variety of alternative symptom-based therapies can also be considered as an add-on therapy. Alternative therapies recommended for the treatment of AR include mast cell stabilizers (cromones), which are available as intranasal and ocular preparations; they are modestly effective at controlling nasal symptoms, and because they are particularly safe, are often used in pregnancy.

Patients whose symptoms are poorly controlled by H1-AHs and nasal corticosteroids alone are prescribed these medications in combination as a second-line treatment; however, there is little data to recommend this practice.

Patients can develop persistent rhinorrhea from vasomotor rhinitis alongside their AR symptoms. If this rhinorrhea is refractory to the standard allergy treatments, these patients are prescribed ipratropium bromide in combination with corticosteroids, as this combination is more effective in treating rhinorrhea than either agent alone. Since ipratropium has no effects on sneezing and nasal discharge, patients with a persistent itch/sneeze are prescribed oral second-generation H1AHs if they are not already taking them.

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In patients with comorbid asthma and AR, a leukotriene receptor antagonist (LRA) can be used to treat catarrh (inflammation of the mucus membranes). Their efficacy is similar to that of AHs, and combination therapy with these two agents is not any better than single-drug treatment.

Patients with persistent nasal blockage can be treated using decongestants and corticosteroids. Decongestants provide short-term relief from nasal obstruction, but do not improve nasal itching, sneezing, or rhinorrhea. They are also associated with side effects, and are therefore only recommended for short-term use. Systemic glucocorticosteroids can be used in patients with severe symptoms who do not respond to other therapies, or who are intolerant to other drugs.

If all the treatment options offered by a PCP or a GP are exhausted, and the patient still experiences inadequate symptomatic relief, they can be referred to a specialist, such as an allergist. A specialist may choose to conduct diagnostic tests such as a skin prick test and/or a specific skin IgE test to identify the offending allergen. A specialist can also elect to initiate allergen-specific immunotherapy. SIT is the only vaccine for respiratory allergies that directly targets the cause of the disease, and was originally discovered in the early 20th century. The WHO considers vaccination with allergens to be the only treatment that can modify the natural course of allergies, and which can also halt the development of asthma in patients with AR and prevent the development of new sensitizations. The ARIA guidelines recommend early treatment with AIT in order to prevent further development of AR and/or the development of asthma.

Immunotherapy, or allergen vaccines, can be used to various types of allergies, such as those to pollen, mites, and animal dander. SIT consists of repeated exposure of patients to a specific allergen to which they have a positive IgE response; this leads to desensitization and long-term tolerance to the allergen. Patients eligible for SIT include those whose symptoms are not adequately controlled by pharmacotherapy, those who do not want to be on long-term pharmacotherapy, and those who cannot tolerate the side effects of pharmacotherapy. SIT is contraindicated in patients who are sensitized to multiple allergens, or those who also have moderate/severe asthma. Three formulations of SIT are currently available: subcutaneous immunotherapy (SCIT) (administered via subcutaneous [SC] injection), sublingual immunotherapy (SLIT) (administered orally under the tongue in a liquid or drop form), and AIT tablets. The treatment is given over a three- to five-year period. For patients with SAR, the treatment can start three months before the beginning of the pollen season, and continue through three to five seasons. Studies investigating the long-term efficacy of SIT are currently ongoing, but this has not yet been established for the current treatments. Many factors can influence the ability to achieve

long-term efficacy with SIT, including continuation of treatment, patient compliance, exposure levels of allergens, and the allergen extract itself.

An increase in the number of SIT formulations is likely to increase the drug treatment rate of patients receiving this type of treatment. The major unmet need in this area is for pharmacist and physician education regarding the treatment guidelines. Should these guidelines be better disseminated among healthcare professionals during the forecast period, patients would achieve symptomatic relief more efficiently.

"We know that about over half the patients with nasal allergies never go see a physician; they treat it [with products sold] over the counter."

US Key Opinion Leader

"Long-term immunity depends on the allergen. If we are talking about birch pollen or [an] other tree pollen allergen, that may be lifelong tolerance; in grass, it is generally five to 10 years; in house dust mites, it is, in general, three to five years only; and in cat [dander], it is less than one year; and in venom, it is well-known that [it] is less than one year [for the] induction of tolerance. So, you cannot say [it takes] three to five years, as many respondents may have said; it's clearly dependent on the allergen and also on the exposure. The exposure to house dust mites [sic] allergens in the UK is, by orders of magnitude, higher than it is in Germany, and therefore, the duration of tolerance may be more limited in the UK than it is…in Germany."

EU Key Opinion Leader

"As I mentioned, the flow is, they [AR patients] usually go first to pharmacists; the second step is the GP, and the third step is the specialist. Usually, when they come [to the specialist], there's a special reasons [sic], or [it's] because they have already got[ten] [a diagnosis of] the disease. And of course, because with the usual treatments, they don't get the sufficient benefit, or because they specifically want to have immunotherapy, for instance, and this is the [turning] point for them.

EU Key Opinion Leader

5.2 US

In the US, according to GlobalData's primary research, approximately 50% of patients with AR self-diagnose, commonly consult a pharmacist, and then self-medicate using OTC treatments, such as AHs and INCS. Approximately 40% of US patients with AR seek treatment from PCPs, who diagnose the condition by assessing the patient's symptoms and clinical history. Approximately 10% of these patients are referred to secondary care, either by a PCP or via a self-referral, typically to an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR by using a skin prick or blood test.

GlobalData's primary research indicated that, as of 2013, approximately 15.2% of the US adult population (age ≥18 years) and 9.1% of individuals age 0–17 years had AR at some point in their life, representing a total of 43 million people. GlobalData estimates that 100% of diagnosed AR patients (by a PCP or specialist) in the US receive a prescription treatment for the disease. However, as with most chronic conditions, patient compliance with the prescribed therapies is low.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in the US was INCS, with 60% of patients having received this therapy type. The second most commonly prescribed therapy was oral AHs, with 59% of patients with AR having received this therapy class. Patient compliance with AR treatment varies according to the therapy type, and is highest for AHs and INCS, with 63% and 66% compliance, respectively.

GlobalData anticipates that the number of patients seeking PCP/allergist advice in the US is likely to decrease following the transition of INCS from prescription to OTC status. Sanofi's Nasacort (triamcinolone acetonide) and GSK's Flonase (fluticasone propionate) switched from prescription to OTC in the US in spring of 2014, representing the first OTC INCS in the US. For the majority of classes of AR therapies in the US, generic drugs are the most frequently prescribed. Sanofi's Allegra (fexofenadine hydrochloride) was the most common oral AH prescribed, and Merck's Nasonex (mometasone furoate) was the most common INCS prescribed. Approximately 43% of patients received a monotherapy, 35% received two drugs in combination, 17% received three drugs in combination, and 5% received more than three drugs in combination.

According to GlobalData's primary research, the most commonly followed guidelines for the management of AR in the US is the ARIA 2010 Revision. However, the diagnosis and management of rhinitis: An updated practice parameter (from the American Academy of Allergy, Asthma, and Immunology [AAAI]), is also commonly used. The 2010 ARIA guidelines differ from the previous

versions in that they classify AR patients according to their symptom severity and age, rather than by the type or frequency of seasonal, perennial, or occupational exposures. The 2010 ARIA guidelines provide a framework for classifying the severity of AR (intermittent, persistent, and mild to moderate or severe), based on a number of criteria.

"If they [AR patients] got a prescription for a medication that they would pay less [for], which would be one driving factor [for a patient to visit a PCP]. Certainly, another one would be failure to get relief from over-the-counter medications, or having side effects from them or [other] concerns about them."

US Key Opinion Leader

Disease Management

Table 20 provides a country profile of the management of AR in the US.

Table 20: Management of AR, Country Profile – US	
Guidelines Used	
Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	The diagnosis and management of rhinitis: An updated practice parameter
Treatments for Seasonal Allergic Rhinitis (2013)	Allergen immunotherapy: A practice parameter third update
Most Prescribed Drugs for AR	
H1AHs	• Fexofenadine hydrochloride (Allegra) • Loratadine (Claritin) • Cetirizine hydrochloride (Zyrtec)
INCS	• Mometasone furoate (Nasonex) • Fluticasone propionate (Flonase) • Fluticasone furoate (Veramyst) • Triamcinolone acetonide (Nasacort)
Cromone	• Cromolyn sodium (Nasalcrom)
Antileukotrienes	• Montelukast sodium, generic
Anticholinergic	• Ipratropium bromide (Atrovent)
Decongestants	• Pseudoephedrine hydrochloride (Sudafed)
Intranasal AHs/corticosteroids	• Azelastine hydrochloride/fluticasone propionate (Dymista)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose and self-medicate (approximately 50% of all AR sufferers). • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 37.4% of adult AR patients are mild, 55.2% are moderate, and 7.4% are severe.
Treatment access	• Medicare: age 65+, some are disabled; Medicaid: some are low-income (most under age 65 years are covered by private insurance; 16% of the population is uninsured) • Primary private insurance covers 56% of the population (both employer-based and individual). • About 55.7% of patients receive prescription drug treatment.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 43,605,512; this number will increase to 46,322,505 in 2024. • In many cases, AR can improve over time, and many adults even become symptom-free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence. • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 40% of patients with AR receive their care from PCPs. • Approximately 10% of AR patients seen by a PCP are referred to an allergist because they have failed to get adequate symptomatic relief, or are not satisfied with the treatments offered. Approximately 50% of AR patients visiting an allergist have self-referred. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely than PCPs.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2013; Brozek et al., 2010; Cox et al., 2011; Glacy et al., 2013; Wallace et al., 2008

5.3 France

In France, approximately 50% of patients with AR self-diagnose, commonly consult a pharmacist, and then self-medicate using OTC treatments such as AHs and INCS (Demoly et al., 2008). Approximately 46% of French patients with AR seek treatment from a GP (known as a "Medicin Generaliste"), who diagnose the condition by assessing the patient's symptoms and clinical history. Approximately 23% of these patients are referred to secondary care by a GP, typically an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR by using a skin prick or blood test.

According to GlobalData's primary research, as of 2013, approximately 18.2% of the French adult population (age ≥18 years) and 30.0% of individuals age 0–17 years had AR at some point in their life, representing a total of 14 million people. GlobalData estimates that only 33% of diagnosed AR patients (by a GP or specialist) in France receive prescription treatment for the disease. However, as with most chronic conditions, patient compliance with prescribed therapies is low.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in France was oral AHs, with 82% of patients with AR having received this therapy class.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in France was oral AHs, with 82% of patients with AR having received this therapy class. The second most commonly prescribed therapy was INCS, with 76% of patients having received this therapy class. Patient compliance with AR treatment varies according to the therapy type, and is highest for AHs and INCS, with 78% and 58% compliance, respectively. Faes Farma's Bilaska (bilastine, marketed by Laboratorios Menarini in France), was the most common oral AH prescribed in France in 2014, while Merck's Nasonex was the most common INCS prescribed. The first generic version of Nasonex (mometasone furoate) was launched in June 2014 by Sandoz. In France, both AHs and corticosteroids are available OTC. In France, branded medicines are most often prescribed across each of the classes of AR therapeutics. Approximately 55% of patients received a monotherapy in 2014, 30% received two drugs in combination, 13% received three drugs in combination, and 3% received more than three drugs in combination.

According to GlobalData's primary research, the most commonly followed guidelines for the management of AR in France is the 2010 ARIA Revision.

Disease Management

Table 21 provides a country profile of the management of AR in France.

Table 21: Management of AR, Country Profile – France	
Guidelines Used	
Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	
Most Prescribed Drugs for AR	
H1AHs	• Bilastine (Bilaska) • Cetirizine hydrochloride • Desloratadine
INCS	• Mometasone furoate (Nasonex) • Fluticasone furoate (Avamys)
Cromone	• Cromolyn sodium (Iomusol)
Antileukotrienes	• Montelukast sodium, generic
Anticholinergics	• Ipratropium bromide (Atrovent)
Intranasal AHs/corticosteroids	• Azelastine hydrochloride/fluticasone propionate (Dymista)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose and self-medicate (approximately 50% of all AR sufferers). • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 32.8% of adult AR patients are mild, 59.5% are moderate, and 3.9% are severe.
Treatment access	• Healthcare is provided publically through the statutory health insurance system, and there is universal access to healthcare services. • 30% is reimbursed by the French public health insurance • 88% of the population has private, complementary, voluntary health insurance. • About 71.8% of AR patients receive prescription drug treatment.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 13,805,838; this number will increase to 14,292,512 in 2024. • In many cases, AR can improve over time, and many adults even become symptom-free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 46% of patients with AR receive their care from GPs. • Approximately 23% of AR patients seen by a GP are referred to an allergist because they have failed to get adequate symptomatic relief, or are not satisfied with the treatments offered. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely than GPs.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2013; Brozek et al., 2010

5.4 Germany

In Germany, approximately 50% of patients with AR do not receive any medication for their symptoms. Approximately 25% of patients self-diagnose and then self-medicate with OTC therapies. The remaining 25% of patients consult a GP. Approximately 55% of patients seen by a GP are referred to a specialist, typically an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR by using a skin prick or blood test.

According to GlobalData's primary research, as of 2013, approximately 20.5% of the German adult population (age ≥18 years) and 30.0% of individuals age 0–17 years had AR at some point in their life, representing a total of 18 million people. GlobalData estimates that only 30% of diagnosed AR patients in Germany receive a prescription treatment from either a GP or a specialist. However, as with most chronic conditions, patient compliance with the prescribed therapies is low.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in Germany was oral AHs, with 82% of drug-treated patients receiving this therapy type. The second most commonly prescribed therapy was INCSs, with 76% of patients with AR receiving this therapy class. Patient compliance with AR treatment varies according to the therapy type, and is highest for AHs and INCS, with 66.5% and 68.5% compliance, respectively. Generic cetirizine hydrochloride was the most common oral AH prescribed in Germany in 2014, while Merck's Nasonex was the most common INCS prescribed. In Germany, both AHs and corticosteroids are available OTC. Approximately 43% of patients received a monotherapy, 37% received two drugs in combination, 13% received three drugs in combination, and 7% received more than three drugs in combination. In Germany the use of non-evidence-based medicine, such as Traditional Chinese Medicine (TCM), acupuncture, and homeopathic remedies, is very common.

According to GlobalData's primary research, the most commonly followed guidelines for the management of AR in Germany is the ARIA 2010 Revision. This means that AIT is offered to all patients with AR, even when their symptoms are controlled by pharmacotherapies. In contrast with other European countries, Germany has many allergists per patient with AR (approximately 6,500 allergists).

A change in reimbursement introduced over 10 years ago has resulted in fewer patients receiving prescription treatments for AR in Germany, as many of them find it cheaper and more convenient to access their treatment OTC.

"Many AR sufferers try to get along without medication, or they use all kinds of other stuff, like my secretary [did,] going to a non-specialist, a non-doctor, who are allowed to treat patients on a private basis, [and] get, receive their remuneration for that, and they consult to use teas and Chinese herbal medicines, and whatsoever. This is very common in Germany; about 50%, and about 50 to 60% of the patients use this non-evidence-based treatments [sic]. Acupuncture, for example, it is also very familiar, and acupuncture is not only performed by physicians, but also by Chinese specialists."

EU Key Opinion Leader

"I think it's very specific in our country that they have excluded [the] most common forms of treatment of allergic rhinitis from reimbursement, so a patient suffering from allergic rhinitis can[not] normally, will not receive a prescription for his allergic rhinitis. He may receive a prescription, but the prescription and medication will not to be reimbursed. This has been introduced from 10 years ago or so, and ever since this happened, the landscape, of course, has dramatically changed, and patients now don't have a motivation to go to a specialists [sic] or a GP, since they know they will not receive a prescription [medication] that can be reimbursed, and then they go directly to the pharmacists and buy their cheap over-the-counter medication, anti-allergic medication. It's only a minority, maybe one to two million of patients per year, out of the many patients having allergic rhinitis or suffering from allergic rhinitis, that really get a state-of-the art prescription [medication]."

EU Key Opinion Leader

"In general, you say one out of three [people] in Germany has the [airborne allergen] sensitization, and so, this would make up something like 28 million Germans being sensitized to airborne allergens. Of these, about 50% suffer from rhinitis symptoms, so that brings it to 14, 15 million sufferers in Germany, and of these, about one half are treated on a regular basis, which brings it to about 7 to 8 million patients [who are] regularly treated, and of these, again, about 50% receive their medication OTC, over the counter, from the pharmacists, and the other half, that brings it to three to four million patients on a yearly basis are seen by physicians, and again, of these, about 50%, 50 to 60% are seen and consult specialist in allergology, so that brings it down to one to two million patients seen on a regular basis by a specialist in allergology."

In general, you say one out of three [people] in Germany has the [airborne allergen] sensitization, and so, this would make up something like 28 million Germans being sensitized to airborne allergens.

EU Key Opinion Leader

Disease Management

"It is clearly stated [in the the guidelines] that you should consider immunotherapy in every patient with allergic rhinitis right from the beginning, whereas in the US system and in the UK system, you say only if AR, if this disease is not controlled by a maximum symptomatic treatment, then you go forward and offer the patient immunotherapy."

EU Key Opinion Leader

"Since around 10 years ago or so, the landscape has dramatically changed, and patients now don't have the motivation to go to a specialist or a GP [for AR treatment], since they know they will not receive a prescription that can be reimbursed, and therefore, they go directly to the pharmacist and buy their cheap over-the-counter medication."

EU Key Opinion Leader

Disease Management

Table 22 provides a country profile of the management of AR in Germany.

Table 22: Management of AR, Country Profile – Germany	
Guidelines Used	
Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	
Most Prescribed Drugs for AR	
H1AHs	• Cetirizine hydrochloride • Loratadine (Lorano) • Fexofenadine hydrochloride (Telfast)
INCS	• Mometasone furoate (Nasonex) • Fluticasone furoate (Veramyst)
Cromone	• Cromolyn sodium
Antileukotrienes	• Montelukast sodium, generic
Anticholinergics	• Ipratropium bromide (Atrovent)
Intranasal AHs/corticosteroids	• Azelastine hydrochloride/fluticasone propionate (Dymista)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose (approximately 75% of all AR sufferers), and 25% self-medicate using OTC and non-evidence-based therapies. • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 32.8% of adult AR patients are mild, 59.5% are moderate, and 3.9% are severe.
Treatment access	• Healthcare is provided publically through Statutory Health Insurance (SHI) system, which is compulsory for all German citizens. • The patient pays 10% of the price of medicines with a minimum of €5 ($5.5) and a maximum of €10 ($11)per prescription, up to an annual upper limit based on patient's income. • Private health insurance covers 10% of the population. • AIT is fully-reimbursed.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 17,836,025; this number will increase to 17,481,034 in 2024. • In many cases, AR can improve over time, and many adults even become symptom free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence. • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 25% of patients with AR receive their care from GPs. • Approximately 50% of AR patients seen by a GP are referred to an allergist because they have failed to get adequate symptomatic relief, or are not satisfied with the treatments offered. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely than GPs.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2013; Brozek et al., 2010

5.5 Italy

In Italy, approximately 55% patients with AR consult a GP, with the remainder either self-medicating or choosing not to treat their symptoms. Approximately 36% of those patients seen by a GP are referred to a specialist, typically an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR by using a skin prick or blood test.

According to GlobalData's primary research, as of 2013, approximately 16.1% of the Italian adult population (age ≥18 years) and 26.1% of individuals 0–17 years of age had AR at some point in their life, representing a total of 11 million people. GlobalData estimates that only 82% of diagnosed AR patients in Italy receive a prescription treatment for the disease. However, as with most chronic conditions, patient compliance with the prescribed therapies is low.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in Italy was INCS, with 74% of patients having received this therapy type. The second most commonly prescribed therapy was oral AHs, with 71% of patients with AR having received this therapy class. Patient compliance with AR treatment varies according to the therapy type, and is highest for AHs and INCS, with 69% and 56% compliance, respectively. Generic loratadine was the most common oral AH prescribed in Italy in 2014, while Merck's Nasonex was the most common INCS prescribed. In Italy, only AHs are available OTC. Approximately 46% of patients received a monotherapy, 33% received two drugs in combination, 14% received three drugs in combination, and 7% received more than three drugs in combination.

Key opinion leaders (KOLs) interviewed by GlobalData noted that patients with AR in Italy prefer to use prescription treatments as opposed to OTC therapies. This is reflected by Italy having the highest rate of patients presenting to a GP for AR treatment. In Italy, branded AR drugs are prescribed more commonly than generics in each of the therapeutic classes. The ARIA 2010 Revision guidelines are commonly used in Italy.

"If you look at the market on generic drugs or over-the-counter drugs, it's quite different in Italy and the UK. In Italy, people like more the brand [drugs] than [the generic ones]. And so, this kind of approach is not so important."

EU Key Opinion Leader

Disease Management

Table 23 provides a country profile of the management of AR in Italy.

Table 23: Management of AR, Country Profile – Italy	
Guidelines Used	
Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	
Most Prescribed Drugs for AR	
H1AHs	• Loratadine • Cetirizine hydrochloride • Desloratadine • Rupatadine
INCS	• Mometasone furoate (Nasonex), • Fluticasone propionate (Flonase) • Fluticasone furoate (Veramyst)
Cromone	• Cromolyn sodium
Antileukotrienes	• Montelukast sodium, generic
Anticholinergics	• Ipratropium bromide (Atrovent)
Intranasal AHs/corticosteroids	• Azelastine hydrochloride/fluticasone propionate (Dymista)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose and self-medicate using OTC and non-evidence-based therapies. • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 32.8% of adult AR patients are mild, 59.5% are moderate and 7.7% are severe.
Treatment access	• Healthcare is provided publically for Italian citizens, and there is universal access to healthcare. • INCS medicines are Class C drugs, and are therefore not reimbursed (the patient pays). • Oral AHs are Class A drugs, and are reimbursed (the patient does not pay). • Private health insurance covers 15% of the population. • Only AHs are available OTC.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 10,956,742; this number will increase to 11,151,368 in 2024. • In many cases, AR can improve over time, and many adults even become symptom-free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 55% of patients with AR visit a GP; approximately 82% of patients receive their care from GPs. • Approximately 36% of AR patients seen by a GP are referred to an allergist because they have failed to get adequate symptomatic relief, or are not satisfied with the treatments offered. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2013; Brozek et al., 2010

5.6 Spain

In Spain, approximately 55% patients with AR consult a GP, with the remainder either self-medicating or choosing not to treat their symptoms. Approximately 36% of patients seen by a physician are referred to a specialist, typically an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR by using a skin prick or blood test.

According to GlobalData's primary research, as of 2013, approximately 15.1% of the Spanish adult population (age ≥18 years) and 38.9% of individuals age 0–17 years had AR at some point in their life, representing a total of 9.2 million people. GlobalData estimates that only 42% of diagnosed AR patients in Spain receive a prescription treatment for the disease. However, as with most chronic conditions, patient compliance with the prescribed therapies is low.

GlobalData estimates that only 42% of diagnosed AR patients in Spain receive a prescription treatment for the disease.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in Spain was oral AHs, with 80% of patients having received this therapy type. The second most commonly prescribed therapy was INCSs, with 69% of patients with AR having received this therapy class. Patient compliance with AR treatment varies according to the therapy type, and is highest for AHs and INCS, with 69% and 56% compliance, respectively. Generic loratadine was the most common oral AH prescribed in Spain, while Merck's Nasonex was the most common INCS prescribed. In Spain, AHs are the only therapies that are available OTC. Approximately 57% of patients received a monotherapy, 32% received two drugs in combination, 8% received three drugs in combination, and 3% received more than three drugs in combination.

KOLs interviewed by GlobalData noted that patients with AR in Spain prefer to use prescription treatments as opposed to OTC therapies. This is reflected by Spain having the highest rate of patients presenting to a PCP for AR treatment. In Spain, branded AR drugs are more commonly prescribed than generics in each of the therapeutic classes. The ARIA guidelines are commonly used in Spain.

Disease Management

Table 24 provides a country profile of the management of AR in Spain.

Table 24: Management of AR Country Profile – Spain	
Guidelines Used	
Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	
Most Prescribed Drugs for AR	
H1AHs	• Ebastine (Amilrall's Ebastine, now generic) • Bilastine (Faes Farma's Bilaxten) • Loratadine • Cetirizine hydrochloride,
INCS	• Mometasone furoate (Nasonex) • Fluticasone propionate (Flonase) • Budesonide
Cromone	• Cromolyn sodium
Antileukotrienes	• Montelukast sodium, generic
Anticholinergics	• Ipratropium bromide (Atrovent)
Intranasal AHs/corticosteroids	• Azelastine hydrochloride/fluticasone propionate (Dymista)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose and self-medicate using OTC and non-evidence-based therapies. • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 32.8% of adult AR patients are mild, 59.5% are moderate, and 7.7% are severe.
Treatment access	• Healthcare is provided publically for Italian citizens, and there is universal access to healthcare. • INCS are Class C drugs, and are not reimbursed (the patient pays). • Oral AHs are Class A drugs, and are reimbursed (the patient does not pay). • Private health Insurance covers 15% of the population. • Only AHs are available OTC.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 9,272,788; this number will increase to 9,930,113 in 2024. • In many cases, AR can improve over time, and many adults even become symptom-free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence. • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 55% of patients with AR visit a GP, and approximately 82% receive their care from GPs. • Approximately 36% of AR patients seen by a GP are referred to an allergist because they have failed to get adequate symptomatic relief, or are not satisfied with the treatments offered. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely than GPs.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2014; Brożek et al., 2010

5.7 UK

In the UK, approximately 37% patients with AR consult a GP, with the remainder either self-medicate or choose not to treat their symptoms. Approximately 4.4% of patients seen by a physician are referred to a specialist, typically an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR using a skin prick or blood test. This is far lower than in other European countries, as there is a distinct shortage of allergy specialists in the UK, with a long waiting time to see a specialist, often over 100 days. This issue is a significant unmet need in the treatment of AR patients in the UK.

According to GlobalData's primary research, as of 2013, approximately 21.8% of the British adult population (age ≥18 years) and 37.4% of individuals age 0–17 years had AR at some point in their life, representing a total of 15.9 million people. GlobalData estimates that only 68% of diagnosed AR patients in the UK receive treatment for the disease, either OTC or prescription. However, as with most chronic conditions, patient compliance with the prescribed therapies is low.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in the UK was oral AH, with 80% of patients having received this therapy type. The second most commonly prescribed therapy was INCS, with 55% of patients with AR having received this therapy class. Patient compliance with AR treatment varies according to the therapy type, and is highest for AHs and INCS, with 83% and 67% compliance, respectively. Generic cetirizine hydrochloride was the most common oral AH prescribed, while beclomethasone dipropionate was the most common INCS prescribed (half of prescriptions were for GSK's Beconase, while the other half were for the generic version). In the UK, both AHs and INCS are available OTC. Approximately 57% of patients received a monotherapy, 33% received two drugs in combination, 8% received three drugs in combination, and 2% received more than three drugs in combination. In the UK, generic AR drugs are more commonly prescribed than branded drugs in each of the therapeutic classes. The ARIA guidelines are commonly used in the UK.

Disease Management

Table 25 provides a country profile of the management of AR in the UK.

Table 25: Management of AR Country Profile – UK	
Guidelines Used	
Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision	BSACI guidelines for the management of allergic and non-allergic rhinitis
Most Prescribed Drugs for AR	
H1AHs	• Cetirizine hydrochloride (10mg, generic) • Loratadine (10mg, generic) • Fexofenadine hydrochloride (180mg, generic)
INCS	• Beclomethasone dipropionate (half as generic, half as Beconase) • Fluticasone propionate (generic) • Mometasone furoate (Nasonex)
Cromone	• Cromolyn sodium
Antileukotrienes	• Montelukast sodium, generic
Decongestants	• Pseudoephedrine hydrochloride (Sudafed Decongestant Tablets 60mg)
Anticholinergics	• Ipratropium bromide (Atrovent)
Intranasal AHs/corticosteroids	• Azelastine hydrochloride/fluticasone propionate (Dymista)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose and self-medicate using OTC and non-evidence-based therapies. • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 32.8% of adult AR patients are mild, 59.5% are moderate and 7.7% are severe.
Treatment access	• Healthcare is provided publically for UK citizens, and there is universal access to healthcare; about 11% of the population is covered by private health insurance. • AHs and INCS are both widely available OTC.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 15,964,254; this number will increase to 16,813,705 in 2024. • In many cases, AR can improve over time, and many adults even become symptom-free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence. • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 37% of patients with AR visit a GP, and approximately 82% of patients receive their care from GPs. • Approximately 36% of AR patients seen by a GP are referred to an allergist because they have failed to get adequate symptomatic relief or are not satisfied with the treatments offered. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely than GPs.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2014; Brozek et al., 2010; Cadding et al., 2008

5.8 Japan

In Japan, approximately 40% patients with AR consult a PCP, with the remainder either self-medicating or choosing not to treat their symptoms. Approximately 20% of AR patients seen by a physician are referred to, or self-refer, to a specialist, typically an allergist, who is able to confirm the clinical diagnosis and determine the cause(s) of their AR using a skin prick or blood test.

According to GlobalData's primary research, as of 2013, approximately 37.64% of the Japanese adult population (age ≥18 years) and 30.04% of individuals age 0–17 years had AR at some point in their life, representing a total of 43.9 million people. GlobalData estimates that only 30% of diagnosed AR patients in Japan receive a prescription treatment for the disease. However, as with most chronic conditions, patient compliance with the prescribed therapies is low.

GlobalData's primary research indicated that the most commonly prescribed therapy in 2014 for patients with AR in Japan was AHs, with 66% of patients having received this therapy type. The second most commonly prescribed therapy was INCS, with 45% of patients with AR having received this therapy class. Patient compliance with AR therapeutics varies according to the therapy type, and is highest for AHs and INCS, with 64% and 67% compliance, respectively. The top-selling AH in Japan in 2014 was Sanofi's Allegra, and the second was Kyowa Hakko Kirin's Alllelock (olopatadine). Other commonly prescribed AHs include GSK's Zaizaru (levocetirizine), Nippon Boehringer Ingelheim's Alesion (epinastine), and Mitsubishi Tanabe's Talion (bepotastine). GSK's Allermist (fluticasone furoate) and Merck's Nasonex were the most common INCS prescribed. In Japan, both AHs and INCS are available OTC. Approximately 50% of patients received a monotherapy, 323.5% received two drugs in combination, 17.5% received three drugs in combination, and 9% received more than three drugs in combination.

The top-selling AH in Japan in 2014 was Sanofi's Allegra, and the second was Kyowa Hakko Kirin's Allelock (olopatadine).

KOLs interviewed by GlobalData claimed that patients with AR in Japan prefer to use prescription treatments as opposed to OTC therapies. In Japan, AR is commonly diagnosed in hospitals, as primary care does not exist as a discipline. About 8.4% of the population has had a diagnosis of AR at some point during their life. For each of the therapeutic classes of AR medications, generic, rather than branded, drugs are most commonly used by patients in Japan. The guidelines most commonly used for the management of AR in Japan are the national guidelines.

Disease Management

"I follow Japanese guideline. I believe [that] ARIA does not match with [the] Japanese AR reality. I don't refer to ARIA, since its disease type classifications are different. In [the] Japanese treatment guide[line], [the] disease types are classified according to [their] causes, such as pollen and house dust mite[s], etcetera. ARIA classifies according to symptom length, and therefore, [the] suggested treatments became very unclear. Hence, I found [the] Japanese treatment [guidelines] more practical and successful. I think [that] for ARIA readers, Europeans, they tend to get hay fevers more, which [is why] their conditions last for a long time. Japan don't [sic] have so much hay fever patients. In Japan, we have lot of cedar pollen cases, [in] which [the] condition[s] rise for only a month or two; we rarely have Gramineae pollen and ragweed pollen cases. I believe ARIA is targeting the US or EU patients who experience mainly hay fevers; those are ecologically different. Ultimately, ARIA does not represent Japanese [AR] patients' symptoms."

Japanese Key Opinion Leader, 2014

Disease Management

Table 26 provides a country profile of the management of AR in Japan.

Table 26: Management of AR, Country Profile – Japan

Guidelines Used	
Japanese Guideline for Allergic Rhinitis (2011)	
Most Prescribed Drugs for AR	
H1AHs	• Allegra (fexofenadine hydrochloride/Sanofi) • Allelock (olopatadine/Kyowa Hakko Kirin). • Zaizaru (levocetirizine/GSK) • Alesion (epinastine/Nippon Boehringer Ingelheim) • Talion (bepotastine/Mitsubishi Tanabe Pharma Corporation)
INCS	• Mometasone furoate (Nasonex) • Allermist (fluticasone furoate)
Intranasal AHs	• Livostin (levocabastine/Nippon Shinyaku)
Cromone	• Cromolyn sodium
Antileukotrienes	• Singulair (montelukast sodium)
Thromboxane A2 (TXA2) receptor antagonists	• Baynas (ramatroban/Nippon Shinyaku)
Anticholinergics	• Ipratropium bromide (Atrovent)
T_H2 cytokine inhibitors	• Suplatast tosilate (IPD®)
Disease Management Criteria	
Diagnostic	• Patients commonly self-diagnose and self-medicate using OTC and non-evidence-based therapies. • Specialists, such as allergists, are able to make a clinical diagnosis. • Most patients note the first onset of symptoms in childhood. • 9% of adult AR patients are mild, and 91% are moderate/severe. • 89.6% of AR patients are allergic to Cryptomeria japonica.
Treatment access	• Most of Japan's health insurance plans are private organizations in terms of administrative law. In practice, however, they have a quasi-public status, as they are largely bound to provide uniform benefits and to cover all eligible beneficiaries. There is universal access to healthcare in Japan. • The differences between insurance plans (which are mandatory) include the level of copayments, which can vary from 10–30% of the cost of a prescription, with a monthly cap. • Both AHs and INCS are available OTC.
Disease outcome	• The estimated number of prevalent cases of AR in 2014 was 43,796,227; this number will increase to 41,435,703 in 2024. • In many cases, AR can improve over time, and many adults even become symptom-free. • Patients with AR can develop asthma as a result of the "atopic march" in adolescence. • It is very rare for a person who is receiving proper treatment to die of AR.
Disease expertise	• About 40% of patients with AR visit a PCP, and approximately 82% of patients receive their care from PCPs. • Approximately 20% of AR patients seen by a PCP are referred to an allergist (or self-refer) because they have failed to get adequate symptomatic relief or are not satisfied with the treatments offered. • AR specialists (allergists) appear to follow the clinical practice guidelines more closely than PCPs.

Source: GlobalData, 2013a; GlobalData, based on prescriber survey completed in 2014; Okubo et al., 2011

6 Competitive Assessment

6.1 Overview

The goal of AR therapy is to relieve the patient's symptoms, which can include a combination of intermittent or persistent nasal conditions, such as a runny, itchy, or blocked nose, with or without sneezing. Symptomatic therapies represent the vast majority of the available treatments for AR, and dominate the well-established and highly-defined treatment algorithm for patients with either seasonal or perennial AR.

Symptomatic therapies represent the vast majority of the available treatments for AR, and dominate the well-established and highly-defined treatment algorithm for patients with either seasonal or perennial AR.

The first treatment recommendation for any individual with AR is allergen avoidance or environmental control of allergens, where possible. Allergen avoidance and environmental control both have several advantages, the greatest being a minimal ongoing cost, although there may be an initial cost to modify the environment. Along with allergen avoidance, where possible, AR sufferers are also advised to conduct regular nasal douching, as it is safe, inexpensive, and reduces symptoms in both adults and children with AR.

However, complete allergen avoidance or eradication is not always possible, as it relies on the correct identification of the allergen. Since routine testing of allergen-specific IgE levels is rarely conducted by PCPs, it is difficult for patients to avoid an unknown allergen. Mite eradication techniques such as chemical barriers (acaricides) and physical barriers (for example, vacuum-cleaning and freezing) often require repeated treatment. For patients with allergies to pollen, avoidance or eradication can be outright impossible. In addition, the majority of patients are sensitized to multiple allergens, making it impractical or even impossible to try to avoid them all.

The first-line treatment strategy for AR focuses on symptom reduction. There is some variation in the pharmacotherapy treatment strategies for AR patients, with the choice of a therapy being dependent on the disease severity (mild or moderate to severe) and on whether the symptoms are intermittent or persistent, according to the ARIA classification of AR (see Figure 2).

Patients with mild, intermittent AR are mostly treated with OTC therapies, including long-acting, non-sedating, second-generation H1 receptor antagonists (H1AHs) and decongestants to relieve congestion or rhinorrhea. These drugs are recommended as a first-line therapy by the widely adopted guidelines of the World Allergy Organization (WAO). Regular therapy with second-generation AHs is more effective than as-needed therapy, and can significantly improve QoL as well as symptoms at non-nasal sites, such as the palate, eyes, skin, and lower airways. It is

recommended that patients with mild persistent or moderate/severe intermittent AR take INCS as a first-line treatment option (see Figure 2). These drugs are available as both OTC and prescription preparations. Nasal corticosteroids are therapeutically superior to AHs; however, they have a slow onset of action and may take two weeks to achieve a maximal effect. For this reason, INCS are often started two weeks prior to the beginning of the pollen season for patients with seasonal allergic rhinitis (SAR). Individuals who fail to respond to first-line treatment with INCS often have their dose increased, are given instruction on their correct application, and are checked periodically to ensure proper administration technique and compliance.

Patients whose symptoms are poorly controlled by H1AHs and nasal corticosteroids alone are prescribed these medications in combination as a second-line treatment; however, there is little data to recommend this practice. The combination of an H1AH and an INCS is also the first-line treatment for patients with moderate/severe, persistent AR.

"We know that about over half the patients with nasal allergies never go see a physician; they treat it [using products sold] over the counter."

US Key Opinion Leader, 2014

Alternative therapies recommended for the treatment of AR include mast cell stabilizers (cromones), which are available as intranasal and ocular preparations. They are modestly effective at controlling nasal symptoms, and because they are particularly safe, they are often used in pregnancy.

Patients can develop persistent rhinorrhea from vasomotor rhinitis alongside their AR symptoms. If this rhinorrhea is refractory to the standard allergy treatments, these patients are prescribed ipratropium bromide in combination with corticosteroids, as this combination is more effective in treating rhinorrhea than either agent alone. Since ipratropium has no effects on sneezing and nasal discharge, patients with a persistent itch/sneeze are prescribed oral second-generation H1AHs, if they are not already taking them.

In patients with comorbid asthma and AR, an antileukotriene can be used to treat catarrh. Their efficacy is similar to that of AHs, and combination therapy with these two agents is not any better than single-drug treatment. Patients with persistent nasal blockage can be treated using decongestants and corticosteroids. Decongestants provide short-term relief from nasal obstruction, but do not improve nasal itching, sneezing or rhinorrhea. They are also associated with side effects, and are therefore only recommended for short-term use. Systemic glucocorticosteroids can

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be used in patients with severe symptoms who do not respond to other therapies, or who are intolerant to other drugs.

Table 27 compares the effects of the main drug classes on the symptoms of AR.

Table 27: Effects of Main Drug Classes on AR Symptoms

Medication	Symptoms				
	Rhinorrhea	Nasal Congestion	Sneezing	Nasal Itch	Eye Symptoms
Oral Ahs	++	+	++	+++	++
Nasal Ahs	++	+	++	++	0
INCS	+++	+++	+++	++	++
Nasal cromones	+	+	+	+	0
Nasal decongestants	0	++++	0	0	0
Nasal anticholinergics	++	0	0	0	0
Antileukotrienes	+	++	0	0	++

Source: GlobalData, adapted from Laine, 2007

If all the treatment options offered by a PCP or GP are exhausted, and the patient still experiences inadequate symptomatic relief, they can be referred to a specialist, such as an allergist. A specialist may choose to conduct diagnostic tests, such as a skin prick and/or allergen-specific skin IgE test to identify the allergen(s) to which the patient has become sensitized. A specialist can also elect to initiate SIT, which is the only treatment for respiratory allergies that directly targets their cause, and was originally discovered in the early 20th century. The WHO considers vaccination with allergens to be the only treatment that can modify the natural course of AR and also halt the development of asthma in patients with AR and prevent the development of new sensitizations. The ARIA guidelines recommend early treatment with AIT in order to prevent the further development of AR and/or the development of asthma as part of the "atopic march." This type of therapy is described in more detail in GlobalData's related report, OpportunityAnalyzer: Allergic Rhinitis: Allergen-Specific Immunotherapy – Opportunity Analysis and Forecast to 2018 (GlobalData, 2014).

Immunotherapy, or allergen vaccines, can be used to treat various types of allergies, such as those to pollen, mites, and animal dander. SIT consists of repeated exposure of patients to a specific allergen to which they have a positive IgE response; this leads to desensitization and long-term tolerance to the allergen. Patients eligible for SIT include those who symptoms are not adequately controlled by pharmacotherapy, those who do not want to be on long-term pharmacotherapy, and those who cannot tolerate the side effects of pharmacotherapy. SIT is contraindicated in patients

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who are polysensitized to multiple allergens or those who also have moderate/severe asthma. There are three formulations of SIT currently commercially available: SCIT, SLIT in a liquid or drop form, and AIT. The treatment is given over a three- to five-year period. For patients with SAR, the treatment can start three months before the beginning of the pollen season and continue through three to five seasons. Studies investigating the long-term efficacy of SIT are currently ongoing. Many factors can influence persistent immunity to SIT, including continuation of treatment, compliance, exposure levels of allergens, and the allergen extract itself.

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Table 28 summarizes the leading branded drugs used to treat AR.

Table 28: Leading Branded Drugs Used to Treat AR, 2014

Drug Class	Company/Brand	Launch Year[a]		
		US	5EU[b]	Japan
Oral Ahs	UCB and Pfizer/Zyrtec	1996	1989	1998
Oral Ahs	Merck (formerly Schering-Plough)/Clarinex	2002	2001	Phase III
Oral Ahs	Sanofi Aventis/Allegra	1996	1997	2000
Oral Ahs	UCB and Sanofi/Xyzal	2007	2001	N/A
Oral Ahs	Merck (formally Schering-Plough)/Claritin	1993	1988	2002
Oral Ahs	Kyowa Hakko Kogyo/Allelock	N/A	N/A	2001
Oral Ahs	Menarini/Ilaxten	N/A	2011	Phase II
Oral Ahs	GSK/Semprex	N/A	1989	N/A
Intranasal AHs	Alcon/Patanase	2008	N/A	N/A
Intranasal AHs	Meda AB/Astelin	1996	2000	N/A
INCS	Sanofi/Nasacort	1991	N/A	N/A
INCS	Merck/Nasonex	1997	1997	N/A
INCS	GSK/Veramyst	2007	2007	N/A
INCS	GSK/Beconase	1976	N/A	N/A
INCS	Nasalide	1998	N/A	N/A
INCS	Omnaris	2008	N/A	N/A
LRAs	Merck/Singulair	1998	2001	2008
Cromones	Nasalcrom	1997	N/A	N/A
Anticholinergic drugs	Boehringer Ingelheim/Atrovent	1979	N/A	N/A
Decongestants	McNeil/Sudafed	N/A	N/A	N/A
Combination therapies	Meda AB/Dymista	2012	2013	N/A
Combination therapies	McNeil/Zyrtec-D	2001	N/A	N/A

Source: GlobalData, Pharma eTrack [Accessed August 12, 2014]
[a]Launch year of the first formulation is listed.
[b]The first launch year in the 5EU countries is listed (there may be differences between the European countries due to the decentralized approval process)

6.2 Oral H1 Antihistamines

6.2.1 Overview

H1AHs are reversible and competitive H1 receptor antagonists. They reduce the symptoms following an allergic response by inhibiting the binding of circulating histamine, a chemical mediator released by mast cells following an allergic reaction, to its receptors. Upon administration of an AH,

there is a general anti-inflammatory effect, as respiratory, vascular, and gastrointestinal smooth muscle constriction is inhibited. In addition, there is a marked decrease in histamine-activated secretion from the salivary and lacrimal glands, as well as a decrease in capillary permeability, which lessens the wheal-and-flare response to an allergen and decreases itching. H1AHs are highly effective and have a rapid onset of action. As such, they are used to treat a variety of conditions, including urticaria, coughs, colds, AR, allergic conjunctivitis, and insomnia (Church et al., 2010). AHs are also the most commonly accessed OTC products. A number of different AH formulations are available, including syrups, oral suspensions, intranasal sprays, and tablets.

H1AHs are generally classified as older (first-generation) "sedating" H1AHs, newer (second-generation) "non-sedating" H1AHs, and newest (third-generation) H1AHs. The first-generation, or sedating, AHs, such as diphenhydramine and chlorpheniramine, have been available clinically since the 1940s and 1950s. However, in addition to causing sedation, they have other adverse effects. They are non-selective receptor antagonists, and can also be moderately to highly potent muscarinic acetylcholine receptor (anticholinergic) antagonists. Furthermore, they also act on α-adrenergic receptors and/or 5-HT receptors. This can result in adverse effects on the central nervous system (CNS), including impaired cognition. Because of their poor receptor selectivity, they have poor tolerability. The severity of the adverse effects varies between different agents within this class. Despite these adverse effects of the first-generation AHs, and the fact that the ARIA guidelines (in collaboration with AllerGen, GA2LEN, and the WHO) reject their use in favor of the second-generation AHs (Church et al., 2010), many are still widely used OTC by patients who self-medicate. This is thought to be due to brand awareness, as many first-generation AHs have been available for decades, and therefore, there is a common misconception among patients that they are efficacious and safe.

Second-generation antihistamines (SGAs) are among the most widely prescribed drugs globally, and are also the first-line treatment for patients with mild intermittent AR.

Second-generation antihistamines (SGAs) are among the most widely prescribed drugs globally, and are also the first-line treatment for patients with mild intermittent AR. There are numerous options available, including terfenadine, astemizole, loratadine, and cetirizine hydrochloride (Small and Kim, 2011). They were introduced in 1980s and have a superior side effect profile compared with the earlier first-generation agents, as they are highly selective for the histamine H1 receptor and have a limited ability to cross the blood-brain barrier (BBB), and therefore, produce fewer anticholinergic effects, including sedation. However, a proarrhythmic effect was noted with the use of certain SGAs in the 1990s. Therefore, the Food and Drug Administration (FDA) mandated the removal of terfenadine (Seldane and other brands) from the market in 1997, while Janssen

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withdrew Hismanal (astemizole) from the market in 1999 due to its fatal cardiac adverse effects, including irregular heart rhythm, resulting from interactions with certain drugs and food.

SGAs are available as oral and nasal preparations, and often have different formulations and dosing regimens to make them suitable for use in the pediatric population. SGAs have been shown to be effective in reducing multiple AR symptoms, including sneezing, itching, and rhinorrhea, when taken regularly, either prior to allergen exposure or at the onset of maximal symptoms (Small and Kim, 2011). They are available in a wide range of generic and OTC products, which are manufactured by several major companies, including Merck, Sanofi Aventis, and GSK. In the past, many of the SGAs were blockbuster drugs; however, this market is now highly genericized as a result of several high-profile patent expiries. Therefore, many companies decided to convert their products to OTC drugs in an effort to maintain their revenues. The first AH to adopt this practice was Schering's Claritin (loratadine), which received approval for OTC status from the FDA in 2002. Aventis' Allegra and Pfizer's Zyrtec (cetirizine hydrochloride) followed shortly thereafter.

The third-generation antihistamines (TGAs) were developed with the aim of increasing efficacy while decreasing adverse effects. In 1996, the FDA approved fexofenadine hydrochloride, the first drug in this class (Handley et al., 1998). Other TGAs include levocetirizine (an enantiomer of the SGA, cetirizine), desloratadine (an active metabolite of the SGA, loratidine), and fexofenadine hydrochloride (an active metabolite of the SGA, terfenadine). Although fexofenadine hydrochloride has a decreased risk of cardiac arrhythmias compared with terfenadine, there is little evidence to suggest the desloratadine and levocetirizine have any advantages over loratadine and cetirizine, respectively.

In 2013, the FDA approved Tris Pharma's Karbinal ER (carbinoxamine maleate extended-release [ER]), as the first liquid sustained-release histamine H1 receptor blocker, which is indicated for the treatment of seasonal and perennial AR in children age two years and older.

Many AHs are commonly combined in fixed-dose preparations with decongestants, such as pseudoephedrine hydrochloride. AH and decongestant combinations are effective in treating AR-induced nasal congestion, sneezing, and rhinorrhea. There numerous generic and OTC combinations available. Common brands include Semprex-D (acrivastine and pseudoephedrine hydrochloride), Clarinex D (desloratadine and pseudoephedrine sulfate), Allegra-D (fexofenadine hydrochloride and pseudoephedrine hydrochloride), and Zyrtec-D (cetirizine hydrochloride and pseudoephedrine hydrochloride). They are available in a wide range of preparations, some of

which are approved for children age two years and older. The evidence suggests that the combination therapy is only as effective as the AH therapy alone after a few days. In addition, the combination is associated with frequent side effects such as agitation, hypertension, insomnia, and tachycardia.

KOLs interviewed by GlobalData noted that the choice of an AH is dependent on several factors, including the pressure to prescribe generic options; patient preferences, particularly to avoid sedation; and brand preference. The brand is particularly important for Italian patients and physicians when selecting an oral AH. However, KOLs also expressed a personal preference for prescribing AHs with which they are familiar.

"[The antihistamine I prescribe] depends, of course, on the patient, and the patient's preferences. If he's worried about sleepiness or so, then [a] compound like fexofenadine would be an option. However, this has to be taken twice daily. Otherwise, the protection after about 20 hours will vanish. Another [factor] could be that a patient needs up-dosing. Then Ebastine would be an option, because that is available at [doses of] 10 and 20mg, and can be prescribed at 20mg and [be] reimbursed. In some patients who also have skin disease, cetirizine or levocetirizine would be an option. Especially in [the] case of severe nasal blockage, this has been shown to be of great help. In other patients with asthmatic symptoms, the antihistamine plus [the] tough antagonist, rupatadine, may be an option. And finally, for patients that I sometimes see that are in Spain, bilastine is the state-of-the-art antihistamine there, which is currently not marketed in Germany, which is why this is not a first-choice option for us here in Germany.'

EU Key Opinion Leader

"Bilastine comes at [a dose of] 20mg, and it is absolutely free from sedation. It has a longer duration of action than fexofenadine, so it is as non-sedating, like fexofenadine. It is as potent as levocetirizine, but does [not] cause sedation. It is as non-sedative [sic] as desloratadine, but has somewhat stronger efficacy. It takes the best from those three compounds, and that's why it would currently be state-of-the-art. It can be up-dosed in patients suffering from chronic severe urticaria, up to four times the normal dose of 20mg, [to] 80mg, and still is non-sedative. So, these are some [of the] advantages [as to] why this could be a compound of choice at the moment."

EU Key Opinion Leader

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"In Italy, people like more the brand[ed antihistamines] than [the] generics. Let me give you an example. For instance, a few years ago, Menarini put on the market a new antihistamine, and they didn't even request a reimbursement. It is paid [for] by the patient, and it is very popular. The company is making a lot of money"

EU Key Opinion Leader

"The one I use often is cetirizine, because it's available over the counter. It's as cheap as chips, and if you use it at night at about eight o'clock, even the roughly 7% of patients who get some sedation will largely not be troubled by it after the first couple of nights; [the] maximum sedation is about eight hours after you take it. So, being sedated at 4 am is not a big problem. So, that will be probably my first-line oral antihistamine for a lot of people. But [for] people who genuinely need to have absolutely no sedation, I would use fexofenadine — for people like pilots. And that is more of a challenge to take, because you must have it on an empty stomach. Otherwise, it's pumped out of the gut again by PgP [P glycoprotein], and you don't get sufficient uptake, so you've got to be more careful about not eating at the same time as [when you are] taking your fexofenadine, and certainly, [you should] not [be] taking grapefruit juice. But otherwise, it's a good antihistamine, especially if you use the 180mg dose."

EU Key Opinion Leader

"In Spain, many people use generic brands because they are controlled by the health authority. Ebastine, followed by, I think, desloratadine, and then bilastine, are the most popular antihistamines. Because ebastine is a Spanish brand, and Almirall had a good marketing [strategy], it's quite popular, so it's in the 'software' of many doctors; it's in the grey matter of the brain, because it has been very popular for many, many, many years. But it's not better than the other[s]. In fact, it's not the best one."

Ebastine, followed by, I think, desloratadine, and then bilastine, are the most popular antihistamines [in Spain].

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"They [the antihistamines] are all [available] over the counter now, so I usually simply advise people to find the [one with the] lowest cost among the couple — I usually mention Claritin and Zyrtec — [that] are in the conversation. I personally happen to like Allegra, because it essentially doesn't make people sleepy, which the others can do in certain patients or [at] higher-than-recommended doses. So, I happen to like Allegra. So, Allegra, Zyrtec, and Claritin are usually [mentioned] in my conversation with the patient for the antihistamines."

US Key Opinion Leader

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Table 29 provides a summary of the major brands of the second- and third-generation non-sedating AHs.

Table 29: Major Brands of Second- and Third-Generation Non-Sedating AHs

Generic Name	Brand Name	Company	Formulation	Usual Daily Adult Dosage	Indicated Use	First Launch Year	Availability
Acrivastine	Semprex	GSK	Oral tablet	One 8mg tablet; maximum dose is three tablets daily	For the symptomatic relief of AR, including hay fever, and chronic idiopathic urticaria in patients age 12–65 years	1989	Generic and OTC
Azelastine hydrochloride	Astepro	Meda AB	Nasal spray	Patients with SAR: Adults: Two sprays per nostril twice daily Children (age 5–11 years): One spray per nostril twice daily	For the treatment of the symptoms of SAR, such as rhinorrhea, sneezing, and nasal pruritus, in adults and children age ≥5 years, and for the treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip, in adults and children age ≥12 years	1997	Generic
Bilastine	Bilaxten	Menarini	Oral tablet	One 20mg tablet once daily on an empty stomach	In seasonal and perennial AR for the relief of symptoms such as sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and tearing, in adults and adolescents age ≥12 years	2011	Prescription only
Cetirizine hydrochloride	Zyrtec	UCB/Pfizer	Oral tablet	One 10mg tablet once daily; ≤5mg for less severe symptoms	Seasonal and perennial AR in adults and children age ≥6 years	1996	Generic and OTC
Desloratadine	Clarinex	Merck	Oral tablet	Adults and adolescents ≥12 years of age and older: Clarinex tablets: One 5mg tablet once daily Clarinex RediTabs tablets: One 5mg tablet	SAR: For the relief of nasal and non-nasal symptoms in patients age ≥2 years PAR: For the relief of nasal and non-nasal symptoms in patients age ≥6 months	2002	Generic

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				once daily Clarinex Oral Solution: Two teaspoonfuls (5mg in 10mL) once daily Children age 6–11 years: Clarinex Oral Solution: one teaspoonful (2.5mg in 5mL) once daily Clarinex RediTabs tablets: one 2.5mg tablet once daily Children age 12 months to 5 years: Clarinex Oral Solution: 1/2 teaspoonful (1.25mg in 2.5mL) once daily Children age 6–11 months: Clarinex Oral Solution: 2mL (1mg) once daily			
Fexofenadine hydrochloride	Allegra	Sanofi Aventis	Oral tablet	SAR: Adults: 120mg once daily Children age 6–12 years: 30mg twice daily	For the relief of symptoms associated with SAR in adults and children age ≥6 years	1996	Generic and OTC
Carbinoxamine maleate ER	Karbinal ER	Tris Pharma	Oral suspension	Adults and adolescents age ≥12 years: 2–7.5mL (6–16mg) every 12 hours Children age 2–11 years: approximately 0.2–0.4mg/kg/day Children age 2–3 years: 3.75–5mL (3–	For the treatment of seasonal and perennial AR in children age ≥2 years	2013	Prescription only

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				4mg) every 12 hours Children age 4–5 years: 3.75–1 mL (3–8mg) every 12 hours Children age 6–11 years: 7.5–15mL (6–12 mg) every 12 hours			
Levocetirizine dihydrochloride	Xyzal	UCB/Sanofi	Oral tablet	One 5mg tablet once daily	For the relief of symptoms associated with SAR in adults and children age ≥6 years	2001	Generic
Loratadine	Claritin	Merck	Oral tablet	Adults and children age ≥12 years: 10mg once daily Children age 2–12 years: 5mg once daily	For the relief of symptoms associated with AR in adults and children age ≥2 years	1993	Generic and OTC
Olopatadine hydrochloride	Patanase	Alcon	Nasal spray	Adults and adolescents age ≥12 years: two sprays per nostril (665 mcg/spray) twice daily Children age 6–11 years: one spray per nostril (665mcg/spray) twice daily	For the reduction of nasal symptoms of SAR in adults and children age ≥6 years	2000	Generic

Source: GlobalData; Clarinex package insert, 2014; Claritin package insert, 2000; Ilaxten summary of product characteristics, 2014; Semprex package insert, 2014; The Medical Letter, 2013; Xyzal package insert, 2012; Zyrtec package insert, 2002

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Table 30 presents a product profile of a typical AH.

Table 30: Product Profile – AHs	
Molecule (Brand)	Various AHs (generic)
Launch Date	N/A
Therapeutic Class	Second-generation, non-sedating oral AHs
Alternative Brand Names	N/A (see tables above)
Developer	N/A (see tables above)
Marketing Partner	N/A
Primary Indication	Indicated for the treatment of the symptoms of SAR, such as rhinorrhea, sneezing, and nasal pruritus, in adults and children.
Formulation and Dosing	N/A
Primary Patent or Exclusivity Expiry	N/A

Source: GlobalData

Drug price sources: Thomson Reuters Red Book; British National Formulary; Rote Liste; Ministère des Affaires Sociales et de la Santé; Agenzia Italiana del Farmaco; Organización Farmacéutica Colegial Sanitarios; SSRI's Yakka (National Health Insurance) drug price database

6.2.2 Efficacy

The efficacy and safety of bilastine was evaluated in a randomized, double-blind, placebo-controlled, parallel-group multicenter study over a period of two weeks (Bachert et al., 2009). Patients age 12–70 years with symptomatic SAR received treatment with bilastine 20mg, desloratadine 5mg, or matched placebo once daily. Compliance was similarly high in all treatment groups (99.4%, 99.6%, and 100% for bilastine, desloratadine, and placebo, respectively). The efficacy measures were calculated from the area under the curve (AUC) over the entire treatment period. Bilastine 20mg significantly reduced the AUC of the Total Symptoms Score (TSS) when compared with placebo (98.4 vs. 118.4 for bilastine and placebo, respectively; $p< 0.001$), but not when compared with desloratadine 5 mg (100.5). Seven factors were assessed in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ): activities, sleep, nasal and eye symptoms, non-hay fever symptoms, practical problems, and emotional symptoms.

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Table 31 shows the efficacy of treatment with bilastine compared with desloratadine and placebo in symptomatic SAR patients age 12–70 years.

Table 31: Efficacy of Bilastine in Symptomatic SAR Patients Age 12–70 Years

	Bilastine 20mg (N=233)	Desloratadine 5mg (N= 242)	Placebo (N= 245)	p-value (ANOVA)
Primary Endpoint				
TSS AUC mean (SE)	98.4 (58.1)	100.5 (54.6)	118.4 (62.7)	
[95% CI]	[90.9–105.9]	[93.6–107.4]	[110.5–126.3]	<0.001
% Change from baseline at Day 7 (SE)	-41.7 (36.4)	-42.9 (35.1)	-28.3 (47.4)	<0.001
% Change from baseline at Day 14 (SE)	-48.9 (38.6)	-49.5 (38.8)	-37.4 (47.0)	0.002
Secondary Endpoints				
Improvement in the nasal symptoms score (NSS) AUC mean (SE)	62.6 (32.8)	63.8 (29.7)	71.6 (32.9)	
[95% CI]	[58.3–66.8]	[60.1–67.6]	[67.4–75.7]	0.004
NNSS (non-nasal symptoms score) AUC mean (SE)	36.5 (29.8)	37.2 (30.8)	47.2 (35.6)	<0.001
RQLQ (Total) AUC mean (SE)	-1.6 (1.2)	-1.6 (1.2)	-1.3 (1.3)	0.005 (Kruskall–Wallis test)

Source: Bachert et al., 2009
ANOVA = analysis of variance; CI = Confidence Interva; SE = Standard Error

6.2.3 Safety

Table 32 shows the adverse events reported during the two weeks of treatment with bilastine 20mg, desloratadine 5mg, and placebo. A total of 207 subjects reported at least one adverse event over the two-week period, the most common being headache, somnolence and fatigue, reported by ≥2% of patients in each of the treatment groups. There were no serious adverse events in any of the treatment groups. Overall, no significant differences were observed across each of the treatment groups in terms of safety.

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Table 32: Safety of Bilastine in Symptomatic SAR Patients Age 12–70 Years			
Adverse Events	Bilastine 20mg (N = 233)	Desloratadine (N= 242)	Placebo (N= 245)
Patients reporting≥1 adverse event	66 (28.3%)	79 (32.6%)	62 (25.3%)
Incidence ≥ 2% in any treatment group:			
Headache	26 (12.0%)	27 (11.2%)	25 (10.2%)
Somnolence	9 (3.9%)	9 (3.7%)	8 (2.4%)
Fatigue	6 (2.6%)	3 (1.2%)	6 (2.4%)
Drug-related adverse events	48 (21%)	48 (20%)	48 (19%)
Withdrawals due to adverse events	1 (<1%)	2 (<1%)	5 (2%)
Source: GlobalData; Bachert et al., 2009; Faes Farma, NCT01108783			

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6.2.4 SWOT Analysis

Table 33 provides a SWOT analysis of the oral AHs.

Table 33: Oral AHs SWOT Analysis, 2014	
Strengths	Relatively inexpensive compared with other AR therapies.
	Widely available as both OTC and prescription drugs.
	Highly effective in relieving symptoms.
	Rapid onset of action; long-acting formulations are available
	Multiple preparations available, including tablets, oral suspensions, and intranasal sprays. Oral tablets are by far the most popular, and are available in once-daily formulations.
	Physician and patient familiarity; a staple of AR treatment for decades.
	Established in the treatment algorithm: first-line therapy in mild intermittent AR, and an adjunct therapy in other AR subtypes.
Weaknesses	Low efficacy compared with INCS
	The market is flooded with generics and OTC preparations.
	Patients with SAR only take AHs for a short period during the year.
	Effectiveness is maximized when taken daily; however, most patients take it on an as-needed basis, which leads to the perception of poor efficacy and low compliance.
	Low patient compliance due to side effects, including sedation
Opportunities	Develop as part of a combination therapy with INCS, which should target the growing moderate to severe AR population.
	Still large revenues to be gained from the large OTC AH market.
	Room for OTC first-generation antihistamines to gain the market share through direct-to-consumer (DTC) advertising
Threats	Prior to the launch of OTC INCS, AHs were the only OTC option for AR patients; however, the launch of OTC INCS in the US will compete for AH market share
	There is increasing pressure from healthcare systems and medical insurance companies for patients to use OTC AH formulations where possible to reduce healthcare costs.

Source: GlobalData

6.2.5 Forecast

Table 34 presents the global sales forecasts for oral AHs from 2014–2024.

Table 34: Global Sales Forecasts ($m) for Oral AHs, 2014–2024

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014–2024) (%)
US	241.2	242.6	244.1	245.5	247.0	248.6	250.1	251.7	253.3	254.9	256.3	0.6%
France	103.1	103.6	104.0	104.4	104.8	105.1	105.4	105.7	106.0	106.3	106.8	0.3%
Germany	210.3	209.9	209.4	209.0	208.6	208.2	207.8	207.4	207.0	206.5	206.2	-0.2%
Italy	86.4	86.7	86.9	87.1	87.2	87.4	87.5	87.6	87.6	87.6	87.9	0.2%
Spain	142.5	143.9	145.2	146.4	147.4	148.4	149.2	149.9	150.5	151.0	152.6	0.7%
UK	19.1	19.2	19.3	19.4	19.5	19.6	19.7	19.8	19.9	20.0	20.1	0.5%
Japan	458.3	456.3	454.8	452.5	449.8	446.9	444.1	441.3	438.4	435.4	433.6	-0.6%
Total	**1261.0**	**1262.1**	**1263.6**	**1264.3**	**1264.4**	**1264.2**	**1263.9**	**1263.4**	**1262.7**	**1261.8**	**1263.4**	**0.0%**

Source: GlobalData
CAGR = Compound Annual Growth Rate

6.3 Intranasal Antihistamines

Nasal preparations of AHs are also available, both as prescription medicines and OTC drugs, and include Astepro (azelastine hydrochloride), Patanase (olopatadine hydrochloride), and Livostin (levocabastine). Livostin is the most commonly used intranasal antihistamine (INAH) in Japan. Due to their localized delivery to the nasal mucosa, intranasal AHs are highly effective in reducing the nasal symptoms of AR, including congestion, with a rapid onset of action and good treatment duration. The available intranasal AHs are generally safe and well-tolerated, the most common side effects being headache, epitaxis, and somnolence. These side effects can affect patient compliance, which is linked to treatment success. However, unlike the systemic oral AHs, intranasal preparations fail to relieve the other symptoms of AR, including sneezing, rhinorrhea, itchiness, watery eyes, and eye redness.

Due to their localized delivery to the nasal mucosa, intranasal AHs are highly effective in reducing the nasal symptoms of AR, including congestion, with a rapid onset of action and good treatment duration.

"Very few children or adults are treated with [a] nasal antihistamine. Around 10%. No more."

EU Key Opinion Leader

Competitive Assessment

"Patients don't like taking intranasal medications very much, unless they have the situation explained to them that they're [only] treating something like 125 square centimeters [of nasal tissue], that actually, they rarely need to treat the whole body. The other thing about intranasal azelastine on its own is [that] it tastes bad to about a third of patients, so it can be challenging to get them to take it."

EU Key Opinion Leader

Competitive Assessment

Table 35 presents the major brands of the intranasal AHs.

Table 35: Major Brands of Intranasal Ahs

Generic Name	Brand Name	Company	Formulation	Usual Daily Adult Dosage	Indicated Use	First Launch Year	Availability
Azelastine hydrochloride	Astepro	Meda AB	Nasal spray	SAR: Adults: two sprays per nostril twice daily Children (age 5–11 years): one spray per nostril twice daily	For the treatment of the symptoms of SAR, such as rhinorrhea, sneezing, and nasal pruritus, in adults and children age ≥5 years, and for the treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip, in adults and children age ≥12 years	1997	Generic
Olopatadine hydrochloride	Patanase	Alcon	Nasal spray	Adults and adolescents ≥12 years: two sprays per nostril (665mcg/spray) twice daily Children age 6–11 years: one spray per nostril (665mcg/spray) twice daily	For the reduction of nasal symptoms of SAR in adults and children age ≥6 years	2000	Generic
Levocabastine	Livostin	Johnson & Johnson (J&J)	Nasal spray	Adults and children: two sprays per nostril, twice daily. The dose may be increased to two sprays 3–4 times daily. The duration of treatment should be limited to 8 weeks.	For the symptomatic treatment of seasonal or perennial AR	1993	Generic (branded in Japan)

Source: GlobalData; Clarinex package insert, 2014; Claritin package insert, 2000; Ilaxten summary of product characteristics, 2014; Livostin package insert, 1998; Semprex package insert, 2014; The Medical Letter, 2013; Xyzal package insert, 2012; Zyrtec package insert, 2012

Competitive Assessment

6.4 Intranasal Corticosteroids

6.4.1 Overview

Intranasal corticosteroids (INCS) have been used to treat both SAR and PAR effectively for over 40 years (Meltzer et al., 2014). They are the first-line treatment option for patients with moderate to severe AR (Brozek et al., 2010). INCS are potent anti-inflammatory therapies that induce strong suppression of all nasal symptoms, including sneezing, itching, discharge, and congestion, and they also reduce the symptoms of ocular allergies. Their exact mechanism of action has not been fully elucidated. However, they are known to inhibit T lymphocytes (T cells), particularly T_H2 cells, and immune responses such as cytokine production or action, and eosinophil recruitment. They are also known to act on inflammatory-associated mediators and cells, including prostaglandins, leukotrienes, and mast cells.

INCS are superior to other pharmacological agents in treating allergic symptoms and improving QoL. They are usually taken once daily, and have an onset of action within 30 minutes, but may take several hours to days to reach a peak effect. However, they may take two to four weeks to become maximally effective in reducing symptoms. Incorrect use can lead to adverse effects such as epistaxis, which occurs in 10–15% of patients. The adverse effects of INCS are generally mild and include localized side effects, such as dryness, irritation, burning, sore throat, and headache. The other effects of INCS, such as odor or aftertaste, may affect patient compliance and can lead to treatment failure (Greiner et al., 2011; The Medical Letter, 2013). There is controversy surrounding the systemic effects of INCS, including their effects on the hypothalamic-pituitary-adrenal (HPA) axis, which is a concern associated with the use of all corticosteroids. However, there are no data to suggest that taking an INCS at the recommended dose can generate adrenal suppression, even with long-term use (Blaiss, 2013). A major concern often cited by those opposed to INCS use, particularly OTC use, is the reduction of growth velocity in prepubescent children. A trial in which children age five to nine years took triamcinolone acetonide continuously for one year suggested that there was a significant, but small (0.25 inch), reduction in height in the treated versus placebo group. Suppression of growth has also been reported for children age six to nine years taking beclomethasone dipropionate twice a day for 12 months, but has not been reported with the newer INCS, such as ciclesonide, fluticasone propionate, and mometasone (Ratner et al., 1992).

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There are several major drug developers in this class. Since the approval of the first INCS in the US in 1981, the patents of several major brands have lapsed, and the drug class is now highly genericized. In July 2013, Sanofi's Nasacort AQ (triamcinolone acetonide) became the first INCS to be approved for OTC use in the US by the FDA. Subsequently, in July 2014, the FDA approved GSK's Flonase for OTC use in the US (GSK, press release, July 24, 2014). In the EU, INCS have been available OTC for some time; for example, fluticasone propionate has been available OTC in the UK for over 10 years, as well as in 11 other countries. Furthermore, since 2001, Nasacort AQ has been approved in the UK for OTC use (sold under the supervision of a pharmacist) in adults 18 years of age and older with SAR.

There is no evidence to suggest that one INCS is superior to another, despite many head-to-head trials. However, there are differences in the product labels regarding the indicated age ranges in which the use of these therapies is suitable (Sur and Scandale, 2010). In addition, Rhinocort (budesonide) is the only INCS that has been given a Pregnancy Category B rating by the FDA.

In March 2012, the FDA approved Qnasl, a dry mist nasal aerosol formulation of beclomethasone dipropionate (80mcg) developed by Teva Pharmaceuticals, which became available in the US by prescription that April. The spray is indicated in adults and children 12 years of age and older with SAR and PAR (Teva, press release, February 22, 2013). In May 2014, Teva filed a supplemental New Drug Application (sNDA) with the FDA for a lower dose (40mcg) of Qnasl for patients age four to 11 years with SAR and PAR, representing the first waterless corticosteroid nasal spray to attempt to gain pediatric approval. Teva received FDA approval in December 2014, and became available on prescription in the US in February 2015 (Teva, press release, December 19, 2014). The company states that Qnasl is protected by various US patents that are expiring between 2014 and 2027 (Teva, press release, February 6, 2014).

There have been several high-profile attempts by generic drug manufacturers to make generic versions of branded INCS prior to their patent expiry. Below are examples of the ongoing challenges in this area.

In addition to Flonase, GSK has Veramyst and Avamys (fluticasone furoate). Veramyst was approved in the US and EU in 2007, and is indicated for the treatment of the symptoms of AR in adults and children age six years and over. Veramyst has US patent protection until 2021, and EU patent protection until 2023. However, Sandoz has challenged the patents for Veramyst, and submitted an Abbreviated New Drug Application (ANDA) with a Paragraph IV Certification in

Competitive Assessment

November 2011. This resulted in GSK initiating a patent infringement suit against Sandoz. However, the two companies were able to reach a settlement, whereby Sandoz was allowed to enter the US market with a generic competitor in Q3 2016 or earlier, under certain circumstances.

Nasonex, which was originally owned by Schering-Plough (now part of Merck), is a blockbuster drug, generating over $1 billion in annual sales. The use/formulation patent expired in 2014, and the formulation patent is set to expire in 2018. Nasonex's pediatric market exclusivity expired in January 2014. Merck faced competition from other drug manufacturers that were attempting to launch generics prior to the expiry of the compound patent. Merck challenged an ANDA submitted by Teva back in Novemeber 2008 by filing a lawsuit against the manufacturer. Following a similar situation involving the Canadian generic manufacturer, Apotex, and another subsequent legal challenge by Merck, a judge ruled that both of Nasonex's 2014 patents were invalid, and that the patent set to expire in October 2017 was valid. After a lengthy appeal, a judge ruled in June 2013 that Apotex's generic version does not infringe upon the 2017 patent. Merck and Apotex were able to reach an agreement for the latter to enter the US market with a generic Nasonex equivalent prior to the patent expiry of the branded drug, provided that the FDA approves Apotex's ANDA. In April 2015, Merck sued Apotex in another lawsuit, claiming the generic spray bottle is not consistent to that resolved in previously settled litigation.

Omnaris (ciclesonide), owned by Sunovion Pharmaceuticals, a division of the Japanese company, Dainippon Sumitomo Pharma, was initially approved in the US in 2006, and has a patent due to expire in October 2017. According to the FDA, Apotex submitted a Paragraph IV Certification in February 2012 as part of an ANDA to manufacture a generic version of Omnaris. Nycomed, the developer of Omnaris, challenged the application, based on an alleged patent infringement, which is ongoing. Following a disruption in the supply of Omnaris by the manufacturer in 2011, there was a significant reduction in the sales of the product in 2012. That year, an additional formulation of ciclesonide, Dainippon Sumitomo Pharma's Zetonna (ciclesonide), was approved and launched in the US as the first dry mist (non-aqueous) nasal aerosol spray for AR, which is indicated for both SAR (ocular and nasal symptoms) and PAR (nasal symptoms).

Despite these ongoing issues regarding the entry of generic versions of the branded INCS, several products in this class have been resilient to generic erosion. This is a result of the manufacturers' strategy of decreasing the price of these products to the extent that they become cheaper than the generic versions. This occurred in the UK with two products, Rhinocort Aqua (budesonide) and Nasofan (fluticasone propionate).

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As with AHs, the prescribing of INCS is highly variable among both physicians and the global markets. KOLs interviewed by GlobalData noted that the choice of an INCS is dependent on several factors, including the pressure to prescribe generic options; patient preferences, particularly to avoid side effects such as epistaxis; and brand preference. The brand is particularly important for physicians in the US when selecting an INCS, since DTC advertising and sales representatives heavily promote the use of Merck's Nasonex. However, KOLs also expressed a personal preference for prescribing INCS with which they are familiar.

"No matter that the studies have clearly shown, at least to the satisfaction of the FDA, that these drugs [INCS] are safe down to the age two or three [years], in terms of [their effects on growth], and therefore, by logic, for [their] other side effects, pediatricians still fear these drugs. I don't blame them, because I don't agree with the FDA's conclusion that they are safe. I think that they do have potential long-term side effects, and [am] opposed [to] the over-the-counter use of these drugs. But, no matter, even though the FDA's rulings say, pediatricians still have fear, and are reluctant to allow the long-term use of these drugs [in children]. So, yes, I think there is room in the market for a drug that has a potential[ly superior] safety profile, and is very close in efficacy. We've never had a drug like that — that is suitable for children — because in children, the nose sprays are much more difficult to use. They don't like — the runoffs problem is worse [in children] than [in] adults, and the taste problems are [also] worse [in children], and getting a child to put something in their nose is not pleasant. So, yes, there is room for improvement, and it would probably lie in the oral field or a more pleasant and easy-to-use nasal drug. Because kids like none of them right now."

US Key Opinion Leader

"Allermist and Nasonex, I use those two. I like those because it [sic] requires only [a] once-a-day regimen, has strong efficacy, and its systemic absorption is nearly zero. It means that its side effect [profile] is also nearly zero, too."

Japanese Key Opinion Leader

"I prescribe fluticasone furoate because it has the strongest [glucocorticoid receptors]-binding properties. In addition, it is the steroid that contains fluorine, meaning [that], among any other nasal spray corticosteroid, fluticasone furoate has the lowest dose. The daily dose is only 100 micrograms. The lower the dosage is, the lower the risk of side effects patients would have."

Japanese Key Opinion Leader

Competitive Assessment

"I would say that majority of those patients who are willing to apply intranasal corticosteroids would receive them. So, it is always a discussion with the patient in the beginning whether he has any concerns regarding intranasal steroids, whether there is corticophobia present in this specific patient, because then, it doesn't make sense to prescribe a drug that he will not use, and it's widespread knowledge in Germany that two out of three of these intranasal steroids are not used by the patient because they have concerns regarding [the] side effects and adverse reactions of these compounds. So, it needs a thorough discussion with the patient whether there are such concerns, such fears, and if that is not the case, of course, an intranasal glucocorticosteroid would be the first choice. However, only those furoates that have a very low bioavailability [would be considered as options] — namely, mometasone furoate, Nasonex, or fluticasone furoate as a mist."

I would say that majority of those patients who are willing to apply intranasal corticosteroids would receive them.

EU Key Opinion Leader

"Well, I do have a couple of favorite [INCS] there. One of my favorites has always been Nasonex, because I helped publish a study showing that it had no effect on the growth of children, and it also had the approval all the way down to two years of age. So, I found it [to be] a very good go-to medication for those two reasons, as well as [because of] studies showing that it was well-tolerated. It doesn't have much taste, smell, sting, or anything like that. I found it to be a good medication, so I often prescribe it. Another one that I prescribe a lot now is fluticasone, which was available as a generic, so it was. I work a little bit in West Virginia, and there, the only medication they [patients] are allowed to get is fluticasone or Flonase as a generic. So, when there is a generic available, a lot of the insurers will only pay [for] that, so I've gotten into the habit of using that one as well. It's actually getting ready to go [to] over-the-counter [status], according to my knowledge."

US Key Opinion Leader

"Merck has always had a very, very strong presence here in our clinic. They bring a lot of samples of Nasonex in. And they have funded a lot of the research that my colleagues here have done. So, Nasonex has been a go-to product for all the people who have worked in this practice for all those multitude[s] of reasons. [However,] I think it [the use of Nasonex] will decrease. I think that more and more, the pharmaceutical [sales] reps are being shut out of doctors' offices; they are not being allowed in. So, that's an increasing trend here right now. So, my opinion is that that will lead to fewer of them [sales representatives], and then I think they will have less of a prominent presence there [in doctors' offices]. But I expect their influence to decline moving forward."

US Key Opinion Leader

Competitive Assessment

"There are many generic brands of intranasal corticosteroids. So, [regarding the] generic brands, I use budesonide spray, and now Avamys is probably the second most popular [INCS] after the generic budesonide, because budesonide is very cheap."

EU Key Opinion Leader

Table 36 presents the major brands of INCS, along with their usual doses and availability.

Table 36: Major Brands of INCS

Generic Name	Brand Name	Company	Formulation	Usual Daily Adult Dosage	Usual Daily Pediatric Dosage	Indicated Use	Availability
Beclomethasone diproprionate	Beconase AQ	GSK, A&H	Metered-dose pump spray (42mcg/spray)	50mcg/nostril twice daily 1–2 sprays per nostril twice daily	Age ≥6 years: 1–2 sprays per nostril twice daily	For the treatment of seasonal and perennial AR in adults and children age ≥6 years	Generic OTC
Budesonide Aqueous 120	Rhinocort Aqua	AstraZeneca	Metered-dose pump spray (32mcg/spray)	64mcg/nostril once daily 1–4 sprays per nostril once daily	Age 6–11 years: 1–2 sprays per nostril once daily	For the treatment of seasonal and perennial AR in adults and children age ≥6 years	Generic
Fluticasone furoate	Veramyst/Avamys	GSK	Metered-dose pump spray (27.5mcg/spray)	55mcg/nostril twice daily 2 sprays/ nostril once daily	Age 2–11 years: 1–2 sprays per nostril once daily	For the management of the symptoms associated with seasonal and perennial AR in adults and children age ≥2 years	Generic
Triamcinolone acetonide	Nasacort AQ	Sanofi-Aventis	Metered-dose pump spray (55mcg/spray)	110mcg/nostril twice daily 2 sprays per nostril once daily	Age 2–5 years: 1 spray per nostril once daily Age 6–11 years: 1–2 sprays per nostril once daily	For the management of the symptoms associated with seasonal and perennial AR in adults and children age ≥6 years	OTC
Mometasone furoate	Nasonex	Schering-Plough	Metered-dose pump spray (55mcg/spray)	100mcg/nostril twice daily 2 sprays per nostril once daily	Age 2–11 years: 1–2 sprays per nostril once daily	Management of the symptoms of seasonal and perennial AR in adults and children age ≥2 years Prevention of	Generic

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						SAR symptoms in adults and children age ≥12 years, starting at 2–4 weeks before the pollen season begins	
Fluticasone propionate	Flixonase/Flutiform Nasofan Flonase	Teva A&H GSK	Metered-dose pump spray (50mcg/spray)	50mcg/nostril twice daily 1–2 sprays per nostril once daily or 1 spray per nostril twice daily	Age ≥4 years: 1–2 sprays per nostril once daily	Management of nasal symptoms associated with seasonal and perennial AR, and NAR	Generic OTC
Ciclesonide	Omnaris	Sunovion Pharmaceuticals (a subsidiary of Sunitomo Dainippon Pharma	Metered-dose pump spray (50mcg/spray)	Two sprays per nostril once daily	Age ≥6 years*: 2 sprays per nostril once daily	Management of nasal symptoms associated with SAR in adults and children ≥6 years, and PAR in adults and children age ≥12 years	On patent in US; not marketed for AR in Japan and the 5EU
Ciclesonide	Zetonna	Sunovion Pharmaceuticals	Metered-dose pump spray (37mcg/spray)	1 spray per nostril once daily (74mcg).	Age 12 years and older. 1 spray per nostril once daily (74mcg)	Seasonal and perennial nasal allergies in adults and children age ≥12 years	On patent in US; not marketed for AR in Japan and the 5EU
Dexamethasone cipecilate	Erizas	Nippon Shinyaku Co., Ltd.	Metered-dose pump spray (200 mcg/spray)	1 spray per nostril once daily (400mcg).	1 spray per nostril once daily (400mcg).	1 spray per nostril once daily (400mcg).	On patent and marketed in Japan
Flunisolide	Syntaris	Teva	Metered-dose pump spray (25mcg/spray)	2 sprays per nostril 2 or 3 times daily	Age 6–14 years: 1 spray per nostril three times daily or 2 sprays per nostril twice daily	Seasonal and perennial AR in adults and children age ≥6 years	Generic

Source: GlobalData; Beconase AQ package insert, 2005; Flonase package insert, 2015; Flunisolide package insert, 2006; Nasacort AQ package insert, 2013; Nasonex package insert, 2013; Omnaris package insert, 2013; Rhinocort Aqua package insert, 2010; The Medical Letter, 2013; Veramyst package insert, 2012; Zetonna package insert, 2014

*Not approved for the treatment of PAR in children age <12 years.

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Table 37 presents a product profile of the INCS.

Table 37: Product Profile – INCS	
Molecule (Brand)	Various INCS (generic)
Launch Date	N/A
Therapeutic Class	Corticosteroids
Alternative Brand Names	N/A (see tables above)
Developer	N/A (see tables above)
Marketing Partner	N/A
Primary Indication	Treatment of seasonal or perennial AR in adults and children; lower age limit is dependent on the product.
Formulation and Dosing	N/A (see above tables)
Primary Patent or Exclusivity Expiry	N/A

Source: GlobalData

Drug price sources: Thomson Reuters Red Book; British National Formulary; Rote Liste; Ministère des Affaires Sociales et de la Santé; Agenzia Italiana del Farmaco; Organización Farmacéutica Colegial Sanitarios; SSRI's Yakka (National Health Insurance) drug price database

6.4.2 Efficacy

The efficacy and safety of two INCS, fluticasone propionate (FP) aqueous nasal spray (FP ANS) and beclomethasone dipropionate aqueous nasal spray (BDP ANS) was investigated in a multicenter, double-blind, randomized, placebo-controlled trial that was conducted during the mountain cedar (Juniperus ashei) pollination season (mid-December to early February) in central Texas (Ratner et al., 1992). Adults age 18–72 years with moderate to severe seasonal AR were given FP ANS 200µg once daily, BDP ANS 168µg twice daily, or placebo for two weeks. Patients were eligible to participate in the study if their total nasal symptom score (TNSS) was ≥200 (out of 400 possible points) on at least four of the seven days during the screening period preceding the start of the treatment. Four nasal symptoms were assessed (obstruction, rhinorrhea, sneezing, and itching) using a visual analog scale from 0 (no symptoms) to 100 (severe symptoms) on daily patient diary cards. Clinicians also assessed the patient's nasal symptoms on Days 1, 8, and 15 of the treatment period, and on Day 22 post-treatment.

As shown in Table 38, FP ANS and BDP ANS were equally effective, as assessed by both patient- and clinician-rated nasal symptom scores throughout the treatment and follow-up periods. Both therapies were more effective than placebo, demonstrating a significant improvement in the clinician-rated mean TNSS after seven days of treatment ($p < 0.001$).

Competitive Assessment

Table 38: Efficacy of FP ANS and BDP ANS in AR Patients Age 18–72 Years

	FP ANS 200µg Once Daily (N = 117)			BDP ANS 168µg Twice Daily (N = 103)			Placebo (N = 245)		
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15
Primary Endpoint									
Mean TNSS									
Clinician-rated (SE)	260	130	95	260	130	97	250	180	140
Patient-rated (SE)	205	115	110	209	115	105	230	195	180
Nasal Obstruction									
Clinician-rated	68	45*	39	71	45*	38*	69	53	46
Patient-rated	71	43*	37*	73	42*	36*	68	54	49
Rhinorrhea									
Clinician-rated	72	38*	26*	72	37*	28*	67	49	41
Patient-rated	71	40*	33*	72	41*	31*	69	53	49
Sneezing									
Clinician-rated	49	20*	13*	50	21*	11*	46	32	21
Patient-rated	60	31*	25*	61	32*	20*	57	40	38
Nasal itching									
Clinician-rated	65	34	23*	63	30*	20*	65	43	35
Patient-rated	35	38*	30*	67	37*	26*	67	48	43

Source: Ratner et al., 1992
*p<0.05 for the change from Day 1 versus placebo
SE = Standard Error

6.4.3 Safety

As shown in Table 39 the number of patients reporting drug-related adverse events in the study was low across all three groups, with no clinically significant differences between each of the two therapies and placebo (Ratner et al., 1992).

Table 39: Safety Profile of FP ANS and BDP ANS in AR Patients Age 18–72 Years

Adverse Events Reported by ≥3 Patients	FP ANS 200µg Once Daily (N) = 106	BDP ANS 168µg Twice Daily (N) = 103	Placebo (N) = 104
Sore throat	2 (2%)	2 (2%)	1 (1%)
Blood in nasal mucus	6 (6%)	1 (1%)	2 (2%)
Nasal burning	5 (5%)	2 (2%)	4 (4%)
Epistaxis	3 (3%)	2 (2%)	0
Headache	0	1 (1%)	3 (3%)
Any event	19 (18%)	10 (10%)	19 (18%)

Source: GlobalData; Ratner et al., 1992

Competitive Assessment

6.4.4 SWOT Analysis

Table 40 provides a SWOT analysis of the INCS.

Table 40: INCS SWOT Analysis, 2014	
Strengths	The most effective symptomatic treatment for AR patients, targeting a wide range of respiratory, nasal, and ocular symptoms
	Relatively inexpensive; many generic formulations are available.
	Widely available; several equally effective brands, including many OTC products, are now available in pharmacies (excluding Spain)
	Physician familiarity; INCS have been available for over three decades, and have a longstanding reputation among medical professionals.
	Well-established in the treatment algorithm in the national AR treatment guidelines as the first-line therapy for mild persistent and moderate to severe AR patients.
Weaknesses	A highly competitive and genericized market, with many prescription and OTC preparations being widely available.
	All INCS have a similar efficacy and safety profile.
	Patients complain of medication taste, odor, medication runoff, and general discomfort.
	Fear of stunted growth in children
	Slower onset of action compared with AHs; can take two weeks to reach maximum effectiveness.
	Intranasal application may not be as popular as oral formulations, particularly for children. Side effect of epistaxis may lead to poor adherence.
Opportunities	Develop as part of a combination therapy with AHs to decrease the number of medications required and to increase compliance in patients who require both therapies simultaneously.
	Moved from Rx-only to OTC status in the US.
Threats	Low patient compliance due to side effects
	The imminent patent expiry of the remaining branded INCS and the entry of new generics will dilute the market share of products even further.
	There is increasing pressure from healthcare systems and medical insurance companies for patients to use INCS OTC formulations where possible to reduce healthcare costs.

Source: GlobalData

6.4.5 Forecast

Table 41 presents the global sales forecasts for INCS from 2014–2024.

Table 41: Global Sales Forecasts ($m) for INCS, 2014–2024

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014–2024) (%)
US	1609.1	1310.2	1271.7	954.7	910.5	896.0	892.4	897.4	879.5	884.4	892.3	-5.7%
France	81.6	57.0	55.1	55.3	52.3	51.3	50.4	49.4	48.5	47.5	46.6	-5.4%
Germany	160.7	111.7	107.3	107.0	100.6	98.3	96.0	93.7	91.5	89.2	86.9	-6.0%
Italy	267.4	192.1	185.3	185.7	175.1	171.8	168.3	164.8	161.2	157.6	154.5	-5.3%
Spain	91.2	70.8	68.7	69.3	65.7	64.7	63.7	62.6	61.5	60.3	59.5	-4.2%
UK	27.0	26.2	25.3	25.5	24.1	23.7	23.3	23.0	22.6	22.1	21.7	-2.2%
Japan	532.4	530.2	528.4	525.7	522.6	519.3	516.0	512.7	509.3	505.9	503.7	-0.6%
Total	**2769.4**	**2298.2**	**2241.8**	**1923.3**	**1850.8**	**1825.1**	**1810.1**	**1803.6**	**1774.0**	**1766.9**	**1765.3**	**-4.4%**

Source: GlobalData
CAGR = Compound Annual Growth Rate

6.5 Combination Intranasal Corticosteroids/Antihistamines

6.5.1 Dymista

6.5.1.1 Overview

Dymista is a fixed-dose combination (FDC) intranasal spray containing the H1 SGA, azelastine hydrochloride, and the corticosteroid, fluticasone propionate. It is a first-in-class drug indicated for the treatment of moderate to severe seasonal perennial AR in patients age six years and older. Dymista, which was developed by the Indian pharmaceutical company, Cipla, was approved in the US in 2012, providing a novel treatment option for AR (Ostrom, 2014). Azelastine is a selective H1 receptor antagonist and inhibits the action of histamine in the allergic cascade. Fluticasone propionate is a synthetic glucocorticoid receptor agonist with potent anti-inflammatory and vasoconstrictor activities. Like other corticosteroids, fluticasone exerts its inflammatory action through the inhibition of cytosolic phospholipase A2 (via the activation of lipocortin-1), which controls the biosynthesis of potent mediators of inflammation, such as the prostaglandins and leukotrienes.

Competitive Assessment

In 2006, Cipla entered into an agreement with the Swedish drug company, Meda, for the clinical development, registration, marketing, and sales rights for Dymista in the US. According to this agreement, Cipla is responsible for manufacturing the drug. The agreement was subsequently extended to include the European market in 2009, and then the global commercialization rights in over 120 markets in 2013, making Meda the sole distributor of the drug. Cipla retains the distribution rights in certain markets. The financial details of the deal were not disclosed.

Dymista was approved in the US by the FDA in May 2012, and in Europe by the EMA in January 2013 through the decentralized registration procedure, for adolescents and adults age 12 years and older.

Dymista was approved in the US by the FDA in May 2012, and in Europe by the EMA in January 2013 through the decentralized registration procedure, for adolescents and adults age 12 years and older. Meda also received extended approval in the US for Dymista to include the pediatric population (age 6–11 years). Both applications were supported by clinical studies in 4,600 patients, in addition to a 600-patient long-term safety study.

The US AR market is large, and is estimated at approximately $6 billion annually. Meda reported that Dymista achieved a 5% market share of the US branded allergy nasal spray segment in 2013, with sales of $59m. The company reported that Dymista's is now the second best-selling brand in the respiratory area in the US (Meda, 2013). In addition, the company claims that the drug has claimed a significant patient share in Austria, Finland, Germany, Ireland, and Italy. Also, Dymista has been approved, or is close to being approved, in several other markets, including Australia, Canada, China, Mexico, the Middle East, South Africa, and Turkey.

Safety restrictions in the product labeling state that the Dymista should be used with caution in pregnant women and nursing mothers. In addition, the label states that the drug may cause drowsiness and advises patients not to drink alcohol when taking Dymista, and to avoid taking any CNS depressants, as they can induce somnolence and impairment of CNS performance.

Competitive Assessment

"It's not really brand awareness per se, but I think what it is, is strength in the sales and marketing arena. For example, three days a week we have an AstraZeneca representative in my office. I never, ever had an empty shelf of samples [of that company's allergy products]; I'm overstocked. Compare that to a company that doesn't have the sales for — who, maybe once every two weeks, is in my office, and the number of samples [that] I have [has] run out. So, when I go to the sample closet, I'm going to — and most of these drugs, almost all, are sampled before we prescribe — I'm going to grab that sample, and I'm going to think about the person I've just seen in the office. It's just human nature. So, a company with a very large sales force and marketing arm that can reach not only to allergy specialists, like Meda, but also to primary care offices, where the majority of the prescriptions, because of the vast number of physicians, are written, yes, I think they would have a greater financial success. It's not that the company is viewed any different[ly] or respected any more [than the others]; it's just that they have more contact, more visibility."

US Key Opinion Leader

"In actuality, the science of the drug [Dymista] is being ignored by the UK; it's not the same as fluticasone and azelastine administered separately. There are two distinct differences, which they're not taking into consideration, in addition to the compliance issue. One, it's a different fluticasone preparation, with a different pharmacologic profile. Two, it's a different delivery device, both of which alter the outcome. So, it's hard to convince [payers] when the bottom line is $1 rather than an improvement in symptoms. I realize that, but I foresee [that], as time goes by, the resistance is going to be diminished. I still foresee an increased use in the combination [drug] over time."

US Key Opinion Leader

Competitive Assessment

"I think what you're going to see, for sure, is a growth of Dymista, especially in Europe. We've had it in the United States for a while, and you're going to see the European guidelines, which I think underestimated it, and did not have respect for intranasal antihistamines according to their true potential. I think you're going to see them change. Dr. Jean Bousquet, he's in charge of the European guidelines, and I think he has finally been sold on the potential effect of intranasal antihistamines, and the combination drug [Dymista]. You're going to see a marked growth in Europe, probably equal to or greater than the growth in the United States, if the price is right and the governments accept it… As this drug gets approved worldwide, it's going to take over the market, I think.

US Key Opinion Leader

"We now have the nasal antihistamine, azelastine, plus the nasal steroid, fluticasone, in one spray as a [fixed-dose] combination [product], which makes it easier for the patient to be compliant. It's [also] reimbursed; there's no problem with reimbursement. But following the basic guideline of the ARIA saying, starting with the tablet, adding a nasal spray, adding eye drops, maybe adding a second tablet… I find that majority of patients are not willing to follow this strategy, and the compliance for such a strategy is rather low."

EU Key Opinion Leader

"I think Dymista is fantastic. I would probably put everyone on it if the insurance would pay. But the problem is [that] even for people that fail everything else, here, if I prescribe it, more than half the time, they [the insurance companies] come back and say they won't pay [for it]. So, then I have to put them [patients] on two separate sprays: Patanase and Nasonex. And then they'll have two sprays, but even though there are two sprays, they get better coverage from insurance. I don't think there's better efficacy with Dymista versus using the two sprays separately. I think the compliance is better, though. Compliance is notoriously horrible in the allergic rhinitis [patient population]."

US Key Opinion Leader

"I would like to prescribe Dymista for my patients, and I can't at our hospital, because they won't put it on the formulary. And so what I have to do is to either ask the GP if they can do [prescribe] it, or issue a private prescription if the patient really wants it. Or, I can give them the two medications separately, which is what I sometimes do as well."

EU Key Opinion Leader

Competitive Assessment

"I think a combination of either another intranasal antihistamine and another steroid, or using azelastine and another nasal steroid, would be financially successful."

US Key Opinion Leader

"A combination of another corticosteroid and [an] antihistamine — I think it would be competitive, and there are other things that play into that. For example, Meda is, as you know, the company that has Dymista, and they're a small company. If you put that drug in the hands of Merck, I think you would have seen [it take off much stronger] with their marketing potential, or [with that of] Glaxo[SmithKline]. I know Glaxo[SmithKline] was working on a similar compound. I think it would have taken off much stronger [with either of these two companies]. So, if you took that combination of drug[s], with a large pharma [company], you probably would have something that would be profitable, very much so, over time."

US Key Opinion Leader

"Dymista is now gaining some terrain. And I guess that's with this combination of antihistamine and nasal steroids, there is some potential in gaining a wider market share."

EU Key Opinion Leader

"Because they say Dymista is more expensive than prescribing the two [drugs] separately; they'll go for the cheap[est option]. This is the crazy thing about formularies; they always go for the cheaper option or [the] cheapest option, disregarding other factors like concordance. Now, if you give patients one spray and ask them to use it twice a day, there's a distinct possibility they will use it once a day. If you give them two sprays and ask them to use them both twice a day, there's a distinct possibility they'll put them in the cupboard and then forget about them because they can't be bothered to do such [a] difficult treatment. Looking at that in real-life — it is something that creeps in. They don't take that into account, and that worries me."

EU Key Opinion Leader

Competitive Assessment

Table 42 presents a product profile of Dymista.

Table 42: Product Profile – Dymista	
Molecule (Brand)	Azelastine hydrochloride/fluticasone propionate (Dymista)
Launch Date	US – 2012; 5EU – 2013; Japan – preregistered, expected launch in 2012
Therapeutic Class	H1 receptor antagonist and corticosteroid
Alternative Brand Names	Dygaro (Italy); Azeflu (France); Dymolin (Germany); Dylastine (Germany, Spain); Dyvistanil (Germany); Synaze (France, Spain); Xatalin (France); Dymol (Spain), Nycena (Italy)
Developer	Cipla
Marketing Partner	Meda
Primary Indication	The relief of symptoms of SAR and PAR in patients age 12 years and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief, when each drug alone is not considered sufficient
Formulation and Dosing	Intranasal spray; recommended dose is one spray per nostril twice daily in adults and adolescents age ≥12 years.
Primary Patent or Exclusivity Expiry	2023–2026 (US, 5EU)

Source: GlobalData; Dymista package insert, 2015; USPTO, 2015

6.5.1.2 Efficacy

The efficacy and safety of Dymista was evaluated in a series of four head-to-head, double-blind placebo- and active-controlled studies in over 4,000 patients age 12 years and older with moderate to severe SAR (Meltzer et al., 2013). The patients were required to have a minimum two-year history of AR-related symptoms and a positive skin prick test to the relevant allergen. The four studies took place over two weeks, following a seven-day run-in period during various pollen seasons. The primary efficacy endpoint was the patient-reported reflective total nasal symptom score (rTNSS) score compared with baseline in 12 hours (AM and PM) assessed over 14 days. The rTNSS was used as a measure of the symptom severity, as it is the only efficacy endpoint accepted by the FDA and EMA. Patients rate four nasal symptoms (nasal congestion, itching, rhinorrhea, and sneezing) twice daily, in the morning and evening, for 14 days on a scale of 0 to 3, with 0 being symptom free and 3 being severe symptoms, generating a maximum daily score of 24.

Error! Reference source not found. shows the change in baseline in rTNSS in the intent-to-treat (ITT) population. In all four studies, Dymista demonstrated superior efficacy compared with intranasal AH and INCS delivered as a monotherapy. All four studies were conducted in a similar manner, with the exception of MP4001, which used the branded version of the AH, Astelin (azelastine). All four drugs were dosed as one spray per nostril twice daily.

Competitive Assessment

Table 43: Efficacy of Dymista

Study	Treatment	Mean Baseline rTNSS (SD)*	Change from Baseline in rTSS (SD)	Treatment Difference	p-value**
MP 4001 2007/2008 Texas Mountain Cedar	Dymista (N = 153)	18.8 (3.1)	-5.3	–	
	Astelin (N = 152)	18.1 (3.7)	-3.3	MP29-02 - FP	0.003
	Fluticasone (N = 150)	18.3 (3.5)	-3.8	MP29-02 -	<0.001
	Placebo (N = 150)	18.7 (3.5)	-2.2	MP29-02 - PLA	<0.001
MP 4002 2008 Spring	Dymista (N = 207)	18.3 (3.0)	-5.5 (5.2)	–	–
	Azelastine (N = 208)	18.2 (3.5)	-4.1 (4.6)	MP29-02 - FP	0.034
	Fluticasone (N = 207)	18.2 (3.2)	-5.0 (4.7)	MP29-02 - AZE	0.002
	Placebo (N = 209)	18.6 (3.2)	-2.6 (3.9)	MP29-02 - PLA	<0.001
MP 4004 2008 Fall	Dymista (N = 193)	18.2 (3.3)	-5.6 (5.2)	–	–
	Azelastine (N = 193)	18.5 (3.1)	-4.4 (4.6)	MP29-02 - FP	0.038
	Fluticasone (N = 188)	18.6 (2.9)	-5.0 (5.2)	MP29-02 - AZE	0.032
	Placebo (N = 199)	18.2 (3.1)	-2.8 (3.9)	MP29-02 - PLA	<0.001
MP4006 2009 Spring and Summer	Dymista (N = 448)	19.4 (2.4)	-5.6 (5.2)	–	–
	Azelastine (N = 443)	19.5 (2.5)	-4.5 (4.8)	MP29-02 - FP	0.029
	Fluticasone (N = 450)	19.4 (2.4)	-5.1 (4.7)	MP29-02 - AZE	0.016
	Placebo (N = 448)	19.4 (2.4)	-3.2 (4.3)	MP29-02 – PLA	<0.001

NCT01165138; Meltzer et al., 2014

*Least-squares mean obtained from analysis of variance (ANOVA) model for baseline or analysis of covariance (ANCOVA) model for overall.

**p-value for comparison between treatment group for baseline was based on an ANOVA model containing the treatment group and site as fixed effects.

AZE = azelastine

6.5.1.3 Safety

The adverse events associated with Dymista are generally mild and infrequent (Meltzer et al., 2014). The most common treatment-related adverse events (TRAEs) experienced by SAR patients following the 14-day treatment included headache, epitaxis, and dysgeusia.

In two recent controlled trials of Dymista, a total of 4,022 patients were evaluated for safety and tolerability. One study, MP4002, was conducted in patients with SAR, in which Dymista was compared with fluticasone propionate, azelastine, and placebo during two weeks of treatment (Meltzer et al., 2014). The other study, MP 4000, was a long-term study in patients with chronic rhinitis (that is, PAR or non-allergic vasomotor rhinitis) in which Dymista was compared with fluticasone propionate during 52 weeks of treatment (Meltzer et al., 2014).

Table 44 provides the results of these two studies, which showed no appreciable difference between the treatment groups in terms of safety. The most common TRAEs in each of the treatment groups in both studies were dysgeusia, epistaxis, and headache.

Table 44: Safety of Dymista

Study	MP4002 SAR Study (2 Weeks)				MP 4000 Chronic Rhinitis Study (52 Weeks)	
TRAEs, N (%)	Dymista 1 Spray/Nostril Twice Daily (N = 207)	Fluticasone Propionate 1 Spray/Nostril Twice Daily (N = 207)	Azelastine 1 Spray/Nostril Twice Daily (N = 208)	Placebo 1 Spray/Nostril Twice Daily (N = 210)	Dymista 1 Spray/Nostril Twice Daily (N = 404)	Fluticasone Propionate 2 Sprays/Nostril Once Daily (N = 207)
Dysgeusia	5 (2.4%)	2 (1.0%)	7 (3.4%)	1 (0.5%)	10 (2.5%)	1 (0.5%)
Epistaxis	2 (1.0%)	5 (2.4%)	4 (1.9%)	2 (1.0%)	5 (1.2%)	1 (0.5%)
Headache	1 (0.5%)	5 (2.4%)	1 (0.5%)	3 (1.4%)	4 (1.0%)	9 (4.3%)

Source: GlobalData; GSK, NCT01165138; Meltzer et al., 2014

Competitive Assessment

6.5.1.4 SWOT Analysis

Table 45 provides a SWOT analysis of Dymista.

Table 45: Dymista SWOT Analysis, 2014

Strengths	Is a first-in-class intranasal combination of an H1 receptor antagonist and an INCS.
	Is rapidly gaining worldwide approval.
	Demonstrated superior efficacy in clinical trials compared with azelastine, fluticasone, and placebo over a 14-day period when administered as a monotherapy.
	Sales have been promising so far, and the company reports that Dymista has rapidly gained market share.
	Dosing (one spray per nostril twice daily) is more convenient than when both agents are administered as a monotherapy. This is likely to increase treatment compliance, and therefore, improve symptom relief.
	Rapid onset of action can be effective within minutes, and produces a significant reduction in symptoms within days.
	Good safety and tolerability profile should improve patient adherence.
	Trial shows improvement over INCS alone, which are currently the gold standard of AR therapy.
	Meda has a strong presence in the respiratory market, with good marketing connections to allergists and asthma specialists.
	Gained expanded approval in the US for children age 6–11 years.
Weaknesses	Is more expensive than prescribing each therapy individually, and considerably more expensive than the cheaper formulary-preferred generic versions of the two individual components.
	Mechanism of action has not been fully-determined.
	ARIA guidelines support the use of oral over intranasal AHs in adults with seasonal or perennial/persistent AR.
	Clinical trials compared monotherapy with each agent with Dymista rather than against taking the two agents concurrently.
	Despite a statistically significant reduction in nasal symptoms in patients treated with Dymista compared with placebo and monotherapy ($p<0.001$), the absolute difference between the treatment arms was small, and might not be clinically relevant enough to warrant the higher price associated with the FDC drug for payers.
	Carries a safety warning stating that patients cannot consume alcohol while taking Dymista.
Opportunities	There is a growing prevalence of moderate to severe AR, and these patients do not find monotherapy with INCS or AH effective.
	Very few branded prescription-only medicines are available, which means there are few choices for people who want to be reimbursed by their insurance in the applicable markets. The out-of-pocket cost for symptomatic AR therapies is increasing, as more treatments are no longer covered by insurance plans.
	Japan is second largest AR market, which has yet to be entered.
	Nasonex is currently the best-selling product in this patient segment in the US, but its patent is due to expire in 2017. However, two high-profile challenges by Teva and Apotex resulted in generic entries in 2014 and 2015, making space for Dymista to become a leading product in the branded AR market.
	Cipla has patented intranasal combinations of the AH, azelastine, with the corticosteroids mometasone furoate, ciclesonide, and fluticasone propionate.
Threats	As there is no clear difference between the various AHs and corticosteroids, it is likely that other combinations will be generated to compete for this new patient segment. Should a company with a bigger sales force than Meda enter the race, it could see substantial sales.
	Many National Health Service (NHS) formularies have released guidance for GPs, instructing them not to prescribe Dymista, citing the lack of evidence to support its improved efficacy and safety compared with cheaper monotherapy combinations.

Source: GlobalData; Dymista package insert, 2015

Despite a statistically significant reduction in nasal symptoms in patients treated with Dymista compared with placebo and monotherapy ($p<0.001$), the absolute difference between the treatment arms was small, and might not be clinically relevant enough to warrant the higher price associated with the FDC drug for payers.

6.5.1.5 *Forecast*

Table 46 presents the global sales forecasts for Dymista from 2014–2024.

Table 46: Global Sales Forecasts ($m) for Dymista, 2014–2024

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014–2024) (%)
US	41.4	67.4	67.8	74.4	74.9	75.4	75.8	82.7	83.2	83.7	84.2	7.3%
France	0.0	7.9	23.8	27.9	28.0	32.1	32.2	36.3	40.5	44.6	48.9	-
Germany	22.6	22.6	33.8	39.3	39.2	44.7	44.7	50.1	55.6	61.0	66.5	11.4%
Italy	48.1	48.3	48.4	48.5	48.6	54.8	60.9	67.1	73.2	79.3	85.7	5.9%
Spain	0.0	13.6	20.6	24.2	24.4	28.0	28.2	31.9	35.5	39.2	43.2	-
UK	1.3	10.2	15.3	18.0	18.1	20.8	20.9	23.6	26.4	29.1	32.0	38.1%
Japan	-	-	-	-	-	-	-	-	-	-	-	-
Total	113.4	169.9	209.7	232.3	233.1	255.8	262.7	291.7	314.4	337.0	360.5	12.3%

Source: GlobalData
CAGR = Compound Annual Growth Rate

6.6 Decongestants

6.6.1 Overview

Decongestants relieve nasal congestion by stimulating alpha-adrenergic receptors or by increasing levels or norepinephrine and epinephrine. This induces localized vasoconstriction of the blood vessels in the upper respiratory tract including in the nose, throat, and sinuses, thereby reducing inflammation and mucus formation. Shrinkage of the nasal mucous membranes helps promote nasal drainage and relieves watery eyes, runny nose, and sneezing.

Decongestants can be administered either orally or intranasally. Intranasal decongestants, such as ephedrine, pseudoephedrine, xylometazoline naphazoline, oxymetazoline, and phenylephrine, are widely available generically and OTC. Intranasal decongestants are potent vasoconstrictive agents that are highly effective in reducing nasal congestion, with a rapid onset of action, working within 10 minutes after application. The effects of short-acting decongestants can last up to four hours; longer-acting formulations can remain effective for up to six to 12 hours. They are available as sprays, gels, drops, and vapors, and are relatively inexpensive. However, patients often abuse these medications by overusing them, and develop rhinitis medicamentosa after prolonged use. This can result in adverse effects such as nasal irritation and increased rhinorrhea. In addition,

abuse of nasal decongestants can result in dependency and rebound nasal congestion as a result of swelling in the nasal cavity. Therefore, it is advisable to only take nasal decongestants continuously for a maximum of three days. The ARIA guidelines state that adults with AR and a severe nasal blockage should use a very short course (a maximum of five days) of an intranasal decongestant, in combination with other drugs. In addition, they also do not recommend the regular use of oral decongestants.

Oral decongestants, such as pseudoephedrine and phenylephrine, are only available in combination with an AH in some countries. Pregnant women and children are advised not to take oral or nasal decongestants for AR. Nasal formulations have a faster onset of action than oral forms, and may not result in as much drowsiness. Nasal and ophthalmic decongestants both lead to tachyphylaxis (a diminished response to successive doses), and therefore, long-term use is not recommended.

While decongestants are widely used in the US and South America, either as a monotherapy or in combination with an oral AH, they are used less often in other parts of the world, particularly in Europe. In Italy they are used very rarely (Pawankar et al., 2011). This is due to their lack of a therapeutic advantage and adverse effects when used longer than several days. These medication are recommended only for short-term use, and are readily accessed by patients OTC.

"I almost never prescribe decongestants. Why? Well, one [reason] is [that] they [patients] can buy them over the counter, anyway, and use them before you [even] see them; something like 26% of patients [with AR] presenting at the hospital clinic will be on decongestants, some of them very regularly, because you get hooked on them. What decongestants do is to squeeze the vasculature of the nose and leave it in fact far too open, and a patient gets used to a very clear, unobstructed nose, which is actually not good because you need the nasal airway to filter, warm, and humidify, and decongestant [use] robs us of quite a lot of its functions. And then, because when they [patients] go off [these drugs], they wear off, [and] you get a rebound [congestion], so the nose blocks up again, [and] they use more. And some of them present with something called rhinitis medicamentosa, which is a completely blocked-up nose, because they've overused the decongestant. And in order not to get into that situation, I think it's easier not to start on [a] decongestant [in the first place]. Now, we used to use, I think, a thing called Dexa-Rhinospray Duo, which had a steroid in it which was dexamethasone, and a low dose of decongestant, of tramazoline. And that was extremely useful, especially for chronic rhinosinusitis, because it hit the osteomeatal complex area and really helped to open it up, and patients could then douche their

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nose and make themselves feel much better. But Boehringer-Ingelheim no longer market[s] that [drug] in the UK, though I think you can get it in places like Germany. So, we don't use it anymore. But there's a bit of evidence that, if you combine a decongestant with a corticosteroid, you're less likely to get the sorts of problems of rhinitis medicamentosa, and it might be useful at the start of therapy to have that combination. I think it's available in the USA."

EU Key Opinion Leader

"Well, patients often use them [decongestants] over the counter as nasal sprays. I don't use the combination of [a] intranasal antihistamine plus [an] oral decongestant due to my concerns about side effects. But there are such combinations available on the German market. And patients can buy them over the counter."

EU Key Opinion Leader

"I do not prescribe decongestants much. I find [there are] a lot of side effects with systemic decongestants. Some adults use them. I usually don't prescribe Allegra-D or Claritin-D to children because [of] the side effects; they get insomnia, they get hyperactive, and [other] things. I do sometimes use the spray, like Afrin, oxymetazoline. I will use that sometimes, like if I have a patient that has allergies, and they are really, really severe. Their nose is totally blocked, and if you spray Nasonex up their nose, it runs right back out. One of the ways I sometimes treat that patient is, I'll open them up with Afrin. And then I'll spray in the Nasonex, the nasal steroid spray. And I will do that for the first three or four days of therapy. And then I'll stop the Afrin and continue the Nasonex. And I don't let people use Afrin for more than three or four days at a time because many of them develop rebound nasal congestion, called rhinitis medicamentosa."

US Key Opinion Leader

"Decongestants are used, but not by the specialist. Or, I would say, not even by the GPs. This [use] is mainly OTC [by patients themselves]."

EU Key Opinion Leader

6.7 Intranasal Anticholinergics

6.7.1 Overview

Ipratropium bromide metered-dose spray is indicated for the symptomatic relief of rhinorrhea associated with allergic and non-allergic perennial rhinitis in adults and children age six years and older. Originally developed by Boehringer Ingelheim, it was approved as Atrovent in 1996, and is now available generically.

Ipratropium bromide blocks muscarinic cholinergic receptors, inhibiting the action of acetylcholine at parasympathetic sites in bronchial smooth muscle, causing bronchodilation. It decreases the contraction of the smooth muscles in the respiratory tract, thereby clearing the respiratory tract and relieving the symptoms of rhinitis. It has a fast onset of action, within 30 minutes. Although ipratropium bromide is effective for all types of watery rhinorrhea, it is unlikely to be beneficial for the other symptoms of AR, including nasal congestion, sneezing, and postnasal drip.

The ARIA guidelines state that intranasal ipratropium bromide should only be used for the treatment of rhinorrhea in patients with persistent AR. It is most effective when co-administered in combination with a nasal corticosteroid. Ipratropium bromide is a very effective nasal treatment for the relief of rhinorrhea, with a good safety profile. However, it has an inconvenient dosing schedule, requiring three applications daily. Also, its adverse effects, while infrequent, include dry nose, epistaxis, urinary retention, and glaucoma. Ipratropium should not be used by people who have glaucoma, or by men who have an enlarged prostate gland. The label advises against using the therapy for more than three weeks.

Ipratropium bromide is a very effective nasal treatment for the relief of rhinorrhea, with a good safety profile. However, it has an inconvenient dosing schedule, requiring three applications daily.

"I rarely prescribe anticholinergics — maybe once or twice a year."

EU Key Opinion Leader

"I do not prescribe anticholinergics as [a] first-line [treatment] at all; [rather,] usually as [a] second- or third-line [treatment]. I'll prescribe the anticholinergics in somebody who has allergic rhinitis who's not responding to a nasal steroid spray, [even] with good adherence and everything else. And I usually, if they still have [a] runny nose as their main symptom, and they are not responding to a nasal steroid spray and an antihistamine, I usually add the anticholinergic in."

US Key Opinion Leader

"Anticholinergics? Yes, I use those, especially if I think the patient has a mixed rhinitis, with a neurogenic element as well as an allergic element, and then ipatropium [bromide] may be very useful. I use ipatropium bromide in the nose."

EU Key Opinion Leader

"I just prescribe anticholinergics for hypersecretion. If there are too many secretion[s], it's used; otherwise, it's not used. So, very seldom [do I use them]."

EU Key Opinion Leader

6.8 Leukotriene Receptor Antagonists

6.8.1 Overview

LRAs, also known as leukotriene inhibitors and antileukotrienes, are oral treatments prescribed for patients who have asthma and/or catarrhal inflammation of the mucous membranes in the nose and respiratory tract. Merck's Singulair (montelukast sodium) is an LRA approved for the relief of AR symptoms. It is a cysteinyl leukotriene receptor 1 ($CysLTR_1$) antagonist, blocking the physiologic actions of cysteinyl leukotriene D4 (LTD-4). LTD-4 belongs to the family of cysteinyl leukotrienes (Cys-LTs), which are potent inflammatory mediators in both AR and asthma that are released from a variety of cells, including mast cells and eosinophils (Lee et al., 2009). They bind to cysteinyl leukotriene receptors (CysLTRs) found in the human airways, triggering bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Cys-LT levels are increased in asthmatics, particularly during the early phase of bronchoconstriction that follows an allergen challenge. Montelukast binds with high affinity and selectivity to the CysLT1 receptor, which is found in the human airways, including in the smooth muscle cells and macrophages of the airways. Since Singulair attenuates leukotriene-modulated signaling, it provides a good alternative to increasing the dose of INCS. The drug is indicated for the relief of the symptoms of AR: SAR in patients age two years and older, and PAR in patients six months of age and older. It can be administered orally in the form of tablets (also chewable) and oral granules, giving it a competitive advantage over intranasal AR medications, especially in pediatric patients.

Antileukotrienes are effective in reducing nasal obstruction, rhinorrhea, and ocular symptoms, in addition to bronchial symptoms, in patients with AR. In the treatment algorithm, they follow INCS and AHs in the treatment of patients with mild persistent, moderate to severe AR, if the patient is

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asthmatic. However, this class of therapy is not consistently effective, and there have been reports of adverse effects, including Churg-Strauss syndrome, headache, gastrointestinal symptoms, and rash (Greiner et al., 2011). The evidence indicates that for the treatment of SAR, montelukast is more beneficial than placebo, but equally effective as loratadine (Claritin). In addition, there is only a slight increase in benefit when using montelukast and loratadine in combination, and neither formulation was superior to INCS in terms of efficacy (Meltzer et al., 2000; Pullerits et al., 2002). Furthermore, a study comparing montelukast with pseudoephedrine demonstrated an equal benefit, with no difference in side effects (Mucha et al., 2006).

Of all the LRAs, only montelukast sodium is approved for use in patients with AR in the US and EU. Singulair received the FDA approval in 1998; however, it wasn't until January 2002 that it was approved for SAR, and in August 2005 for PAR. The drug reached blockbuster status, with $5.5 billion in sales in 2011. Singulair lost its patent protection in the US in 2012, and has since suffered massive generic erosion. There are currently 11 generic manufacturers that market generic versions of Singulair in the US, putting Singulair in a very unfavorable position (FDA, 2013). Singulair's 2012 revenues reached $3.9 billion, with $2.8 billion coming from the first half of the year. Sales of Singulair declined to $1.2 billion in 2013, and Merck lost nearly all sales of Singulair in the US, where they dropped to negligible $60m.

Since their discovery, Cys-LT antagonists have been regarded as candidate drugs for treating AR. Generic pranlukast hydrate, originally developed by Ono Pharmaceutical Co., Ltd., is a $CysLT_1$ receptor antagonist that is widely used in Japan. It was originally approved in a capsule formulation for AR in January 2000, and the dry syrup formulation was approved for AR in December 2011. The dry syrup formulation, Onon Dry Syrup, was approved and launched in 2000, but only for pediatric patients with bronchial asthma. It has a Pregnancy B Category rating, making it safe for use by expectant mothers. In addition to being indicated for patients with AR, it can also be used as a treatment for other respiratory conditions — namely, asthma and chronic obstructive pulmonary disease (COPD).

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"Singulair is the only one [LRA] available currently on the German market, but I only can prescribe it if the patient has a documented asthma. And it's not [a] first-line treatment for asthma, either. So, it would be prescription [prescribed] to a patient who is on an inhaled steroid, has allergic rhinitis, and the allergic rhinitis with asthma would not be sufficiently controlled by a nasal steroid, plus the inhaled steroid sometimes in combination with a beta-2 agonist. So, you can imagine that this is a very low proportion of patients that will receive this kind of treatment."

EU Key Opinion Leader

"I see a lot of people with allergic rhinitis and asthma. And if it's on the milder side, I usually will prescribe Singulair for both their allergy and their asthma. So yes, I do [prescribe it]. I see a lot of children. I particularly believe that that's a good option in children who have allergy and asthma, rather than pouring steroids into both airways, because we don't know the safety implications…[of] pouring steroids into both airways in children."

US Key Opinion Leader

"There's no doubt that inhaled corticosteroid is superior to antileukotriene. When you look at real life, actually, antileukotriene does remarkably well, because people like taking a tablet. So, one does need more real-life work in this area."

EU Key Opinion Leader

"No. I don't use antileukotrienes because they're not useful for allergic rhinitis, although, they are in the guidelines."

EU Key Opinion Leader

"In Japan, I hear complaints about the cost of leukotriene antagonists; leukotriene antagonists are very costly. So, I get complaints from patients when I prescribed leukotriene antagonist for a month or two."

Japanese Key Opinion Leader

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6.9 Cromones

6.9.1 Overview

Cromones, such as sodium cromoglycate and nedocromil sodium, are mast cell stabilizers and are available as both ocular and intranasal preparations for the treatment of allergic conjunctivitis and rhinitis, respectively. They are more commonly prescribed as an ocular preparation for patients with allergic conjunctivitis. They are considered less effective than INCS and other treatment options for AR symptoms, and have a short-lasting effect (Ratner et al., 2002). The ARIA guidelines recommend them for the treatment of mild persistent or moderate/severe intermittent AR as an add-on therapy. The mechanism of action of cromones is poorly understood. As both intranasal and intraocular cromones have a short duration of action, they require repeated administration, often four times daily, which can have a negative impact on patient compliance.

Both cromolyn and nedocromil are rated Pregnancy Category B, based primarily on their safety in animal reproduction studies. Intranasal cromones are normally used in the treatment of SAR, but can also be used to treat mild PAR. As they can take a couple of weeks to become fully effective, it is recommended that patients start therapy two weeks prior to the beginning of the pollen season.

This is a highly genericized drug class, with many formulations being available OTC, such as intranasal sodium cromoglycate (Angier et al., 2010). They are rarely prescribed, and therefore, GlobalData excluded this drug class from the forecast.

"I don't prescribe cromones, no. Except sometimes for eye use, but normally not for nasal use."

EU Key Opinion Leader

"Well, I did prescribe cromones, but now you really can't. Most of them are not available anymore because of the CFC [chlorofluorocarbon]-to-HFA [hydrofluoroalkane] propellant change that occurred. There's very low cromones used here in the US anymore. The people complained about it [the fact that it's no longer available], they loved it, they wished it was back, but I haven't prescribed — I think Nasalcrom [cromolyn sodium] is still available, but it's [now] over-the-counter."

US Key Opinion Leader

"I find cromones useful for small children. I still some sometimes [use] nedocromil also, in the eyes, which is a cromone. There's only twice-a-day use, and that's pretty effective, although I think Patanol has largely replaced that.'

EU Key Opinion Leader

"Cromones — no. I don't prescribe them."

EU Key Opinion Leader

6.10 Thromboxane A2 Receptor Antagonists

6.10.1 Overview

The Japanese AR treatment guidelines recommend the use of a dual thromboxane A2 (TXA2)/CRTH2 receptor antagonist for patients suffering from nasal blockage as the major symptom. TXA2 receptor antagonists are considered to be more effective for nasal blockage than a second-generation AH, and can also improve sneezing and rhinorrhea symptoms when administered for more than two weeks. The only approved medication in Japan of this class is Baynas (ramatroban), marketed by Nippon Shinyaku Co., Ltd. Baynas was originally developed in Japan by the German pharmaceutical company, Bayer, and was launched in the Japanese market as a first-in-class molecule for the AR indication in May 2000. In April 2006, Bayer Yakuhin, Ltd. agreed to transfer the marketing rights to Baynas to Nippon Shinyaku Co., Ltd. The drug works by increasing the vascular permeability of the nasal mucosa. In addition, it can prevent eosinophil migration by blocking TXA2 receptors as well as CRTH2 receptors, which are a type of prostaglandin D2 (PGD2) receptor. The drug is administered at a dosage of one 75mg tablet twice daily. Baynas has a slow onset of action, and reaches peak efficacy after four weeks. Although Baynas can interact with other medications, it does not induce sedation.

"Also, Baynas, [which is a] thromboxane A2 [receptor] antagonist, is costly. So, I try to be clear about [the] price estimate when I prescribe Baynas. I ask [the] patient's permissions before prescribing [it]. Those patients won't necessarily give up their treatment due to the cost issue. They typically have [a] severe case of [a] stuffy nose."

Japanese Key Opinion Leader

"Baynas is for severe stuffy nose symptoms. I prescribe Baynas to 10% of my patients. Most of my patients are satisfied with this. Rarely, [do] I hear [about] the side effects or [the] gastrointestinal problem. But it's rare."

Japanese Key Opinion Leader

6.11 T_H2 Cytokine Inhibitors

6.11.1 Overview

The Japanese guidelines also recommend the use of T_H2 cytokine inhibitors in patients with AR. There is only one marketed product in this class in Japan: suplatast tosilate (IPD®). The drug was originally developed by a private pharmaceutical company Taiho Pharmaceuticals. It is approved for the treatment of allergic diseases, including bronchial asthma, AR, and atopic dermatitis. IPD® acts by inhibiting the production of T_H2 cytokines through the selective inhibition of IL-4 and IL-5 production by T_H2 cells, to alleviate allergic inflammation. In addition, IPD® inhibits eosinophil infiltration in the airway mucosa and alleviates airway hypersensitivity. However, it does not induce somnolence. The drug is available as an oral formulation, which is administered as one 100mg tablet taken three times daily with meals. It has a very gradual onset of action, and requires administration for six to eight weeks prior to producing any clinical benefit. IPD® is now available generically, with five other companies marketing equivalent products. However, Taiho is the only company that sells a dry syrup formulation (5%) aimed at the pediatric population.

"In Japan, we only have IPD®. That's the only one which is approved in Japan. I rarely prescribe this. Well, I don't use IPD for simple allergy patients; I use this for severe sinus inflammation. For that, it's very effective. [For] adult patients. For children, I won't use it. I believe IPD® is not authorized to [be] use[d] for underaged patients. I think it was from Taiho Pharmaceutical Co., Ltd., but they didn't allow [it for] children's use. I mean, IPD® does not have any syrup [formulation]. So, it's not for kids."

Japanese Key Opinion Leader

7 Unmet Need and Opportunity

7.1 Overview

AR is becoming an increasingly prevalent condition, with the most common form being moderate to severe in nature. According to the European Federation of Allergy and Airway Diseases (EFA), 50% of Europeans will suffer from an allergy by 2015 (Turjanmaa et al., 2006). AR symptoms can be controlled in the majority of patients using the current standard therapies, which are mainly based on combinations of AHs, INCS, and oral leukotriene inhibitors. INCS and AHs are the gold-standard first-line therapies for AR patients. However despite receiving maximum doses of evidence-based therapy as directed by the ARIA guidelines, a significant percentage (approximately 20%) of patients with AR, particularly moderate to severe AR, have inadequately-controlled symptoms (Bousquet et al., 2010). Refractory patients are often diagnosed with severe chronic upper airway disease (SCUAD), and represent a therapeutic challenge clinically. Furthermore, AR is often undiagnosed; in Europe, as many as 25–60% of patients with AR are not diagnosed (Bauchau and Durham, 2004). Therefore, there are considerably high unmet needs within the indication, which are both clinical and environmental in nature. Overall, these needs mainly reflect the primary care culture, which often dismisses AR as a minor condition, despite the huge socioeconomic and morbidity costs associated with the disease. This leads to poor diagnosis of the disease, lack of patient compliance with the standard therapies, and inadequate symptom-related treatment.

However despite receiving maximum doses of evidence-based therapy as directed by the ARIA guidelines, a significant percentage (approximately 20%) of patients with AR, particularly moderate to severe AR, have inadequately-controlled symptoms.

The level of environmental unmet need in AR is high. Patients and PCPs alike have a low awareness of the impact of AR. This directly impacts the drug treatment rate, with many patients not taking any therapy for their AR. In addition, physicians often underappreciate the prevalence of mixed rhinitis, which consists of a combination of allergic and non-allergic rhinitis components, and they face challenges in its diagnosis and treatment. These patient-related factors, combined with inadequate treatment options, means that the majority of AR patients continue to experience symptoms even though they have received guideline-directed treatment. Patients are often highly dissatisfied with their treatment options, are non-compliant, and often self-adjust their prescription medication with OTC products due to a lack of adequate efficacy or a perceived reduction in efficacy over time. Patients often try several medications, with approximately 75% taking more than one symptomatic therapy simultaneously in search of a medication that works (Demoly et al., 2002).

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There is little room for new entrants in this market, which is well-served by a wealth of symptomatic therapies. The environment is becoming increasingly competitive, as several blockbuster drugs are losing patent protection, so the market for AR therapies is becoming less lucrative. This is likely the reason why there are currently no breakthrough symptomatic therapy products in clinical development. Therefore, the remaining clinical unmet needs include the requirement for more efficacious products, and the underserved area of causative therapies, such as immunotherapies, which target the underlying cause of the disease.

Table 47 lists the prominent unmet needs and opportunities in the AR market, along with a numerical value depicting the level of attainment of these needs in different markets (1 = low attainment; 5 = high attainment). The table also ranks the relative importance of each of the unmet needs on a scale of low, moderate, or high. These ratings are subjective, and are based on GlobalData's primary research and discussions with KOLs.

Table 47: Unmet Need and Opportunity in AR

Unmet Need	Relative Importance	Current Level of Attainment	Gap Analysis: Product or Initiative Poised to Meet Need	Future Level of Attainment
Pharmacist education	High	2	New online courses for pharmacists are being offered, and guidelines are being distributed to pharmacies to improve awareness.	3
Patient compliance	High	2	HFA-propelled, dry mist INCS have been launched, including Teva's Qnasl and Sunovion's Zetonna. The delivery devices could be improved to enhance patient compliance.	3
Immunotherapies	High	1	Tablet formulations of AITs covering 80% of the most prevalent global allergies are being developed. This effort is being spearheaded by ALK-Abello and Stallergenes, each of which has an extensive AIT portfolio.	3
PCP education	Moderate	2	Educational programs to raise the profile and awareness of the well-defined, evidence-based ARIA guidelines among clinicians are a remaining goal.	2

Source: GlobalData, based on primary research interviews with allergists and PCPs/GPs in the 7MM

7.2 Pharmacist Education

7.2.1 Unmet Need

The majority of AR therapies are now available OTC at local pharmacies as a result of an Rx-to-OTC switch. This includes the first-line therapies, AHs and INCS. The pharmacy is often the first place patients go to when seeking symptomatic relief, with pharmacists playing a crucial role assisting with a diagnosis of rhinitis and educating the patient by recommending the correct symptom-directed medication and advising on how to use it. However, pharmacist knowledge of the AR treatment guidelines is currently inadequate (Canonica et al., 2013).

Pharmaceutical companies spend a considerable amount of money every year on DTC advertising for AR products in this multibillion dollar market. AR therapies are one of the most commonly sold OTC products, and the majority of AR patients use OTC remedies, often without ever seeing a physician (which is particularly true of those with mild allergies), and even to supplement prescription treatments, in search of improved relief from symptoms. Studies in Europe show that only 45% of patients with AR seek medical advice or treatment (Canonica et al., 2007). According to GlobalData's primary research, of all drug-treated AR patients, approximately 50% of EU patients and 60% of US patients use OTC therapies before seeing a physician. These therapies have been on the pharmacy shelves for a long time, and patients are very familiar with the OTC AH and decongestant brands.

Allergies are responsible for a significant portion of healthcare costs, which include the cost of physician visits, medications, and hospital admissions. In cost-conscious healthcare systems, to relieve the financial strain, physicians often recommend OTC treatments, which are cheaper than the cost of a prescription co-payment. However, patients often fail to obtain adequate relief of their symptoms when self-medicating, and as a result, feel resigned to tolerating their symptoms. This is often because patients either receive incorrect guidance from pharmacists or none at all. This problem is compounded by an underappreciation of the negative impact of allergies on QoL, and the economic impact of missed work. Allergies are a particularly important issue for children, as they negatively affect school attendance and academic performance.

The available OTC AR medications are first-generation, oral H1AHs, which cause somnolence. As the brands in this drug class are some of the oldest available on pharmacy shelves, patients often use them, owing to brand awareness. However, patients are often unaware of the differences

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between AHs, and can mistakenly alternate brands from different generations in search of superior efficacy.

The current evidence-based guidelines recommend using INCS a first-line treatment option for patients with moderate to severe AR, which is the most common and increasingly prevalent patient segment. However, patients are unaware of this treatment option when searching for an OTC remedy. In addition, they are often reluctant to self-medicate using an intranasal spray because of the controversy surrounding their safety. Patients are also unaware of the differences in AR treatments, particularly between AHs and INCS, in terms of their efficacy in alleviating symptoms. The approval of the first OTC INCS in the US in 2014 will require a concerted effort by pharmacists to improve awareness of this product, as it this will be the first time patients are able to access it without a prescription.

The lack of awareness of AR has often resulted in patients receiving incorrect advice and inappropriate treatment when visiting a physician, while appropriate OTC therapies are available that can provide adequate relief of their symptoms. This is frustrating for the patient, and also creates an unnecessary financial burden. In addition, it contributes to the vast number of AR patients who have poor symptomatic control. It also creates apathy among patients, who are resigned to tolerating their symptoms because they believe that all AR treatments are ineffective, which ultimately drives down the drug treatment rate.

Surveys have demonstrated that approximately 60–80% of children with asthma have AR as a comorbidity (de Groot et al., 2012). To further complicate the treatment of AR, many patients are sensitized to multiple allergens, which makes allergen avoidance impractical. In addition, many patients have both allergic and NAR components, which is referred to as mixed AR. If mixed AR is misdiagnosed, patients are likely to fail to obtain relief from AR therapies. It is therefore essential that pharmacists be trained in the diagnosis of allergic disorders, and be knowledgeable about referring patients to PCPs and specialists, where appropriate.

Unmet Need and Opportunity

"The ARIA Guidelines — don't forget that there are also other guidelines for pharmacists, which is quite important, because there is a flow of the patients [through the healthcare system]. And so, there are [sic] a clear indication, also, for pharmacists, where and when to address the patient, [and whether to] refer [the patient] to [a] GP or directly to the specialist. Unfortunately, in the survey we did, there was no awareness in most of the pharmacists about that. I feel like there is an initiative gap, and that should be improved just to keep the awareness higher than it is now."

EU Key Opinion Leader, 2014

"I don't think pharmacists are knowledgeable about the different treatments [for AR]. And this is based on [the] experience that I have [had] with medical education — continuous medical education meetings that I had with pharmacists, and in general, these pharmacists would not be knowledgeable about the ARIA guidelines. They would generally tend to dispense either cetirizine or loratadine in such patients with allergic rhinitis, and only if [the] patients insisted on having a nasal spray, then they might dispense a spray containing beclomethasone, and [this was] usually [because of their] not being so aware about the difference between a nasal antihistamine and a nasal steroid. This is the feedback that I have [gotten] from some of these meetings."

EU Key Opinion Leader

7.2.2 Gap Analysis

In 2003, ARIA released a pocket guide that was specifically designed to assist pharmacists in the diagnosis and treatment of AR, using its evidence-based treatment algorithm for AR patients. This pocket guide, which was developed based on the ARIA workshop report, has been translated into more than 50 languages (Anon 2004). However KOLs interviewed by GlobalData noted that there was little awareness of the ARIA guidelines among pharmacists, and that there is a large unmet need for the appropriate treatment of patients with AR by the pharmacist community.

On a national level, several allergy authorities are expanding their campaigns to pharmacists to make them aware of the ARIA guidelines. Healthcare departments are also seeking to increase pharmacist awareness of allergies. GlobalData believes that the organizers of the ARIA pharmacist pocket guide should increase their efforts to educate pharmacists on the correct treatment strategy. In the UK, the NHS has produced laminated treatment algorithms, which it has distributed to over 40,000 pharmacies across the UK, in time for the peak allergy season. In the US, educational grants provided by the leading pharmaceutical companies in AR, including Meda, Merck, and

In the US, educational grants provided by the leading pharmaceutical companies in AR, including Meda, Merck, and Chattem, have supported the development of online courses regarding the role of pharmacists in counseling AR patients, as part of the continuing education for accredited pharmacists.

Chattem, have supported the development of online courses regarding the role of pharmacists in counseling AR patients, as part of the continuing education for accredited pharmacists.

"But what we did one year was to do an algorithm, a laminated algorithm for the walls of pharmacies, that we handed out with the managing chemist and druggist [to] about 40,000 pharmacists in the UK."

EU Key Opinion Leader, 2014

"And many of them [AR patients] are really well-treated by simple measures, like a nasal steroid or a very mild antihistamine which is non-sedating. The pharmacist can deal with all of that, and if they [pharmacists] taught them [patients] to use the steroid as well, that's important; how to put it into the nose matters. If they'd only teach that [to patients]."

EU Key Opinion Leader, 2014

7.2.3 Opportunity

Given the healthcare cost restrictions in Europe, pharmacists play a vital role in the diagnosis, treatment, and management of patients with AR. The responsibility of pharmacists for AR patients is central to the appropriate management of the disease and maintaining the flow of patients through the healthcare system. Patients are often confused about the numerous AT treatments available OTC. Qualified pharmacists must be trained to educate patients regarding allergen avoidance strategies; the use of symptom-appropriate medication, including its side effects, and up- and down-dosing schedules; as well as the impact of AR on asthma, where relevant.

The development of additional training materials and programs designed to continuously update pharmacists' skills and competence are vital to ensuring their active participation in the prevention and treatment of AR. Cooperation between patients and pharmacists and other healthcare professionals is also essential in order to provide early diagnosis and adequate management, ensure patient QoL, and reduce the frequency and severity of comorbidities.

Despite the current wealth of knowledge and clinical experience regarding AR, including the availability of evidence-based treatment guidelines, efforts by ARIA via the WHO to disseminate treatment recommendations by producing and distributing guidelines and other documents have failed to sufficiently influence pharmacists. As a result, AR remains a considerably underdiagnosed condition. AR is also often misdiagnosed, owing to a number of common comorbidities, which include acute and chronic rhinosinusitis, otitis, and bronchial asthma. Particularly in the case of

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comorbid asthma, early diagnosis and symptom control is imperative in preventing exacerbations and progression of the disease.

Pharmacists are the most accessible source of health information, and are being required to play an increasingly greater role in helping to meet the demands of modern healthcare systems. By providing patient counseling and advice on disease prevention and adequate disease therapy, they contribute to public health development and are playing a progressively more vital role in supporting overwhelmed healthcare systems. By using their skills and competence, pharmacists can help ensure the optimal use of OTC allergy therapies, thereby allowing for optimal efficacy and reducing the disease burden on healthcare systems.

There are several ways to increase the awareness of AR guidelines and competence among pharmacists, which include generating media campaigns and publishing information in professional pharmacist journals. This information could also be disseminated through websites and blogs that are commonly used by pharmacies. Through these methods, pharmacists' skills, including their awareness and knowledge of the ARIA guidelines, could be improved. Increasing the distribution of news across websites, including links to manufacturers, allergy societies, patient organizations, and educational sites would also be useful. An increase in company-sponsored training courses across Europe may also improve the continuing education of pharmacists once they become qualified. Given the launch of OTC INCS in the US for the first time in 2014, a drug class that has been available OTC in the EU for many years, it is particularly timely to increase pharmacists' awareness of the new guidelines.

Ultimately, if the guidelines are distributed effectively, and pharmacists have had adequate training in treating respiratory allergies, a significant number of AR patients could be treated using OTC drugs and pharmacist-only medicines (POMs), without the need to visit a physician, at either the primary or secondary level, thereby reducing the burden on healthcare systems. Pharmacists would also able to advise patients to see a physician, if required, and could be instrumental in identifying common comorbidities in AR patients, including asthma and NAR, thus reducing the number of patients who fail to obtain adequate relief of their symptoms.

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7.3 Patient Compliance With Intranasal Corticosteroids and Antihistamines

7.3.1 Unmet Need

INCS and INAHs are efficacious topical therapies for the treatment of AR. The topical application of these agents limits their systemic bioavailability, and allows for the use of lower drug doses. National and international task forces, as well as the ARIA guidelines, recommend INCS as the first-line therapy for patients with moderate to severe, persistent AR, who represent approximately three quarters of the AR population.

INCS are the most effective pharmacological agents for AR, and improve all nasal symptoms, including congestion, rhinorrhea, itching, sneezing, blockage, and the TNSS, more than AHs. Leukotriene antagonists are not as effective as AHs, and are not very effective when used in combination with AHs compared with INCS. INAHs have a rapid onset of action and are equally or more efficacious than their oral second-generation counterparts. Two commercially available INAHs are azelastine and olopatadine. Several INCS are also commercially available, including beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. They are equally efficacious in treating both SAR and PAR, as demonstrated in numerous well-controlled studies.

However, intranasal therapies are associated with poor adherence and patient compliance, which are two of the main obstacles in AR treatment. GlobalData's primary research indicated that adherence to this type of therapy can be as low as 20%. Uncontrolled symptoms may occur as a result of an incorrect diagnosis, poor compliance, or poor administration technique, with the latter two often being interrelated. The reasons for non-adherence are numerous, and include patient difficulties with intranasal devices and unfounded fears about long-the term side effects of INCS use, such as HPA suppression. In addition, other side effects, such as nasal burning, stinging, and irritation, local dryness, headaches, and epistaxis, are experienced by 5–10% of patients (Greiner and Meltzer, 2012). However, one of the biggest reasons for non-adherence seems to be patients' dissatisfaction with the negative sensory attributes of INCS, such as smell, taste, and aftertaste.

Although solid evidence in this area is scarce, it is believed that poor compliance is also partially attributed to poor patient technique when using nasal drug delivery devices, which can result in reduced efficacy and the induction of adverse effects related to the prolonged use of nasal sprays.

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Side effects such as nasal crusting and epistaxis, are usually caused by poor administration technique (Hellings et al., 2013). In addition, INCS have a slower onset of action compared with oral and intranasal H1AHs; however, they have superior efficacy when taken persistently. In addition, as-needed use of INCS is associated with reduced efficacy compared with continuous use, and therefore, patients should be advised to start treatment prior to the onset of the allergy season (Kaszuba et al., 2001). Despite this widely held knowledge, patients often complain of the side effects associated to this medication type, and instead choose to take an oral formulation, most commonly, oral H1AHs.

Uncontrolled AR can often be attributed to poor adherence, and therefore, improved compliance with the use of inhaled therapies is a very large unmet need in the AR space. However, in order for this unmet need to be fulfilled, patients need to experience greater satisfaction with these treatments and a reduction in their side effects.

Uncontrolled AR can often be attributed to poor adherence, and therefore, improved compliance with the use of inhaled therapies is a very large unmet need in the AR space.

"In terms of the taste issue, there is a drug called Dymista, containing azelastine. This tastes bad. In Japan, we don't use that kind of drug. [The] Japanese have weak taste buds. Bitter ones [tastes] are not preferred. Azelastine was developed in Japan, but it has not been used. Of course, drugs won't be used if patients would not like their tastes. Fewer side effects are important, but usability are [sic] too."

Japanese Key Opinion Leader, 2014

"Burning and stinging with nasal sprays. I think a lot of people get these symptoms, and they stop using [nasal sprays]. We say, 'Well, they're not getting better because they are not using the medication.' But some people don't use the medication[s] because they did use them, and they didn't get better, too, or they had side effects [with them]. We like to say, as doctors, that everything [that goes wrong with the therapy] is because people aren't compliant. But I think compliance and efficacy and safety issues are all closely tied in together."

US Key Opinion Leader, 2014

7.3.2 Gap Analysis

As a result of the FDA's decision in 2011 to phase out all metered-dose inhalers (MDIs) that used ozone-depleting chlorofluorocarbon (CFC) propellants, INCS and INAHs are now predominantly available as aqueous formulations (Salib and Howarth, 2003). However, the sensory disturbances associated with these drugs can be attributed to formulation-related factors. Aqueous INCS

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preparations are associated with a wet feeling and nasal runoff. Excipients, such as formulation preservatives, may produce nasal irritation, thereby reducing tolerability. In addition, the surfactant benzalkonium chloride (BKC), which is present as a preservative in nearly all intranasal formulations, has an unpleasant bitter taste, and has been reported to produce a consistent and significant increase in nasal irritation, a burning sensation, and a postnasal drip, immediately after administration (Riechelmann et al., 2010). In addition, the long-term use of nasal sprays that contain BKC appears to increase the susceptibility to rhinitis medicamentosa. Alcohols are used to improve the sensory attributes of nasal sprays, but may irritate and dry out the nasal mucosa. Carboxymethylcellulose is a thixotropic agent that is used to impart a high viscosity to nasal suspensions, but it also has a drying effect, which may contribute to increased epistaxis.

Two FDA-approved hydrofluoroalkane (HFA)-propelled, non-aqueous aerosol nasal preparations are beclomethasone dipropionate HFA (Teva's Qnasl) and ciclesonide HFA (Sunovion's Zetonna), which are both once-daily treatments for SAR and PAR. These new dry-mist (non-aqueous) formulations replaced the previous "wet" formulations, GSK's Beconase and Sunovion's Omnaris, respectively. The new HFA formulations have advantages over the aqueous formulations, as they generate a fine mist that does not cause postnasal drip, and have longer retention in the nasal cavity, a potentially better taste, and once-daily dosing. In addition, they show reduced anterior and posterior runoff, which lead to throat irritation and pharyngitis. The disadvantages of HFA formulations include a higher incidence of epistaxis and burning. Aqueous INCS are commonly preferred, as patients are familiar with their delivery devices, and may also find their moistening effect soothing. These devices are pressurized, odorless, and environmentally-friendly, with a built-in dose counter. Also, a wide variety of product options are available, with established safety and efficacy.

In January 2012, Zetonna was the first non-aqueous (dry mist) aerosol nasal spray to be approved by the FDA for the treatment of PAR and SAR in children older than 12 years, and features once-daily dosing of one spray per nostril. Although Sunovion stated that it did not wish to pursue an indication in the 6-to-11 years' age group, it has had recent discussions with the FDA regarding a path forward to the pediatric program for Zetonna. In December 2014, Teva was awarded an sNDA for Qnasl 40mcg nasal aerosol for the treatment of PAR and SAR in children age 4–11 years, which became available by prescription in February 2015.

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"I felt sure that when these drugs [Zetonna and Qnasl] were released, [that] they would account for 25% of the sales [of AR therapies]. I was grossly incorrect. A part of that [my assumption] was simply due to [an] overestimation of their acceptance in a more competitive market. The second thing is that, [for] the preparations [that are] available, even though studies have shown that they don't have an overly-powerful spray, the perception when you use them is that the spray is very uncomfortable to use. It has a very strong 'impact' [on the nasal cavity], which patients don't like, and which I have used myself, which I find distasteful. So, the preparations themselves are a little bit different. Then, physicians were very eager to get them back on the market because of the complaints that we hear [about], [such as] runoff down the back of the throat, which prohibit their use in some patients. The complaint stuck out in our mind greater in number[s] than they really were, I think. So that when these drugs came on the market, the niche was much smaller than we had anticipated. Instead of being one in five, in my practice now, it's about one in 15 to one in 20, at the best. So that I was thinking that I had a lot of patients who would be very good candidates for this, and then when real life came about, it's very rare. It's not as common as I anticipated it to be."

US Key Opinion Leader, 2014

7.3.3 Opportunity

Currently, HFA-propelled INCS are available only in the US, and not in the EU or Japan. Also, there are no approved HFA intranasal AHs. Despite considerable patient dissatisfaction with the aqueous intranasal INCS drugs for AR, the uptake of both Qnasl and Zetonna has been extremely modest, and they have failed to capture a significant patient share of the R1A1 INCS (INCS without anti-infectives) market. Both drugs had poor initial sales compared with their projected revenues prior to launch, and for this reason, Zetonna is no longer being actively promoted in the US.

KOLs interviewed by GlobalData highlighted that a key problem with the new INCS formulations is the delivery device itself, because when patients administer these medications, they perceive them as having a strong "impact" on the nasal cavity, which is characterized by a sharp or unpleasant sensation. An additional concern when prescribing these medications is their relatively high cost when compared with the other generic aqueous INCS, which are widely available. As INCS are likely to remain the gold-standard treatment for AR, there is an opportunity to improve the delivery of the fine-mist spray in order to treat patients who commonly report dissatisfaction with the symptomatic AR treatments.

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Some lessons could be learned from the new combination intranasal sprays, such as Dymista, which is a combination INCS/AH product. This drug is highly effective in reducing nasal symptoms associated with AR. However, Dymista is an aqueous formulation of azelastine, a drug that is associated with a bitter taste sensation. KOLs noted that future combinations of AHs and INCS in a single device consisting of an HFA dry aerosol could include a different AH or INCS, with an improved "softer" delivery device, in order to improve patient satisfaction and increase their compliance with therapy.

There is a large window of opportunity for novel drugs with even more convenient dosing or better and/or cheaper nasal sprays. However, convenient dosing is not enough, as the role of healthcare workers, including pharmacists and physicians, needs to change significantly, as they need to adequately inform patients about the importance of adhering to therapies for AR, even in the absence of symptoms.

A study conducted by Varshney and colleagues demonstrated that AR patients prefer fluticasone over ciclesonide when using an INCS, owing to its pleasant scent, soothing feel, and decreased nasal irritation (Varshney et al., 2012). Developing a formulation containing fluticasone as an alternative drug is an opportunity for companies to improve the current "dry" INCS market.

"Azelastine. This tastes bad. In Japan, we don't use that kind of drug. Japanese have weak taste buds. Bitter [drugs] are not preferred. Azelastine was developed in Japan, but it has not been used. Of course, drugs won't be used if patients would not like their tastes. Fewer side effects are important, but usability are [sic] too."

Japanese Key Opinion Leader, 2014

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"So, a drug like azelastine, does much more than treat allergy. It has a number of different other therapeutic effects, and when you combine them with intranasal steroids, you have a very potent anti-inflammatory package. But even with that, these patients often do not respond as well as we would like, and we do need additional therapies. The most resistant symptom of those [patients] is postnasal drainage — that's fluid production that drains down the back of the throat."

"When you use azelastine alone, one gets a taste perversion, which has been one of the major causes [reasons] that patients are dissatisfied with it. In combination with fluticasone, which is in [a] benzyl alcohol solution, [which]…is somewhat of a taste-masker. The drug Dymista is not often associated with that complaint, [but] it does occur occasionally. So, patient satisfaction has really been quite good in our experience, and I think statistically, looking at the data, that upholds that opinion. But the fact of the matter is that even with that drug, we do get treatment failures, especially in terms of the symptom of [postnasal] drainage."

When you use azelastine alone, one gets a taste perversion, which has been one of the major causes [reasons] that patients are dissatisfied with it.

US Key Opinion Leader, 2014

"I think that another 'me-too' drug, meaning another [intranasal] steroid, would not work."

US Key Opinion Leader, 2014

"I think a combination of either another intranasal antihistamine and another steroid, or using azelastine and another nasal steroid would be financially successful."

US Key Opinion Leader, 2014

"Decadron Turbinaire [dexamethasone], which was available for use through the 60s and 70s, which, hands down, is the most effective drug we've ever had to treat rhinitis patients — far more than any of the present steroids. But [it is] associated with potential side effects which have never been evaluated adequately, because there's not been studies on it. But we who've been practicing [for] a long time know that it was the best drug we've ever had. If a[nother] drug like that came out, which had no unwelcome side effects, or equal side effects to [the] present intranasal steroids, yes, there would be room in the market, clearly. It was air pressure-delivered, it was an aerosol, which was very gentle, and it was clearly much better than anything we have now."

US Key Opinion Leader, 2014

7.4 More Convenient and More Patient-Friendly Immunotherapies

7.4.1 Unmet Need

The AR market is highly saturated and genericized, with little space for any additional symptomatic treatments. Therefore, any new symptomatic treatments would have to show a highly significant increase in efficacy, in addition to having a novel mechanism of action to penetrate market share. There is, however, a remaining clinical unmet need for a causative treatment to "cure" patients of AR.

Specific allergen immunotherapy (SIT) is the only AR therapy that has disease-modifying potential and is effective in treating multiple allergic diseases, including asthma, conjunctivitis, and rhinitis (Moote and Kim, 2011). If taken correctly, it has the potential to change the underlying immune response and decrease the symptoms triggered by some allergens, thereby preventing recurrence of the disease in the long-term. In some instances, AIT is capable of "curing" patients of AR.

SIT uptake is currently very low, despite a report stating that 18% of patients in the 5EU, and 14.8% in the US, fail to obtain adequate relief from their symptoms when taking the conventional symptomatic drugs (Canonica et al., 2007; Schatz, 2007). GlobalData estimates that in the US, approximately 5% of patients with an AR diagnosis receive SIT, chiefly in the form of SCIT (Hankin et al., 2013). In Europe, this figure is lower, at 2.3%, and in Japan, very few patients are treated with immunotherapy.

The reasons most often cited by patients for the low uptake of AIT include the inconvenient and time-consuming nature of the treatments, particularly with regard to SCIT, which requires frequent in-clinic visits for a minimum of three years. In addition, the issue of needle-phobia is particularly evident in children, who arguably benefit the most from receiving this treatment prior to the onset of the "atopic march" (the progression of allergic manifestations with age). Financial issues can be another major barrier to the uptake of immunotherapies, as SIT has a high annual cost of therapy (ACOT), and is not fully reimbursed in some parts of the US, Europe, and Japan. Other concerns associated with AIT include potential safety issues and side effects, including the risk of systemic reactions/anaphylaxis.

Unmet Need and Opportunity

"Immunotherapy is very important, particularly in childhood. Of course, we have to treat children with sensitivities as soon as possible, because this treatment is more relevant and more effective in this kind of patient. In this patient, chronic inflammation is less than in adults, and for this reason, it is possible to modify the history of the disease in [a] better way than in adults."

EU Key Opinion Leader

According to KOLs interviewed by GlobalData, there is a large unmet need for a curative therapy that targets the underlying cause of AR. Despite a number of SIT options being available, there are several unmet needs, which are often country-specific. These include the lack of affordable specific immunotherapies in countries without full reimbursement, the lack of immunotherapy treatment guidelines, and the lack of tablet formulations for every allergen, as well as the need for increased physician referral to specialists for diagnosis and the initiation of immunotherapy, and for clinical evidence supporting the use of SIT in polysensitized patients.

"The problem is that [allergen immunotherapy] is not affordable for many patients because it is quite expensive. For this reason, we have to distance [ourselves] from a clinical point of view, as it is influenced by [the] economic crisis problem. For this reason, we are forced to reduce the number of patients treated with both sublingual and subcutaneous immunotherapy."

EU Key Opinion Leader

"Our patient goes to their GP, or goes to tell about this [allergen immunotherapy] prescription in the family, then…decide[s] not to start it because…the cost of the treatment is not affordable."

EU Key Opinion Leader

7.4.2 Gap Analysis

Some immunotherapy manufacturers have developed AITs to overcome the challenges associated with the current AR therapies. For example, SCIT is inconvenient, and there are concerns surrounding SLIT drops, such as localized allergic reactions, poor compliance, and their limited ability to be shipped. AITs have frequently been used in Europe during the past decade, and have recently been launched in the US and Japan through several partnerships. However, the development of these therapies is costly and involves lengthy, large-scale clinical trials.

Unmet Need and Opportunity

"The approval of [allergy immunotherapy] tablets will help [the use of immunotherapy] because they can, again, be administered at home. So, I think you know that will help, at least in some [patient] groups, and [it] may help someone [in] pediatrics as far as needle phobia [is concerned]. So, I think it will increase the numbers [of treated patients], at least if we start [tablet] immunotherapy."

US Key Opinion Leader

This effort is being spearheaded by two companies, ALK-Abello and Stallergenes, whose tablet portfolios are focused on the most prevalent causes of AR, including HDM, ragweed, and grass. Stallergenes has stated that its tablets cover 80% of the most prevalent global allergens. However, allergen extract requirements vary globally due to geographical differences in the prevalence of allergens, particularly pollens. For example, Japanese cedar pollen is highly prevalent in Japan, and is particularly problematic for Japanese AR sufferers; however, it is not present in either the EU or the US. Similarly, certain highly prevalent pollens that cause AR in the northern US are not as prevalent in the southern states. In addition, the lack of cross-reactivity between the allergens contained in the currently available tablets limits their use. Furthermore, polysensitization to several allergens is common in patients with AR. In the EU, where treatment with the single largest cause of an individual's AR is recommended, single-allergen tablet preparations are acceptable. However, for the US and Japanese markets, where treatment of more than one allergen sensitization is preferred, the use of this treatment will be limited. A US KOL interviewed by GlobalData suggested that treatment using AITs will be limited to patients who are either needle-phobic or refuse the other forms of treatment due to cost or inconvenience.

"Here is the way I look at this. I am in the southeastern part of the United States. The major grass we have is Bermuda. These tablets [Grazax and Oralair] do not cross-react with Bermuda [grass]."

US Key Opinion Leader

Unmet Need and Opportunity

"I see this treatment [AITs] being used, if it is used by allergists and ENTs [ear, nose, and throat specialists] in the United States, and I think that's a big 'if'…. It will be a second-line treatment. In other words, you come to me and I test you, and in [the] Memphis area, you have allergies to grass, and let's say its Timothy and Bermuda [grass], and you had [an] allergy to dust mite[s] and to ragweed. Okay, I am going to offer you an immunotherapy by injection first to cover everything you are allergic to. [If patients refuse SCIT because] it's too costly or cannot come in weekly for allergy shots, then I go, 'Well, I can treat you for part of your allergies with this new tablet, and I don't know how much improvement you will get because you don't cover everything you are allergic to, but we can try.' "

US Key Opinion Leader

"The general introduction of immunotherapy tablets for practically every allergen is an unmet need. In Germany, we have tablets from the Italian company [Lofarma], but there should be competition from other companies, so that there would be more acceptances in the market. Such developments are ongoing in the United States for house dust mites and for the ragweed tablet, [and] in Japan for Japanese cedar tablets. So, I think this will take another five years or so, and [at that point,] we will have tablets for practically every allergen on the worldwide market."

The general introduction of immunotherapy tablets for practically every allergen is an unmet need.

EU Key Opinion Leader

7.4.3 Opportunity

AITs that contain multiple allergens have a significant opportunity in the AR market. However, further research, which is currently ongoing, will need to prove the efficacy of treating polysensitized patients in this manner. KOLs also said that they would like a larger portfolio of treatments for the many causes of AR, such as cat allergens. At present, there are very few AITs available across the US Japan, with a limited selection in the EU, but none in Japan. Both the increase in the number of different allergen extracts available and competition from multiple manufacturers for the same allergen therapy will increase the size of the AIT market through increased awareness and competitive pricing.

The lengthy treatment duration of AIT represents the largest hurdle for patients to overcome. This often results in poor compliance and failed treatment results. Research and development (R&D) is ongoing to chemically modify allergen extracts in order to expand and accelerate their immunotherapeutic effects, while reducing the potential for serious adverse effects. Furthermore,

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new routes of administration, such as intralymphatic delivery, have the potential to significantly reduce the number of injections required.

7.5 Primary Care Physician Education

7.5.1 Unmet Need

AR is becoming an increasingly prevalent condition, but is often overlooked and dismissed as being nothing more than an unimportant nuisance. However, its impact on QoL, including work and school attendance and productivity, is substantial (Meltzer, Eli O., Gross, Gary N., Katial, Rohit, Storms, 2012). Despite there being a wealth of symptomatic therapies available, both by prescription and OTC, many patients are dissatisfied with the efficacy of their treatment and fail to obtain adequate relief, and thus, suffer with the condition daily (Small et al., 2013).

GlobalData's interviews with KOLs indicated that AR still appears to be considered a minor disease by many physicians and patients, despite the fact that it is highly prevalent and impacts sufferers' QoL immensely. In addition, it has been shown that AR has a major impact on asthma morbidity in adults. However, the treatment of AR can improve asthma control, and should therefore be considered an essential element of the treatment of bronchial asthma and an important part of asthma prevention.

In many countries, the gold-standard therapies for AR — namely, INCS and AHs — are available OTC. However, several factors prompt patients to visit a physician for treatment, including poor symptomatic relief from self-medicating and the desire for a reimbursed drug. Despite clear, well-defined, state-of-the-art, evidence-based guidelines produced specifically to assist physicians in the diagnosis and management of AR patients, KOLs indicated there is a high and pressing need for a greater awareness of the AR treatment guidelines among physicians.

AR is often misdiagnosed, owing to a wealth of common comorbidities, including acute and chronic rhinosinusitis, otitis, and bronchial asthma. Studies have shown that patients with AR are 3.5 times more likely to develop asthma, suggesting its nature as a risk factor for asthma. At the same time, the findings of these studies also indicate that AR is prevalent in about 85% of asthmatics, signifying its existence as a comorbid condition in asthmatics. It is therefore essential that physicians be trained in the diagnosis of allergic disorders, including how to correctly examine the nasal passages, and that they be knowledgeable about referring patients to specialist, where appropriate.

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"People perceive rhinitis not to be a very serious illness. [However,] it really does affect the peoples' quality of life, [making them] miss work days, and [also,] their concentration skills or writing the GCSE [General Certificate of Secondary Education] exams [are] compromised. It is particularly evident in the middle of the pollen season, so if you are 18 and have got a terrible hay fever and [are] trying to go to [take an] exam, it's not very easy. And then, [if you] take [an] antihistamine, it makes you drowsy. So, there are lots of merits in immunotherapy, but it's just the [high] cost, I think, [that limits its use]."

EU Key Opinion Leader, 2014

"Clearly, if family doctors cured patients enough, [allergy] specialists would not exist. [Yet] we exist still. This fact suggests they're [family doctors] incompetent when prescribing [allergy] treatments, [and] are not following any guidelines."

Japanese Key Opinion Leader, 2014

"I think [the] family doctors' treatment success rate [for AR] is low. General doctors don't have knowledge about detailed treatments. [In contrast,] specialists are well-prepared. So, our treatment success rates are definitely higher than [those of] family doctors."

Japanese Key Opinion Leader, 2014

"Family doctors do not grasp [the AR] guidelines. They tend to provide only antihistamine drugs. I guess they are not aware [of AR] as much as [allergy] specialists. They casually prescribe [an] antihistamine just to get by the situations. As a result, severe patients end up in big hospitals."

Japanese Key Opinion Leader, 2014

"[The] education of primary care docs on the guidelines for [the management of] rhinitis has really fallen short; it gets very little attention here. There is so much emphasis placed on educating primary care docs in [the] asthma care guidelines. I think rhinitis has gotten the short end of the stick."

US Key Opinion Leader, 2014

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"They [PCPs] know how and when to refer patients to us [allergy specialists]. In other words, if there is a patient that has nothing, and can be treated with one pill or antihistamine, today, it's fine. They can do it. But if there is something that is not so, let's say, easy, they [allergy specialists] simply refer to us."

EU Key Opinion Leader, 2014

7.5.2 Gap Analysis

Recently, ARIA released new evidence-based guidelines for AR management (ARIA, 2010). These guidelines emphasize strategies for the optimal treatment of patients, and for increased awareness among physicians of the need for tight and timely stepwise therapy based on the stages of disease severity. National-level education programs are being developed to educate PCPs, not only regarding the ARIA treatment guidelines, but also to emphasize that, although AR is not an acute or life-threatening illness, its impact on QoL is significant, and it therefore deserves thorough attention and care.

In 2013, The European Academy of Allergy and Clinical Immunology (EAACI) and the European Union of Medical Specialists (UEMS) Section and Board (S&B) on Allergology, collaboratively published a position paper known as the "Allergy Blueprint," which outlines the minimum training requirements for allergy care, and the roles of the GP and specialist in the treatment of patients with allergic disease (deMonchy et al., 2013). In addition, the EFA generated a position paper, with support from both the EAACI and the UEMS, in which it requested endorsement of the European Commission and Parliament to increase the quality and complementary education of specialists and GPs in the allergy field. Furthermore, the EAACI established the Primary Care Interest Group, which is aimed at optimizing interactions between specialists and PCPs in order to foster synchronization between the two groups, and to design and disseminate education tools.

Given the high prevalence of respiratory allergies, it is imperative that allergy training be incorporated into the general professional training of both GPs and allergy specialists.

Despite these initiatives, training in the diagnosis and treatment of AR is still largely inefficient. Given the high prevalence of respiratory allergies, it is imperative that allergy training be incorporated into the general professional training of both GPs and allergy specialists.

"That's why we are more and more — we also schedule a lot of events to educate, or for educational program[s], to improve the [allergy] knowledge of GPs. And I just this morning, discussed it — another program all over Italy, based on local events — to train better the GPs."

EU Key Opinion Leader

Unmet Need and Opportunity

7.5.3 Opportunity

The treatment of allergic diseases represents a large and growing economic burden for national healthcare systems. If educational programs are successful in raising the profile and awareness of the well-defined, evidence-based ARIA guidelines among clinicians, then the number of allergy patients with a poor QoL and poor symptom control will decrease.

Although the new ARIA guidelines help focus attention on the progress and challenges in AR, the changes that are actually incorporated into practice tend to be incremental in nature. Despite the existence of these guidelines, the unmet need for physician education will persist for years to come, as most patients are managed in the primary care setting, where, according to the GlobalData's interviews with the KOLs, physicians are often not adequately informed about the specialist guidelines. Nevertheless, this more informative approach to AR treatment, when eventually and properly implemented into clinical settings, will open a large window of opportunity for the recently approved drugs and will decrease the number of patients who have unsatisfactory symptomatic relief. In addition, increasing physician awareness of the wider implications of poorly-controlled AR will hopefully encourage physicians to better advise patients on the importance of compliance with drug treatment and the correct application of intranasal formulations.

In the US and EU, surveys have shown that approximately one third of school-age children may have undiagnosed AR. This can result in patients being untreated, which may cause exacerbation of the disease and a decrease in QoL. In addition, the underdiagnosis of AR increases the risk of patients developing asthma by approximately three-fold, negatively affects asthma exacerbations, and can increase the probability of hospitalization by 50% (Pawankar et al., 2011).

There is a need for physicians to conduct tests to determine the cause of AR, which would allow them to advise patients about allergen avoidance. In addition, in light of the EAACI-UEMS Allergy Blueprint, it would be beneficial for physicians, including respiratory and ENT specialists, to examine the nasal cavity and lower airways to determine if there are any physical factors (such as non-allergic rhinitis [NAR]) or comorbidities (such as asthma) that could be contributing to patients' symptoms and possibly explain why they are not responding to conventional treatment.

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"I think it's simple to test for specific patient allergen sensitivities. [But doctors] don't have the time, and they don't want to do a skin prick test in general practice, largely because they're [the tests] a little bit time-consuming, and they're [doctors] worried about them being dangerous. I've campaigned to try and get them doing it for years, but they won't."

EU Key Opinion Leader

"Yes, I think there's still a shortage of allergists, and even then, some allergists don't really look at the nose and know enough about the nose, and that is a problem — that they need to improve their ability to deal with noses, because an awful lot of nasal disease is seen by ENT surgeons, who are terrific people and skilled operators. But a lot of them are not interested in diagnosing and treating allergy; it's not what they're trained for. But they're seeing those patients. So, the patients are going to the wrong specialist, and we ought to have more allergists doing better nasal work or, and/or involve ENT surgeons more in the medical aspects of ENT. And some of them, when we do do it, do it superbly. I'm always trying to persuade chest physicians to look at the nose and treat the nose. But again, they by-and-large are not interested in doing it, because they're trained as chest physicians, and they're not interested in the bit before the larynx. So, I do think that we need to widen everybody's horizons a bit — get everybody to look at the big picture. There is a united airway, and what goes on in the nose matters to the chest, and chest physicians ought to be able to deal with them."

EU Key Opinion Leader

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The AR treatment paradigm is well-defined, and the AR market is mature and highly genericized, with numerous drug classes that provide symptomatic therapy by targeting a number of nasal symptoms associated with the disease. Following the high-profile patent expiries of several blockbuster drugs marketed by the leading manufacturers in this area, a wealth of inexpensive generic options became available, both by prescription and OTC. As the market is very saturated, the average daily cost of therapy is exceedingly low for all the drug classes. Companies have been employing a strategy known as the Rx-to-OTC switch to extend the lifecycle of their drugs and ensure considerable continuing revenue. In addition, there is a strong drive to transfer the patient flow to pharmacists, thereby saving money for healthcare systems and insurance companies. One method that companies use to ensure this Rx-to-OTC switch is to price the prescription option higher (through a copayment) than the OTC version.

The AR market is extremely lucrative, with billions of dollars being spent every year on symptomatic relief.

The AR market is extremely lucrative, with billions of dollars being spent every year on symptomatic relief. In addition, patients are often dissatisfied with their treatment, and the drug landscape is fluid, with patients switching treatments frequently and trying a number of options in combination in an attempt to gain control over their symptoms. Previously, there had been many promising novel drugs in the development for AR treatment, including H3, H4, and H1/H3 receptor antagonists; mast cell inhibitors; T_H2 immunomodulators, such as TLR agonists and PGD2 antagonists; and antibodies, as well as drugs targeting other molecular targets. However, they all failed in late-stage trials. There are now only a few drugs in late-stage clinical development for AR, but they all face a strong barrier to market entry and a stiff competition, in particular, from an increasing number of OTC drugs. This is the reason for the low development activity in this space, which is exemplified by an extremely weak pipeline.

Japan represents one of the largest markets for AR therapies. Both of the products that are in late-stage development are being tested, primarily in the Japanese population. In addition, systemic tape formulations have become increasingly popular in Japan, and therefore, Hisamitsu Pharmaceutical is developing one such formulation, HP-3060. While the exact composition of the drug is unknown, its unusual method of application could add a novelty element to the treatment in a tired market.

Several novel antagonists of the PGD2 ligand, including those targeting the D prostanoid 1 (DP1) and CRTH2 (D prostanoid 2 [DP2]) receptors, have been studied in AR R&D. However, there is

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controversy regarding the effectiveness of this drug target, as several late-stage projects focusing on it were terminated early, including Boehringer Ingelheim's BI-671800 and Actelion's setipiprant. Nevertheless, Shionogi is developing a PGD2 receptor antagonist, S555739, which is the most promising therapy for AR patients in Phase III development in Japan.

The largest area of investigation is the development of immunotherapies. This is a pressing clinical unmet need in AR, as patients want a "cure" for the disease. This issue is discussed in detail in a related GlobalData report, OpportunityAnalyzer: Allergic Rhinitis: Allergen-Specific Immunotherapy – Opportunity Analysis and Forecast to 2018 (GlobalData, 2014).

"I don't think that any twiddling of [an] antihistamine, either oral or intranasal, is going to make a major difference to what happens. I think antihistamines alone are relatively ineffective in treating [the] symptoms [of AR]. You have to treat something like 15 patients before you make one better with allergic rhinitis, so I don't think doing that alone is going to make a big difference."

EU Key Opinion Leader, 2014

8.1 Promising Drugs in Clinical Development

Table 48 summarizes the promising compounds (excluding immunotherapies) in late-stage development for the treatment of AR. These drugs are included in GlobalData's 2014–2024 forecast.

Table 48: Late-Stage Pipeline for AR, 2014

Drug Name	Company	Therapy Class	Phase
S-555739	Shionogi	PGD2 receptor antagonist	Phase III
HP-3060	Hisamitsu Pharmaceutical	Systemic tape formulation (active ingredient not disclosed)	Phase III

Source: GlobalData, Pharma eTrack [Accessed January 20, 2015]

8.1.1 S-555739

8.1.1.1 Overview

Shionogi is developing S-555739, a PGD2 receptor antagonist for oral administration, in-house. PGD2 is a key mediator in the cyclooxygenase (COX) pathway, and is implicated in the pathophysiology of allergic diseases, such as AR and asthma. PGD2 is a prostanoid, postulated to be secreted from mast cells during allergen activation of FCεRIs. Higher sputum levels of PGD2 are associated with the more severe stages of asthma. In addition, a specific subtype PGD2-

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producing mast cells are found in the airway submucosa and epithelium of asthmatic patients. Two receptors activated by PGD2 are DP1 and DP2/CRTH2. S-555731 targets the DP1 receptor. Drugs from this class, including Merck and Co.'s laropiprant, and Shionogi's S-5751, failed to show any benefit in asthma and AR in clinical trials. The failure of both these compounds suggests that PGD2 activation of the DP1 receptor may not be involved in the pathogenesis of either AR or asthma. Furthermore, the DP1 receptor is thought to mediate multiple anti-inflammatory actions, as opposed to pro-inflammatory actions.

However, Shionogi, stated that, based on pharmacokinetic (PK) and pharmacodynamic (PD) studies, the failure of S-5751 in the Phase II trial was attributable to poor exposure of the compound to the target receptor, as opposed to a the hypothesis that PD_1 had a limited role in the pathogenesis of the disease. Therefore, the company continued studies in the reserve compound, S-555739, which had a distinctly superior PK profile and a stronger PD_1 antagonistic capability than its predecessor.

S-555739 is a first-in-class drug in development for the treatment of allergic diseases. It is in the proof-of mechanism (POM) stage in the 5EU, and in Phase IIa of development in the US, in addition to having completed Phase III of development in Japan for SAR and PAR.

Table 49 presents a product profile of S-555739.

Table 49: Product Profile – S-555739	
Molecule	S-555739
Therapeutic Class	PGD2 receptor antagonist (targeting the DP1 receptor)
Development stage	Phase IIa (US); POM (5EU); Phase III completed (Japan)
Anticipated Launch Date (Approval for AR)	2017 (Japan) 2018 (US)
Alternative Brand Names	N/A
Developer	Shionogi & Co., Ltd.
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	AR
Targeted Patient Pool (based on clinical trials	Adults with AR
Formulation and Dosing	Oral, once-daily
Treatment Cost	$562 (Japan)

Source: GlobalData

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8.1.1.2 Efficacy

In June 2012, Shionogi completed a Phase II, multicenter, double-blind, parallel-group, placebo- and active comparator-controlled clinical trial to evaluate the efficacy and safety of the combination of S-555739 and the AH, cetirizine hydrochloride, in 779 adult Japanese patients with SAR (Shionogi, NCT01651871). The study was designed to evaluate the drug (at both a high and a low dose) in combination with cetirizine hydrochloride (at a constant dose) in comparison with each drug delivered as a monotherapy and a placebo. The primary outcome measure was the change in the average morning/evening (AM/PM) rTNSS in addition to the incidence of adverse events. The secondary outcome measures included the change in the average AM/PM instantaneous total nasal symptom score (iTNSS), the change in average AM/PM total ocular symptom score, QoL, vital signs, other clinical laboratory parameters, and electrocardiogram (ECG) findings.

The company reported that combination therapy with S-555739 and cetirizine hydrochloride demonstrated a reproducible significant effect in the change from baseline in two of the coprimary endpoints — nasal symptoms of AR and QoL — compared with the AH alone (Shionogi, press release, June 14, 2012). However, clinical trial results reported in a sales call indicated that there was no significant difference between S-555739 in combination with the AH compared with the AH alone in the primary endpoint of rTNSS. Shionogi offered the explanation that there was a severe reduction in the pollen levels following the entry of patients into the trial, which affected the results. The company indicated that it intends to conduct the Phase III trial of S-555739 in patients with PAR (Q1 2013 conference call financial results, August 2, 2013).

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Table 50 lists the completed clinical trials conducted to evaluate the efficacy and safety of S-555739 in AR patients.

Table 50: Completed Clinical Trials of S-555739 in AR Patients

Trial ID	Trial Title	Phase	Date of Registration
JPRN-JapicCTI-132222	A multicenter double blind randomized controlled trial to investigate the efficacy of S-555739 in perennial allergic rhinitis	Phase III	13/2/2014
JPRN-JapicCTI-132046	Phase III Study of S-555739 in Patients with Seasonal Allergic Rhinitis	Phase III	13/2/2014
JPRN-JapicCTI-121981	Phase II Study of S-555739 in Patients with Japanese Cedar Polinosis in an Environmental Challenge Chamber	Phase II	10/10/2013
JPRN-JapicCTI-111698	Phase IIb Study of S-555739 in Patients with Seasonal Allergic Rhinitis	Phase IIb	2/11/2012
NCT01651871	Combination Study Of S-555739/Cetirizine HCl In Adult Patients With Seasonal Allergic Rhinitis	Phase II	17/7/2012
JPRN-JapicCTI-101361	Phase IIa Study of S-555739 in Patients with Seasonal Allergic Rhinitis	Phase IIa	10/8/2011
JPRN-JapicCTI-090875	Phase IIa Study of S-555739 in Patients with Perennial Allergic Rhinitis	Phase IIa	12/7/2010
EUCTR2008-006787-11-GB	A randomized, double blind, placebo-controlled, 2-period cross over study to evaluate effects of S-555739 on prostaglandin D2 (PGD2) induced nasal airway resistance in healthy adult volunteers	Phase I	20/1/2009
EUCTR2008-006788-35-FR	A randomised, double-blind, placebo-controlled, 2-period crossover study to evaluate effects of multiple oral doses of S-555739 on nasal allergen challenge in subjects with intermittent grass pollen sensitive allergic rhinitis.	Phase I	14/11/2008

Source: GlobalData

In February 2013, Shionogi registered two new Phase III trials of S-555739 for the treatment of SAR and PAR in Japan, and a Phase IIa study in the US. The Japanese trial was registered with the JAPIC Clinical Trials Information.

8.1.1.3 Safety

The company stated that S-555739 demonstrated good tolerability in Phase II trials evaluating the drug in combination with the AH cetirizine hydrochloride.

8.1.1.4 Dosing and Formulation

Based on the completed Phase III clinical trials, S-555739 will be administered as a tablet, once daily. The once-daily administration represents an improvement over the current gold-standard treatment with INCS, which are dosed twice-daily by inhalation.

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8.1.1.5 Potential Commercial Positioning

Shionogi is one of the top leaders in the Japanese prescription drug market, and focuses on three therapeutic areas: infectious diseases, pain, and metabolic syndrome. Although the company does not have any products in the respiratory space, it has abundant resources for the marketing and commercialization of S555739, which has a large target patient pool. Clinical trials are evaluating the drug in adults and adolescents 16 years of age and older. The commercial attributes of the drug are enhanced by the fact that it is undergoing clinical development across the US, Europe, and Japan. Shionogi is in a strong position to successfully market this first-to-the-market, once-daily PGD2 therapy for AR globally. The drug will likely have a faster uptake in Japan, due the historical trend of Japanese consumers having a preference for domestic brands.

Shionogi is also attempting to enter the respiratory market in Japan through a collaboration with the AIT manufacturer, Stallergenes, which entered into an exclusive partnership with Shionogi on September 6, 2010. The agreement covers the clinical development, registration, marketing, and sales of two SLIT tablets from the Stalair program: the prevalent Japanese allergens, HDM (in Japan and Taiwan) and Japanese cedar pollen (in Japan). Shionogi submitted an NDA to the Japanese authorities in April 2014 for the AIT HDM tablet, which empowers the company with a promising commercial stance with respect to its PGD2 drug candidate.

8.1.1.6 Potential Clinical Positioning

S-555739, Shionogi's novel, first-in-class DP1 PGD2 receptor antagonist therapy for AR, will target both SAR and PAR patients 16 years of age and older. Phase II clinical trials investigated the use of S-555739 in combination with the second-generation AH, cetirizine hydrochloride. However, the Phase III trials tested S-555739 as a monotherapy.

There are no products commercially available in the markets covered in this report with the same mechanism of action as S-555739. However, in the Japanese market, a TXA2/PGD2 receptor antagonist, ramatroban , has been marketed for patients with AR under the trade name Baynas by Nippon Shinyaku Co. Ltd. since May 2000. In Japan, Baynas is used for patients with moderate-to-severe PAR with nasal blockage, as an optional treatment for use in combination with nasal steroids. Unlike S555739, which targets the DP1 PGD2 receptor, Baynas targets the PD_2/CRTH2 PGD2 receptor. Although DP1 and CRTH2 share a common ligand, PGD2, they are structurally unrelated and have distinct signaling pathways. Through their complementary activities, they both contribute to the development and maintenance of allergic inflammation.

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S-555739's once-daily regimen would offer an improvement over the currently marketed product, Baynas, which is dosed twice daily and must be taken with meals. GlobalData expects that if S-555739 is approved as a monotherapy (that is, not for use in combination with an AH), then it will only steal a small market share from the other therapies. Should S555739 be approved in Japan, it is anticipated to directly compete with Baynas for patient share in the treatment of AR (which accounts for approximately 10% of the prescription-treated AR population). Sales of Baynas were approximately $25m in 2006.

S-555739's once-daily regimen would offer an improvement over the currently marketed product, Baynas, which is dosed twice daily and must be taken with meals.

8.1.1.7 SWOT Analysis

Table 51 provides a SWOT analysis of S-555739.

Table 51: S-555739 SWOT Analysis, 2014

Strengths	Has a novel mechanism of action; if approved, will be the first drug in its class.
	Seeking approval for both SAR and PAR.
	Once-daily oral formulation
	Developed by Shionogi, which has significant brand power in Japan.
Weaknesses	Being evaluated only in adults.
	There is skepticism among KOLs about the efficacy of a DP1 PGD2 receptor antagonist, given the failure of other molecules in this drug class during clinical evaluation.
	Many competing products in the treatment of AR (including generics)
	If S-555739 competes with Baynas alone, it will only take a portion of a small patient share of the AR market.
	If the efficacy of S555739 is similar to Baynas (for patients with a blocked nose, as per the recommendation of Japanese guidelines), it will be used as a third-line therapy after AHs and INCS.
Opportunities	In addition to being developed in Japan, the drug is being evaluated in the US, and is set to be evaluated in the EU, where it is currently in the preclinical stage.
Threats	Uncertain efficacy; mechanism of action has yet to be fully elucidated.
	Increasing generic entries in the Japanese and US markets may increase the difficulty of new drugs obtaining AR market share.

Source: GlobalData

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8.1.1.8 Forecast

Table 52 presents the global sales forecasts for S-555739 from 2014–2024.

Table 52: Global Sales Forecasts ($) for S-555739, 2014–2024

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014–2024) (%)
US	–	–	–	55.4	111.4	140.2	141.1	147.6	160.0	172.5	172.5	N/A
France	–	–	–	–	–	–	–	–	–	–	–	N/A
Germany	–	–	–	–	–	–	–	–	–	–	–	N/A
Italy	–	–	–	–	–	–	–	–	–	–	–	N/A
Spain	–	–	–	–	–	–	–	–	–	–	–	N/A
UK	–	–	–	–	–	–	–	–	–	–	–	N/A
Japan	–	–	–	49.7	74.1	98.2	97.5	109.0	113.1	114.8	114.8	N/A
Total	–	–	–	**105.1**	**185.5**	**238.4**	**238.6**	**256.7**	**273.1**	**287.3**	**287.3**	**N/A**

Source: GlobalData
CAGR = Compound Annual Growth Rate

8.1.2 HP-3060

8.1.2.1 Overview

Hisamitsu Pharmaceutical has developed HP-3060, a systemic transdermal tape formulation that uses its proprietary TDDS (Transdermal Drug Delivery System) technology. HP-3060 represents a novel option for treatment of AR. Hisamitsu is the top maker of transdermal antiphlogistic and analgesic agents in Japan. The demand for transdermal delivery of pharmacological drugs in a patch formulation is increasing, and therefore, there is a trend among drug manufacturers to develop such formulations for a variety of diseases, as they are expected to improve patient compliance with treatment.

Hisamitsu markets Allegra, which was the top-selling prescription AH in Japan, and later became a very successful OTC product after making the switch in November in 2012. Therefore, the company has a strong reputation in the respiratory space.

Hisamitsu has yet to release any information regarding the active pharmaceutical drug incorporated into the TDDS. However, the company did disclose that it is a reformulation of a currently marketed drug. Clinical studies have demonstrated that HP-3060 is capable of maintaining a stable blood drug concentration, resulting in long-lasting treatment effects. HP-3060 was evaluated in Phase II

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clinical trials against a placebo control. Hisamitsu reported that, following successful Phase II trial results, it intends to begin a Phase III trial in 2015 in Japan, with an anticipated approval in Japan in 2017.

Table 53 presents a product profile of HP-3060.

Table 53: Product Profile – HP-3060	
Molecule	Active pharmaceutical Ingredient (API) not revealed.
Therapeutic Class	Transdermal delivery system for the treatment of AR
Development stage	Phase III (Japan)
Anticipated Launch Date (Approval for AR)	2017 (Japan)
Alternative Brand Names	N/A
Developer	Hisamitsu Pharmaceutical Co., Inc.
Marketing Partner	N/A
Targeted Indication (Based on Clinical Trials)	AR
Targeted Patient Pool (Based on Clinical Trials	Adult patients with AR
Formulation and Dosing	Transdermal patch
Treatment Cost	

Source: GlobalData

8.1.2.2 Efficacy

Hisamitsu conducted a randomized, parallel-group, double-blind, placebo-controlled, multiple-dose, Phase I/II study of HP-3060 in patients with PAR in Japan. The trial (Japan trial code, JapicCTI-132187), which was designed to study the PKs, efficacy, and safety of repeated-dose administration of HP-3060 compared with placebo, was initiated in July 2013, and included patients with a history of AR for two years or more, with a positive result from serum-specific IgE testing.

The company reported that HP-3060 met its primary efficacy endpoint, with a statistically significant improvement in symptoms compared with the placebo control, in addition to maintaining a stable blood drug concentration.

In May 2014, Hisamitsu announced the results of the Phase I/II clinical study of HP-3060. The company reported that HP-3060 met its primary efficacy endpoint, with a statistically significant improvement in symptoms compared with the placebo control, in addition to maintaining a stable blood drug concentration. Hisamitsu stated that, based on the results of the Phase I/II study, it will commence a Phase III trial in the second half of 2015. In addition to verifying the efficacy of HP-3060 in a Phase III clinical study, Hisamitsu will confirm its stability and efficacy in long-term administration (Hisamitsu Pharmaceutical Co., press release, May 7, 2014).

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8.1.2.3 Safety

Hisamitsu stated there were no serious adverse reactions observed during the Phase I/II study of HP-3060 (Hisamitsu Pharmaceutical Co., press release, May 7, 2014).

8.1.2.4 Dosing and Formulation

Based on the completed Phase I/II clinical trial, HP-3060 will be administered by a transdermal patch delivery system. However, the frequency with which the patch must be applied has not been disclosed publically. Should HP-3060 be approved in Japan, this will represent a novel delivery system for AR treatments.

8.1.2.5 Potential Commercial Positioning

Hisamitsu is an established player in the AR market, in collaboration with the Sanofi subsidiary, Sanofi-aventis KK (SaKK). The two companies market the leading OTC allergy product in Japan, the AH Allegra FX (fexofenadine hydrochloride), with a 51%/49% split in share, respectively. Prior to the product's switch to OTC in 2012, it was the top-selling prescription allergy medication in Japan, and was typically prescribed at a 60mg dose, as compared with 180mg, which is the most common dose prescribed the US and 5EU. Therefore, Hisamitsu has abundant resources for HP-3060's development and commercialization in Japan. Currently, its clinical development is limited to Japan. Hisamitsu will likely attempt to leverage the novelty of the delivery mechanism of this therapy in marketing it for AR. The company will likely have to price HP-3060 relatively low to make it a desirable option for both payers and physicians, as the AR market is highly genericized and crowded, consisting of inexpensive products. This is further impacted by the National Health Insurance (NHI) drug price revision.

Hisamitsu acquired US-based Noven Pharmaceuticals in 2009, creating a US marketing and distribution arm, should it wish to develop HP-3060 for the US market. To develop and commercialize HP-3060 in Europe, Hisamitsu would need to partner with a company with a presence in this market.

8.1.2.6 Potential Clinical Positioning

Based on the limited information released about HP-3060, it is evident that the drug is intended to treat adult patients with AR. GlobalData predicts that, given the novelty of this treatment, in conjunction with the increasing popularity of transdermal delivery systems in Japan, it will be popular among a small population of patients. However, in Japan, transdermal delivery systems

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are typically used to deliver pain and anti-inflammatory medications to elderly patients who have trouble swallowing tablets and/or to increase adherence to medication, as they allow the caregiver to easily determine whether the patient has received the recommended dose. However, wearing a patch, as opposed to taking a once-daily tablet (as for most drugs used to treat AR), would be undesirable for most adult AR patients, unless the patch is shown to demonstrate superior efficacy. While transdermal patches are becoming increasingly popular in Japan for the aging population, AR is a condition that mainly affects children and young adults. Also, for children with AR, there is already a wealth of orodispersible tablets or flavored syrups available.

In addition, as there are many therapies for AR that have saturated the market, Hisamitsu will have to show that its drug has a substantial level of differentiation and superiority in reducing AR symptoms in order to penetrate this narrow patient niche in the AR market.

Finally, it is unlikely that the drug contained within HP-3060 is a corticosteroid, because systemic bioavailability would be undesirable in AR. In addition, it is unlikely to be a reformulation of an intranasal drug, such as an INCS, as the benefit of these drugs is that they act topically to reduce symptoms at the source. Therefore, this treatment is likely to contain an alternative formulation of an existing tablet drug, such as an AH or an LRA.

8.1.2.7 SWOT Analysis

Table 54 provides a SWOT analysis of HP-3060.

Table 54: HP-3060 SWOT Analysis, 2014

Strengths	Can help increase patient compliance with treatment.
	As a novel formulation for AR treatment, has first-in-class status.
	Would likely be more popular if it made were available by prescription, which means it would potentially be cheaper than OTC products, such as Allegra FX.
Weaknesses	Is currently only being developed for adults in Japan; the patients who are most likely to prefer this option are small children who cannot easily swallow tablets.
	Many patients would prefer a once-daily tablet, as opposed to a patch.
Opportunities	Patients may prefer HP-3060 if clinical trials can demonstrate its superior efficacy as compared with oral formulations.
	Hisamitsu is the only company developing this novel drug formulation.
	Sustained-release tape formulations are an increasingly popular trend in Japan.
Threats	The company is focusing only on the Japanese market, which is in a recession and under increased pressure to decrease healthcare expenditures through the NHI drug price revision.

Source: GlobalData

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8.1.2.8 Forecast

Table 55 presents the global sales forecasts for HP-3060 from 2014–2024.

Table 55: Global Sales Forecasts ($) for HP-3060, 2014–2024

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014–2024) (%)
US	–	–	–	–	–	–	–	–	–	–	–	N/A
France	–	–	–	–	–	–	–	–	–	–	–	N/A
Germany	–	–	–	–	–	–	–	–	–	–	–	N/A
Italy	–	–	–	–	–	–	–	–	–	–	–	N/A
Spain	–	–	–	–	–	–	–	–	–	–	–	N/A
UK	–	–	–	–	–	–	–	–	–	–	–	N/A
Japan	–	–	–	74.7	74.3	73.8	97.8	97.2	96.5	95.9	95.9	N/A
Total	**–**	**–**	**–**	**74.7**	**74.3**	**73.8**	**97.8**	**97.2**	**96.5**	**95.9**	**95.9**	**N/A**

Source: GlobalData
CAGR = Compound Annual Growth Rate

9 Current and Future Players

9.1 Overview

Historically, the AR market has been very large, with several companies launching drugs that gained blockbuster status. In particular, Merck & Co. has had a very strong presence, leading the AR market with its franchises, Nasonex, Singulair, and Clarinex (desloratidine). Other players defining the AR market include GSK, Sanofi, and Teva. However, over the past decade, almost all the key drugs for the treatment of AR symptoms have lost patent protection, including Sanofi's Allegra, Pfizer/UCB Pharma's Zyrtec, and two of Merck's blockbuster drugs, Singulair and Nasonex. As a result, AR, which was once a blockbuster-status therapy area, is now highly saturated and genericized, with companies seeing large declines in the sales of their respiratory portfolios due to generic erosion.

In an attempt to retain a revenue stream from branded generics, companies have sought a successful strategy to convert their AR prescription drugs to OTC status, known as the Rx-to-OTC switch, transferring these products to their respective consumer care units. The most recent examples of this are the FDA's approval of OTC status for Sanofi's Nasacort Allergy 24HR (triamcinolone intranasal) and GSK's Flonase, the first INCS to be available OTC in the US. Recently, there has been a trend for large pharmaceutical companies to divest their consumer healthcare units in order to focus their sales efforts on key products. For example, Merck sold its consumer unit to Bayer for $14.2 billion in 2014. On the other hand, GSK combined its consumer health business with that of Novartis' to create one of the world's largest consumer divisions. The joint venture, which was completed in March 2015, includes GSK's Flonase/Pirinase (fluticasone propionate). Teva and Proctor & Gamble (P&G) formed a joint consumer healthcare venture in 2011 to strengthen both businesses and expand their OTC offerings into additional markets. In 2006, J&J acquired Pfizer Consumer Healthcare for $16.6 billion, including the US OTC rights to Zyrtec.

There is an extremely sparse pipeline for new AR treatments. With the exception of Merck, which partnered with the European company, ALK, to bring tablet AITs to the North American markets, there are no current players with drugs in development for AR, and there are no clear future players over the 10-year forecast period.

There is an extremely sparse pipeline for new AR treatments.

Current and Future Players

GlobalData expects large pharmaceutical companies with a previously strong foothold in the AR market, such as GSK, to become increasingly less focused on AR drugs. While these major players are still investing in R&D for respiratory indications, it is for asthma and COPD, rather than AR.

Table 56 lists the major companies in the AR market and their portfolios.

Table 56: Major Companies in the AR Market and Their Portfolios, 2014

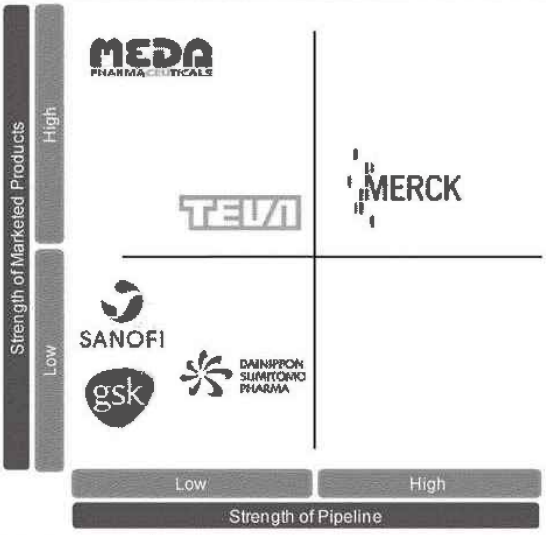
Company/Partner	Brand (Molecule)	Strategic Importance	Highest Phase	Launch Date	Patent Expiry
Merck & Co.	Nasonex	Medium	Marketed	1997	Expired (use/formulation) 2018 (formulation)
Merck & Co.	Singulair	Low	Marketed	1998	Expired
Merck & Co.	Clarinex	Low	Marketed	2001	Expired
Merck & Co.	Claritin	Low	Marketed	1993	Expired
Merck & Co.	MK-7243 (Grastek)	Low	Marketed	2006 (EU) 2014 (US)	–
Merck & Co.	MK-3641 (Ragwitek)	Low	Marketed (US)	2014	–
GSK	Avamys/Veramyst (fluticasone furoate)	Low	Marketed	2007	2021 (US) 2023 (EU)
GSK	Xyzal (levocetirizine dihydrochloride)	Low	Marketed	2007	Expired
GSK	Flixonase/Flonase (fluticasone propionate)	Low	Marketed	1994	Expired
AstraZeneca	Rhinocort (budenoside)	Low	Marketed	1994	Expired
Sanofi	Allegra (fexofenadine hydrochloride)	Low	Marketed	1996	Expired
Teva	Qnasl (nasal beclomethasone dipropionate)	High	Marketed	2012	–
UCB/Pfizer	Zyrtec	Low	Marketed	1996	Expired

Source: GlobalData; AstraZeneca, 2014; GSK, 2014; Merck & Co., 2014; Sanofi, 2014; Teva, press release, March 26, 2012

Current and Future Players

Figure 8 provides an analysis of the company portfolio gap in AR during the forecast period.

Figure 8: Company Portfolio Gap Analysis in AR, 2014–2024



Source: GlobalData

9.2 Trends in Corporate Strategy

Companies in the AR space have been undertaking various strategies to overcome the inevitable generic erosion, and to prolong the lifecycle of their products. Merck, Sanofi, and UCB, with their leading prescription AHs (Claritin, Allegra, and Zyrtec, respectively) have all previously developed reformulations, for example, by combining AH and decongestant products (Claritin D [loratadine and pseudoephedrine hydrochloride], Allegra D [fexofenadine hydrochloride and pseudoephedrine hydrochloride], and Zyrtec D [cetirizine hydrochloride and pseudoephedrine hydrochloride]). Formulating novel FDCs to provide consumers with added convenience is a strategy that many companies use as part of the lifecycle management of their drugs in order to extend their patent life and gain increased market presence. However, all of the line extensions seem to have come to the end of their exclusivity, and as a result, AR is becoming a truly genericized space.

Merck's blockbuster drug, Singulair, has suffered massive generic erosion since its patent expiry in 2012. In addition, generic erosion of Nasonex is expected soon, although it is not expected to be

aggressive, since it is more difficult to replicate nasal inhalers than oral drugs. Nasonex's formulation patent is valid until 2018, and Merck is trying to fight off many patent challenges. Nevertheless, generic versions are soon expected, as drug manufacturers, such as Teva and Apotex, are attempting to launch generics in the US prior to the end of the patent protection for the Nasonex formulation (Nasonex generics were introduced into the European market in 2014). Due to the patent expiry of these leading products, GlobalData expects Merck to lose its leading role in the AR space. As the AR market becomes fully-genericized, and given that all the historically important players in this space hardly have any promising drugs in development for this disease (not accounting for immunotherapies, which are described in GlobalData's report: OpportunityAnalyzer: Allergic Rhinitis: Allergen-Specific Immunotherapy – Opportunity Analysis and Forecast to 2018 [GlobalData, 2014]), the future AR players will be defined only by their marketing forces and efforts in DTC advertising. Switching INCS drugs from prescription to OTC status is another strategy that is particularly evident in the US market. In addition, some companies with branded products in the AR space are decreasing the prices of their products to the extent that they become cheaper than the generic versions. As a result of this approach, several INCS drugs have been resilient to generic erosion (for example, Rhinocort Aqua and Nasofan in the UK).

Several novel therapies that are in late-stage development, including S555739, HP-3060, and WF10, will have difficulty penetrating this highly genericized market.

9.3 Major Companies

9.3.1 Merck & Co.

9.3.1.1 Overview

Merck & Co. (Merck Sharp & Dohme outside the US and Canada) was founded in 1891 as the US subsidiary of the German company that is now known as Merck KGaA. The company was taken over by the US government during World War I, and subsequently became independent. The company's overall portfolio includes human healthcare and pharmaceutical products encompassing dozens of therapeutic areas. Merck's AR portfolio includes several marketed products: Nasonex, an INCS for the treatment of nasal allergy symptoms; Singulair, which is indicated for the chronic treatment of asthma and the relief of the symptoms of AR; and two AITs. Merck also manufactures Clarinex, one of the leading AHs.

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As part of the divestiture of Merck's consumer unit in 2014, Bayer acquired the OTC allergy products Afrin, Chlor-Trimeton (chlorpheniramine), and Claritin. In addition to these products, Bayer acquired the rights to Claritin and Afrin in the international markets, where they are available only by prescription, representing approximately $200m in sales in 2013.

Worldwide sales of Singulair for both asthma and AR reached their peak in 2011, when they stood at $5.5 billion, making Singulair Merck's best-selling drug at the time. However, these sales significantly declined to $3.85 billion in 2012, following the drug's patent expiry in August of that year. In 2013, Singulair suffered massive generic erosion, and its sales declined to $1.2 billion, driven primarily by lower sales in the US and Europe. Merck lost nearly all sales of Singulair in the US, where they dropped to a negligible $60m. The market exclusivity for Singulair expired in a number of major European markets in February 2013, and will expire in Japan in 2016. Merck applied for OTC status for Singulair for adults age 18 years and older with hay fever and other respiratory allergies. However, in May 2014, the FDA expert committee voted against (11 to 4) even limited OTC use of the allergy medication. The committee commented that the safety of Singulair as an OTC treatment had not been established, and there was also a concern regarding its off-label use for more serious conditions, such as asthma.

Merck's next best-selling AR product, Nasonex, achieved a slight growth in sales, from $1.27 billion in 2012 to $1.33 billion in 2013. However, the drug's sales declined year-on-year in 2014, generating $1.01 billion. Nasonex was approved by the FDA in December 2004, and is protected by a US formulation patent that expires in 2018. However, Apotex challenged the patent in an attempt to introduce a generic version of Nasonex. Following a district court decision, a court of appeals found that Apotex's application does not infringe upon Merck's formulation patent. At this point, Merck has exhausted all its appeal options for Nasonex. Therefore, should Apotex's application to the FDA be approved, it is likely that a generic version of Nasonex will be launched immediately in the US. This will significantly impact the US INCS market, as Nasonex was the best-selling branded prescription INCS in 2014 by a considerable margin, and the last drug with blockbuster status in the AR space.

In 2014, Teva submitted an ANDA with a Paragraph IV Certification to introduce a generic version of Nasonex, before its patent expiry. Merck sued Teva in July 2014, alleging that Teva's plans to manufacture a generic version of Nasonex were infringing on Merck's patent on the drug. The lawsuit automatically delayed the FDA approval of Teva's application until November 2016, unless a district court intervenes.

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Nasonex lost patent protection in most European markets on January 1, 2014, and generic versions have since been launched in these markets. Merck stated that it anticipates rapid and strong generic erosion of Nasonex revenues from these markets.

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One novel mode of action being investigated by Merck and ALK-Abello is in the area of SLIT. A grass pollen immunotherapy vaccine, Grastek has been approved in Europe since 2006, and in February 2014, was launched in the US, together with another immunotherapy, Ragwitek (ragweed). ALK has formed strategic alliances to ensure its global access to the allergy immunotherapy markets by entering into licensing partnerships to develop, register, and commercialize AITs with Merck in North America. The partnership with Merck covers the development, registration, and commercialization of a portfolio of AITs against grass pollen, ragweed, and HDM allergies in the US, Canada, and Mexico. ALK maintains responsibility for the production and supply of the tablets. As part of the licensing deal with Merck, ALK will receive $40m in addition to the $55m in development milestone payments that it has already received. The deal also includes undisclosed royalties and $190m in sales milestones.

Merck successfully submitted Biologics License Applications (BLAs) to the FDA for Grastek, known as Grazax in Europe (where it is already approved in several markets), and Ragwitek, which contains Timothy grass and short ragweed (*Ambrosia artemisiifolia*) allergens. Both tablets were approved in April 2014, representing an important advance in the US allergy immunotherapy market. The expansion of the US market to include orally-administered SIT is an important step forward for the US, where the allergy immunotherapy market is currently dominated by SCIT — "shot" treatments that are prepared by specialists for individual patients.

ALK is currently conducting the Phase III GAP (Grazax Asthma Prevention) clinical trial to determine whether Grazax has the potential to reduce the development of asthma in children age 5–12 years suffering from AR, and to ascertain if this effect is sustained for two years after the completion of treatment. The five-year trial is due to complete in September 2015 (Valovirta, 2011).

An agreement between Merck and ALK for the co-promotion of Grazax in France has enhanced ALK's access to the second-largest SIT market globally. Grazax is in direct competition with Oralair for patients with grass allergen-induced AR in the US, where both tablets were launched in Q2 2014. Both tablets were launched after the pre-seasonal initiation date required for them to maximize their 2014 sales. Although no head-to-head clinical trials have been conducted, Oralair has a shorter treatment duration of around six to eight months, depending on the location and

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season, and contains five subtypes of grass pollen, whereas Grazax is taken throughout the year and contains a single grass extract.

Ragwitek is approved only for patients age 18–65 years, which is a significant weakness of the drug, as children and adolescents are a key patient population that ALK needs to target with tablet immunotherapy. This younger patient pool is likely to benefit from the early treatment of symptoms, and these patients also dislike SC formulations. In addition to the grass and ragweed immunotherapy tablets, Merck is also developing a tablet formulation against the perennial allergen, HDMs, and GlobalData estimates that it could be launched during 2016.

As shown in Table 57, Merck has a relatively important product portfolio of marketed drugs in AR. However, the sales of all Merck's AR drugs have been rapidly decreasing. With the Singulair and Nasonex era coming to an end, GlobalData expects Merck to be increasingly less focused on respiratory diseases in general, and to lose its leading role in the AR space. This expectation is based on the fact that Merck has no pipeline products in this therapeutic area. Despite having divested its consumer unit, Merck has had to make significant cutbacks owing to the loss of revenue from these key products. On a more positive note, sales of AIT are expected to be high, filling a significant clinical unmet need for a convenient, patient-friendly, causative therapy. However, this treatment is also associated with drawbacks, including the length of therapy, high price, and debatable efficacy in real-world patients.

Table 57: Merck's AR Portfolio Assessment, 2014

Brand	Strategic Importance	Partner	Highest Development Phase	Launch Date	Patent Expiry
Nasonex	Medium	N/A	Marketed	1997	2014 (use/formulation) 2018 (formulation)
Singulair	Low	N/A	Marketed	1998	Expired
Clarinex	Low	N/A	Marketed	2001	Expired
MK-7243 (Grastek)	Medium	ALK	Marketed	2014 (US)	–
MK-3641 (Ragwitek)	Medium	ALK	Marketed (US)	2014 (US)	–
MK-8237 (HDM)	Medium	ALK	Phase III	2016 (US, estimated)	–

Source: GlobalData; Merck & Co., 2014

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9.3.2 GlaxoSmithKline

9.3.2.1 Overview

GlaxoSmithKline (GSK) is a British multinational company, and one of the largest pharmaceutical companies in the world. It was formed in 2000 by a merger between two companies: Glaxo Welcome and SmithKline Beecham. The company produces medicines across multiple therapeutic areas, including respiratory and heart diseases, oncology, diabetes, and human immunodeficiency virus (HIV). GSK currently has the world's most successful respiratory drug franchise. However, owing to a number of patent expiries across its portfolio, GSK's global respiratory product sales are in considerable decline, having fallen 10% in 2014, compared with 2013. The company's new asthma medications, which are currently in the pre-registration phase, are promising; however, there are no products in development for AR. GSK also has a range of oral AHs and INCS, which are mainly generic, but are widely used. In 2014, GSK received approval for one of its oral AHs, Xyzal (levocetirizine dihydrochloride), for the treatment of AR; however, the patent for the drug expired in 2013.

GSK currently has one patented drug for AR: Avamys/Veramyst. The drug was approved in the US and EU in 2007 for the treatment of the symptoms of AR, and has patent protection until 2021 and 2023 in the US and EU, respectively. However, Sandoz challenged the patents for Veramyst, and submitted an ANDA with a Paragraph IV Certification in November 2011. Although GSK subsequently initiated a lawsuit against Sandoz, the two companies reached a settlement that allowed Sandoz to enter the US market with a generic competitor in Q3 2016 or earlier, under certain circumstances.

GSK launched Xyzal in Japan in December 2010. It was the first new AH in this market in eight years, and is approved for AR and a number of allergic conditions in adults and children age seven years and older. Xyzal is an improved follow-on product of the successful Zyrtec, which was developed by the Belgian pharmaceutical company, UCB. GSK obtained the development and marketing rights to Xyzal in Japan from UCB. GSK received an eight-year re-examination period for Xyzal in Japan (term for carrying out post-marketing examination to ensure efficacy and safety of the drug; no marketing application for generic drugs is allowed during this term). According to GSK's 2014 annual report, sales of Xyzal are currently being generated almost exclusively from the Japanese market, totaling $188m ($214m in global sales) in 2014, an 8% increase over its 2013 sales in Japan.

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GSK's Flonase/Flixonase, containing fluticasone propionate, was approved in 1994 in the US, and was a highly successful blockbuster, with peak sales of $1.3 billion prior to the entry of multiple generic formulations in February 2006. Flonase continued to be sold by prescription in the US until the FDA granted GSK approval to switch the drug from prescription to OTC status in July 2014. The OTC version was launched in pharmacies in early 2015, closely following the first OTC INCS in the US, Sanofi's Nasacort, which was launched in 2014. Fluticasone propionate is the most commonly prescribed allergy medication. Flonase OTC, which will be sold under the company's new umbrella consumer care unit in partnership with Novartis, has the potential to be very successful in the US. GSK is investing in an aggressive DTC advertising campaign highlighting the benefits of Flonase to the consumer. However, the company's claims, including one stating that Flonase outperforms the "No. 1 allergy pill," and controls six allergy symptoms, while the leading pill controls only one symptom, have been disputed by rival allergy drug manufacturer, J&J. In fact, J&J (whose McNeil consumer health unit sells Zyrtec and Benadryl [diphenhydramine]) sued GSK, seeking an injunction to stop the advertising, asserting that the company was attempting to steal its market share, without any scientific support for its claims.

As shown in Table 58, GSK has a relatively important portfolio of marketed drugs in AR. Xyzal will face decreasing revenues following generic penetration. Similarly, the imminent entry of a Veramyst generic from Sandoz will mean that GSK will no longer have any branded products in the AR space. The lack of products in development for AR will decrease GSK's position in the AR space relative to that of generic manufacturers. GSK will likely maintain significant revenue from OTC sales of Flonase in the US, prior to the inevitable generic competition in the OTC space.

Table 58: GSK's AR Portfolio Assessment, 2014

Brand	Strategic Importance	Partner	Highest Development Phase	Launch Date	Patent Expiry
Avamys/Veramyst (fluticasone furoate)	Low	N/A	Marketed	2007	2021 (US) 2023 (EU)
Xyzal (levocetirizine dihydrochloride)	Low	UCB	Marketed	2007	2013
Flixonase/Flonase (fluticasone propionate)	Low	N/A	Marketed	1994	Expired

Source: GlobalData; GSK, 2014

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9.3.3 Sumitomo Dainippon Pharma

9.3.3.1 Overview

Sumitomo Dainippon Pharma Co., Ltd. (Sumitomo Dainippon Pharma) is headquartered in Chuo-ku, Osaka, Japan. The company develops and manufactures a range a pharmaceutical products across many therapy areas, including CNS, cardiovascular, diabetes, cancer, and infectious diseases. Sumitomo Dainippon Pharma operates through its subsidiaries, as well as several branches and distribution centers, which are located both in Japan and overseas. The company offers its products across Japan, North America, China, and other regions. It reported revenues of JPY387,693m ($3,876.93m) for the fiscal year ended March 2014, an increase of 11.5% over FY2013.

Sumitomo Dainippon Pharma sells two key allergy products under license from Takeda, Omnaris and Zetonna, both of which contain ciclesonide as an active ingredient. In January 2008, Sunovion and Nycomed entered into an exclusive development, marketing, and commercialization agreement for ciclesonide in the US for $5.6 billion. Following this agreement, Sunovion launched Omnaris in the US in April 2008. As part of the agreement, Sunovion obtained the development rights to several extension products, including a Phase III candidate of an MDI formulation of ciclesonide, which is now marketed as Zetonna. Currently, the ciclesonide franchise is the fifth highest revenue stream for Sunovion. In 2010, Dainippon Sumitomo acquired Sunovion (formerly known as Sepracor), which then became its wholly-owned US subsidiary (Dainippon Sumitomo, 2011).

In May 2011, Takeda acquired the Zurich-headquartered Nycomed (excluding the US dermatology business) for $13.4 billion. Omnaris and Zetonna are marketed in the US by Sunovion, and by Takeda in the Canadian, Brazilian, Australian, and Mexican markets (Handok Inc. markets the two products in South Korea). Neither of these products is approved in the EU or Japan.

Due to a manufacturing defect that caused an interruption in the supply of Omnaris at the end of 2011, the drug experienced a significant decrease in US sales in FY2012 to $24m, compared with $65m in FY2011.

Omnaris is an aqueous formulation of ciclesonide, and was approved in the US in 2006. Omnaris is an inhaled corticosteroid (ICS) indicated in the treatment of SAR in adults and children age six years and older, and for the treatment of PAR in adults and adolescents age 12 years and older. Due to a manufacturing defect that caused an interruption in the supply of Omnaris at the end of 2011, the drug experienced a significant decrease in US sales in FY2012 to $24m, compared with $65m in FY2011. Following the manufacturing setback, and the cannibalization of Omnaris' sales by the launch of Zetonna, the first-in-class dry INCS, in the US in July 2012, US sales of Omnaris

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in FY2013 were even lower, at $25.62m. This indicates that Zetonna is competing directly with Omnaris for patient share, as opposed to increasing the overall size of the INCS market.

Zetonna was the first non-aqueous nasal aerosol spray for AR, and is administered once daily as one spray per nostril. Sales of Zetonna were $5m in FY2012, and $23.18m in FY2013. The ciclesonide franchise in the US (which includes, Alvesco, Omnaris, and Zetonna) has achieved positive year-on-year growth in the US, generating $67m in FY2012 and $81m in FY2013, and is on course to generate $68m in FY2014 (based on Sumitomo Dainippon Pharma's Q3 2014 filings).

Both Omnaris and Zetonna had US marketing exclusivity until January 20, 2015. There are six US patents protecting Omnaris, which are due to expire in October 24, 2017. Apotex submitted an ANDA with an accompanying Paragraph IV Certification on August 2, 2012 to manufacture a generic version of Omnaris. Nycomed fought the application on the grounds of patent infringement.

Seven US patents protect Zetonna, with expiration dates ranging from November 2014 to August 2027. Its composition of matter patent expires on October 24, 2017. If Omnaris and Zetonna both lose patent protection in 2017 (generics are already in development), then, in line with the other products in this drug class, they stand to undergo strong generic erosion.

Despite the launch of Zetonna, sales for the ciclesonide franchise have been lackluster, and it has failed to capture significant patient share in the INCS AR market in the US. The uptake of Zetonna has been particularly slow, and failed to meet the expectations set at launch, despite the fact that the drug shows multi-symptom nasal allergy improvement. This demonstrates the extremely hostile conditions faced by a new entrant in the AR space.

As shown in Table 59, Sumitomo Dainippon Pharma has two marketed drugs for AR.

Table 59: Sumitomo Dainippon Pharma's AR Portfolio Assessment, 2014

Brand	Strategic Importance	Partner	Highest Development Phase	Launch Date	Patent Expiry
Omnaris (ciclesonide)	Low	N/A	Marketed	2006	2017
Zetonna (ciclesonide)	Low	N/A	Marketed	2012	2017

Source: GlobalData; AstraZeneca, 2014

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9.3.4 Sanofi

9.3.4.1 Overview

Sanofi is a global biopharmaceutical company headquartered in Paris, France. Sanofi's complex history can be traced as far back as the 18th century. The modern Sanofi is a result of several key mergers and acquisitions (M&As). In 1999, Sanofi and Synthélabo merged to form Sanofi-Synthélabo, which then acquired Aventis in 2004 to form Sanofi-Aventis. In 2011, Sanofi-Aventis simplified its name to Sanofi. The company's strategic vision is based on seven growth platforms: diabetes, vaccines, consumer health products, the emerging markets, innovative drug design, animal health, and the sustained growth of Genzyme, which Sanofi acquired in 2011 (Sanofi, press release, February 16, 2011). Among these strategic priorities, the first two, diabetes and vaccines, have comprised a key component of Sanofi's recent history, and will continue to do so in the foreseeable future. In 2013, Sanofi's best-selling drug was the diabetes therapy, Lantus (insulin glargine), which posted global sales of $7.59 billion.

Historically, Sanofi has marketed some of the leading drugs in the global AR market in terms of revenue share. Its AR products include Allegra, Xyzal, Nasacort, and Nasacort AQ, as well as Allegra-D 12Hour and Allegra-D 24Hour (fexofenadine hydrochloride and pseudoephedrine hydrochloride ER formulation).

Allegra, a non-sedating AH, is one of the world's best-selling AHs in terms of both sales and units, and is available in over 80 countries worldwide. It was approved by the FDA in 1996 for adults and children age two years and older with AR. Allegra reached annual peak sales of $1.87 billion in 2004. The patent for Allegra expired in 2005, generics were launched, and Sanofi entered into an agreement with Prasco Pharmaceuticals to launch an authorized generic, which, in December 2006, accounted for 40% of its total prescription sales (the Allegra brand had 5% of the market). On January 5, 2011, the FDA approved Allegra for OTC use, at which time it was the highest-prescribed AH in the US, and Sanofi's generic version was launched on March 4, 2011. Global sales of Allegra, which is indicated for both SAR and urticaria, were $522m in 2013 (excluding OTC sales), and came predominantly from non-US and European markets. Allegra has suffered substantial generic erosion in both the US and European markets.

Allegra was launched in Japan in 2000, and was the best-selling AH in the country prior to its patent expiry and the launch of competing authorized generics, which entered the market in 2013. It was also launched in the Japanese OTC market in November 2012, but remains available by

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prescription. In May 2010, Sanofi and Nichi-Iko Pharmaceutical established a joint venture company in Japan, called sanofi-aventis Nichi-Iko K.K., which was given permission to exclusively produce and market Sanik, the authorized generic version of Allegra, on April 16, 2013. The approval was awarded by the Ministry of Health, Labour and Welfare (MHLW) on February 15, 2013, ahead of the launch of competitors to generic Allegra. This is the first authorized generic version of Allegra, and is aimed at limiting the impact of generic erosion. It is rumored that the relationship between the two companies became strained as a result of a problem with the marketing strategy for generic Allegra, which lagged behind the non-authorized generic competitors in reaching the market. Sanofi also launched a dry syrup formulation of Allegra in Japan on January 19, 2015, which is indicated for AR, urticaria, and itching associated with dermatological diseases (eczema, dermatitis, dermal pruritus, and atopic dermatitis) in infants and children age six months and older. The formulation is available in a strawberry flavor to ease administration in pediatric patients. Due to a supply chain problem with the manufacturing contractor (the Italian drug maker, Aptalis), the launch of the drug was delayed, despite its having been on the NHI price list in April 2014. Since its launch, Sanofi's generic Allegra has achieved a 40% market share among the Allegra generics.

In the US, Allegra transitioned to OTC status in 2011, and is indicated for use in adults and children age two years and older. It was also launched in the Japanese OTC market in November 2012, but remains available by prescription in this market. Allegra is the top-selling AH in Japan, while Xyzal is vying for third place.

Sanofi also markets Allegra-D 24 Hour ER, which consists of an FDC of Allegra and a decongestant, for effective, non-drowsy relief of seasonal allergy symptoms. Sanofi launched the once-daily Allegra-D 24 in July 2005. It is marketed in the US (but not in the EU or Japan), where it has been available OTC since 2011, along with the entire Allegra franchise (both adult and pediatric formulations) in Sanofi's consumer care unit, which is a wholly-owned subsidiary of US-based Chattem. In 2013, Sanofi was the third largest player in the consumer healthcare market, with 3.1% of the global OTC market.

Xyzal is owned by UCB, and is widely marketed in multiple countries, including in the 7MM. Xyzal was approved in the US in October 2007, where it is co-marketed by Sanofi. In Japan, Xyzal is marketed by GSK. Xyzal generated revenues of $7.7m in 2012 and $7.7m in the US in 2013. The FDA received an ANDA containing a Paragraph IV Certification for Xyzal from Synthon in December 2007. As Xyzal is only protected by new product exclusivity, as opposed to new

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chemical entity exclusivity, the patent was expected to be challenged readily. However, in April 2008, UCB and its partner, Sepracor, sued Synthon for alleged patent infringement. Ultimately, Synthon's ANDA was approved, with 180 days of generic exclusivity awarded by the FDA in November 2010.

Nasacort Allergy 24HR was initially approved as a prescription-only product in the US in 1996. Nasacort Allergy 24HR was launched OTC in the US in February 2014, becoming the first drug in its class (INCS) to be available as an OTC nasal spray, and is indicated for SAR and PAR in adults and in children age two years and older. Nasacort AQ is also available in the US, having been approved in 1996 for adults and adolescents age 12 years and older. The label was extended twice, first in 1997 to include children age 6–11 years, and again in 2008 to include children age 2–5 years. Nasacort, which was approved in 1991, has been discontinued. Teva launched a Nasacort generic in June 2011, following extensive litigation with Sanofi. Peak annual sales of Nasacort were $402m in 2007. The company is hoping to regain its sales for this drug, which, in 2012, generated just under $100m in global sales.

Sanofi has four marketed drugs for AR, as listed in Table 60. With the exception of Xyzal, which is now available generically, all of Sanofi's products have all transitioned to OTC status. Sanofi does not have any respiratory-based products in its late-stage development pipeline. GlobalData expects Sanofi's hold on the AR space to become increasingly weaker in the coming years.

Table 60: Sanofi's AR Portfolio Assessment, 2014

Brand	Strategic Importance	Partner	Highest Development Phase	Launch Date	Patent Expiry
Allegra/Telfast (fexofenadine)	Low	Chattem	Marketed	1996	Expired
Xyzal (levocetirizine dihydrochloride)	Low	UCB	Marketed	2008	Expired
Nasacort (triamcinolone acetonide)	Low	Chattem	Marketed	1996	Expired
Allegra D 12H/24H (fexofenadine hydrochloride and pseudoephedrine hydrochloride ER)	Low	Chattem	Marketed	2005	Expired

Source: GlobalData; Sanofi, 2014

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9.3.5 Teva

9.3.5.1 Overview

Teva Pharmaceutical Industries is an international company specializing in generic and proprietary pharmaceuticals, and is the largest generic drug manufacturer in the world. The company is committed to become a leading player in the respiratory market by delivering a range of medicines for asthma, COPD, and AR. Teva has broad experience in the development, manufacturing, and marketing of inhaled respiratory drugs.

Teva's respiratory medicines brought in revenues of $905m in 2013, an increase of 6% from $856m in 2012. The increase was primarily due to higher revenues from its asthma drugs (QVAR [beclomethasone dipropionate HFA] and ProAir [albuterol sulfate]), as well as its AR drug, Qnasl, a dry-mist nasal HFA aerosol formulation of beclomethasone dipropionate that is indicated for both SAR and PAR. Qnasl 80mcg was approved by the FDA in March 2012. In December 2014, Teva announced that the FDA had approved Qnasl 40mcg for AR in children age 4–11 years. The 40 mcg strength was launched in the US in February 2015, and is also available only by prescription. Qnasl is protected by several US patents covering the active ingredient and device, with expiry dates of February 2014 to January 2027, respectively. Market exclusivity for the 80mcg strength expired in March 2015, while the new 40mcg strength is covered until December 2017. The US is the only market in which Qnasl is approved.

Qnasl has poor market share and competes directly with Zetonna, both of which have failed to meet analysts' expectations.

A primary area of Teva's focus in the respiratory space is the development of products that are based on the company's proprietary delivery systems. Qnasl has poor market share and competes directly with Zetonna, both of which have failed to meet analysts' expectations. Similar to Sumitomo Dainippon Pharma, Teva has experienced difficulties in launching a new product in the AR space, despite improving what was deemed to be a significant limitation of an existing therapy.

Teva has one marketed drug for AR, which is listed in Table 61.

Table 61: Teva's AR Portfolio Assessment, 2014

Brand	Strategic Importance	Partner	Highest Development Phase	Launch Date	Patent Expiry
Qnasl (nasal beclomethasone dipropionate)	High	N/A	Marketed	2012	2014–2017

Source: GlobalData; Teva, 2015

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9.3.6 Meda AB

9.3.6.1 Overview

Meda AB (Meda) is a Swedish international specialty pharmaceutical company that was established in 1995. Meda develops, manufactures, and markets specialty pharmaceutical products, OTC drugs, branded generics, and other products in various therapy areas. Meda Pharmaceuticals, the branded pharmaceuticals division of Meda US, covers a variety of therapeutic areas, including cardiac conditions, pain and inflammation, CNS diseases, gastroenterological conditions, and respiratory and dermatological conditions, with focus on respiratory and dermatological diseases. The company has operations in over 60 countries and sells its products in more than 120 countries. Meda has stated its intention to form long-term partnerships, and to proceed with the acquisition of other companies and product rights in order to grow into a leading global specialty pharmaceutical company, in addition to capitalizing in rapidly expanding markets.

Meda markets multiple products for respiratory indications, including two drugs that are indicated for AR: Dymista and Astepro. It also markets the COPD and/or asthma drugs, Formatris Novolizer (formoterol), Novopulmon Novolizer (budesonide), and Aerospan (flunisolide). The company reported revenues of $2,011m (SEK13,114m) in FY2013, an increase of 0.9% over FY2012 (Meda, 2013). The company reported revenues of $495m (SEK 3,356m) for the third quarter ended September 2014, a decrease of 51% over the previous quarter.

Meda does not conduct any in-house, early-stage pharmaceutical development. Instead, the company expands its product portfolio via the acquisition of companies and product rights, as well as through partnerships with other pharmaceutical companies. Meda's key acquisitions include the purchase of 3M Co.'s European business in 2006, MedPointe in 2007, and Valeant's pharmaceutical business in Western and Eastern Europe in 2008. Through its acquisition of 3M Co.'s European business for $857m, Meda strengthened its position in the European markets and also acquired products in the cardiovascular and dermatology/oncology therapy areas. The acquisition of the MedPointe for $520m strengthened Meda's focus in the allergy area, and provided a substantial opportunity to expand its product portfolio; it also established Meda in the US. In addition, Meda obtained MedPointe's allergy franchise, including the market-leading AH products, Astelin and Optivar, which both contain the active ingredient azelastine. As a result of Meda's acquisition of US-based Valeant's pharmaceutical business in Western and Eastern Europe for $392m, the company acquired many products in the neurology and dermatology

therapy areas, in accordance with the company's product portfolio. This deal also allowed Meda to enter the Russian market, and to strengthen its position in the UK and Eastern Europe. In addition, Meda and Valeant entered into a joint venture for Meda to seek approval and commercialize its products in Canada, Mexico, and Australia. However, Valeant's divestiture excluded a number of central European countries, including Poland, the Czech Republic, Hungary, and Slovakia. Meda also acquired the US development company, Acton Pharmaceuticals, for $135m, including the asthma product, Aerospan, thereby expanding its respiratory portfolio.

In 2006, Meda and the Indian pharmaceutical company, Cipla, entered into an agreement regarding Dymista in the US market. Cipla retained the responsibility for the product's formulation, while Meda is responsible for its clinical development, registration, marketing, and sales. In 2009, the agreement was expanded, whereby Cipla granted Meda the global commercialization rights to Dymista, which included more than 120 markets and expanded coverage in the emerging markets of Latin and South America, the Middle East, Africa, and Asia. Cipla retained rights to some undisclosed markets (Meda, 2013).

Astelin, an intranasal AH, was approved in 1996 and launched in the US in 1997. Its patent expired in 2011. Astepro/Rhinolast (azelastine hydrochloride) is an improved version of Astelin, with a better efficacy and tolerability profile and a faster onset of action. Astepro, which is a lifecycle management product, received US approval in 2008, and European approval in 2012. The FDA awarded an additional approval for a more powerful version of Astepro in 2009. Annual sales of Astepro are approximately $97m. The US patent for Astepro was awarded to Meda AB by the US Patent and Trademark Office (USPTO) in 2012, and is valid until 2028. On January 23, 2012, Meda Pharmaceuticals sued the generic drug makers, Perrigo and Apotex, accusing them of infringing on a US patent for Astepro (Anon n.d.). Meda brought an additional lawsuit against Perrigo and Impax Laboratories in February 2014, alleging infringement of Astepro's patent. However, Perrigo received final approval from the FDA on its ANDA for azelastine hydrochloride nasal spray on May 14, 2014, and will share certain costs and benefits of this product with Impax.

Dymista nasal spray is a first-in-class combination AH and corticosteroid. It is currently the only such combination marketed. It is approved in the US as a treatment for SAR, and in the EU for both SAR and PAR. The drug was launched in September 2012 and 2013 in the US and EU, respectively. In addition, Meda intends to launch Dymista in the emerging markets in 2015. Within the lucrative prescription INCS market, Dymista has made significant gains, showing steady growth in most markets where it was launched, and was Meda's top-selling brand in Q4 2014. US FY2014

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sales of Dymista were $81.29m, up 30% from $62.89m in FY2013. Meda has the exclusive licenses to US patents 8,163,723 and 8,168,620, which cover the Dymista composition and its approved uses, respectively, and expire in 2026.

Meda and Cipla filed a lawsuit against Apotex on December 3, 2014 to defend the Dymista patents following Apotex's submission of an ANDA and accompanying Paragraph IV Certification, seeking approval to market a generic version of Dymista prior to the expiration of its patents. The defendants filed the suit within 45 days of receiving Apotex's Paragraph IV Certification notice, thus triggering an automatic stay preventing the FDA from approving Apotex's ANDA for 30 months from receipt of the notice, unless ordered otherwise by a district court (Anon n.d.). Should Apotex be successful in launching a generic version of Dymista before the original patent expiries, this will have a substantial impact on Dymista's sales and Meda's annual revenue. The price of Dymista relative to the cost of its inexpensive generic INCS and oral AH components is high. This has been problematic in cost-conscious markets, such as the UK and France, where reimbursement rulings have limited drug uptake. Thus, GlobalData estimates that any generic competitor to Dymista will have a significant impact on the market and will be very successful.

Meda has two marketed drugs for AR, which are described in Table 62.

Table 62: Meda's AR Portfolio Assessment, 2014

Brand	Strategic Importance	Partner	Highest Development Phase	Launch Date	Patent Expiry
Dymista (azelastine hydrochloride/fluticasone propionate)	High	Cipla	Marketed	2012	2023
Astepro/Rhinolast (azelastine hydrochloride)	Low	N/A	Marketed	2012	2028

Source: GlobalData; Meda; 2014

10 Market Outlook

10.1 Global Markets

10.1.1 Forecast

This report focuses on the 7MM (US, France, Germany, Italy, Spain, UK, and Japan). These seven markets are collectively referred to as the global markets. The global prescription AR market was valued at around $7.2 billion in 2014, the base year of the forecast period. At 38% of the overall AR market, the US is clearly the dominant market, totaling $2.8 billion in 2014. This is mainly due to the much higher prices of AR medications in the US, and the lack of OTC INCS in this market. For example, the average annual cost of Nasonex in the US is over $650, while the same therapy in Europe costs around $40. In the US, branded, HFA-propelled, dry-mist devices, including Qnasl and Zetonna, are also available, unlike in the other markets. In the EU and Japan, the OTC INCS market is extensive. As INCS are the recommended first-line therapy by the ARIA guidelines for persistent and moderate to severe AR patients, the FDA's recent granting of OTC status for these drugs is generally expected to shrink the size of the patient population that is seeking and utilizing prescription INCS, as well as other prescription AR therapies.

As INCS are the recommended first-line therapy by the ARIA guidelines for persistent and moderate to severe AR patients, the FDA's recent granting of OTC status for these drugs is generally expected to shrink the size of the patient population that is seeking and utilizing prescription INCS, as well as other prescription AR therapies.

The next-largest individual AR market was Japan, at 26% of the global AR market in 2014, totaling $1.9 billion. This is mainly due to the larger patient population and the somewhat higher cost of AR treatment in Japan than in Europe. The 5EU countries together made up 35% of the global AR market in 2014.

INCS are the leading drug class in terms of market value, and currently capture almost half of the total AR market. However, their market share will shrink to 30% as SITs enter the market over the forecast period and start dominating this space, growing from 14% to 26% of the total AR sales. The uptake of these novel drugs will be a major driver of AR market growth, and will offset the dip in sales caused by the recent Singulair patent expiry, as well as the patent expiry of numerous AH and INCS products by 2017. Over the forecast period, the global AR market will grow to $7.27 billion, at a Compound Annual Growth Rate (CAGR) of 0.1%. The US market will shrink marginally, at a CAGR of 0.1%, due to the surge in generic and OTC competition. In 2024, the US will represent 38% of the total AR market, stealing a small portion of market share from all the other countries.

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The best-selling INCS, Merck's Nasonex, is the market leader in the entire AR space, with $915m in 2014 sales coming from the AR indication alone in the 7MM. Nasonex lost patent protection in Europe, and generics began entering the market in 2014. There was also an attempt by Apotex to introduce a generic version of Nasonex in the US market prior to its patent expiry. Despite an unsuccessful lawsuit brought by Merck against Apotex, the two companies reached an agreement, whereby a generic version of Nasonex can enter the US market, which GlobalData expects will occur in the US in 2015. GlobalData also expects Nasonex generics to enter the Japanese market in the latter half of 2015. Therefore, Nasonex will slowly but surely lose its dominant position in global AR market, shrinking at a negative CAGR of 32.80%, and achieving sales of $17.2m in 2024. The numerous product patent expiries will bring down the cost of INCS therapy, and the INCS market will become increasingly diluted with generic options. In addition to the surge of INCS generics, product Rx-to-OTC switches in the US will lead to an increased number of patients seeking OTC remedies.

GlobalData believes that generic versions of AHs, INCS, anticholinergics, and LRAs, together with the novel immunotherapy formulations that mark the new era of a causative approach to treating severe AR, will dominate the AR market in 2024.

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Table 63 presents the global sales forecasts for AR products from 2014–2024.

Table 63: Global Sales Forecasts ($m) for AR, 2014–2024

Year	2014	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2023	2024	CAGR (2014–2024) (%)
Oral H1Ahs	1261.0	1262.1	1263.6	1264.3	1264.4	1264.2	1263.9	1263.4	1262.7	1261.8	1263.4	-0.0%
Intranasal H1Ahs	621.7	416.7	409.7	410.9	403.4	387.4	379.7	380.5	381.3	373.3	374.3	-0.0%
INCS	3293.3	2807.1	2736.1	2378.9	2299.9	2281.9	2265.3	2259.6	2227.8	2218.5	2215.9	-0.0%
Erizas capsule	141.6	141.0	140.5	139.8	138.9	138.1	137.2	136.3	135.4	134.5	133.6	0.0
Nasacort	11.1	11.1	11.1	5.6	1.1	0.6	0.6	0.6	0.6	0.6	0.6	-0.3
Nasacort, generic	0.0	0.0	0.0	3.0	6.1	6.1	6.1	6.1	6.1	6.2	6.2	
Nasonex	915.3	411.0	388.7	87.5	31.4	20.1	20.1	20.1	20.1	17.2	17.2	-0.3
Nasonex, generic	8.5	225.9	239.2	274.5	281.1	307.3	316.9	320.0	320.2	320.3	320.6	
Omnaris	22.2	14.9	13.9	7.5	5.0	2.5	2.6	2.6	2.6	1.3	1.3	-0.2
Omnaris, generic	0.0	0.0	0.0	1.5	2.2	2.5	2.5	2.4	2.4	2.3	2.3	
Qnasl	45.8	48.0	50.2	52.5	54.7	57.0	59.4	61.7	64.1	66.6	66.9	0.0
Veramyst (Avamys/ Allermist)	200.4	195.3	180.4	163.6	150.3	148.9	141.6	139.1	138.8	138.4	138.4	0.0
Veramyst, generic	0.0	0.0	9.4	9.5	9.5	9.6	9.6	9.7	9.8	9.8	9.9	
Zetonna	24.6	29.7	37.4	10.0	9.1	8.6	8.2	7.7	8.3	8.8	8.9	-0.1
Zetonna, generic	0.0	0.0	0.0	7.8	8.6	9.0	9.4	9.7	10.4	11.5	12.7	
Anticholinergic drugs	80.3	72.5	72.9	73.3	73.6	74.0	74.4	74.8	75.1	75.5	70.4	0.0
Decongestants	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8	0.0
Mast cell stabilizers (cromones)	1.8	1.8	1.8	1.8	1.8	1.8	1.7	1.7	1.7	1.7	1.7	0.0
TAX2 antagonists (Baynas)	83.0	82.7	82.4	82.0	74.1	66.3	65.8	58.2	57.8	57.4	57.1	0.0
T_H2 cytokine inhibitors (IPD®)	22.1	22.0	22.0	21.9	21.7	21.6	21.5	21.3	21.2	21.0	20.9	0.0
LRAs (all markets)	681.2	687.3	670.0	586.1	591.1	596.1	595.4	595.7	595.8	601.4	602.5	0.0
Singulair	223.4	222.4	175.0	4.6	3.5	2.3	1.1	1.1	0.9	0.8	0.6	-0.4
Montelukast	0.0	0.0	28.5	113.6	118.6	123.4	122.5	121.9	121.1	125.7	125.2	

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sodium												
Generic pranlukast	76.7	76.4	76.1	75.7	75.3	74.8	74.3	73.8	73.4	72.9	72.6	0.0
Dymista	113.4	169.9	209.7	232.3	233.1	255.8	262.7	291.7	314.4	337.0	360.5	0.1
SITs	1,020.5	1,087.2	1,248.4	1,345.6	1,463.8	1,622.8	1,667.6	1,743.2	1,798.4	1,862.8	1,912.1	0.1
SI-555739	0.0	0.0	0.0	105.1	185.5	238.4	238.6	256.7	273.1	287.3	287.7	
HP-3060	0.0	0.0	0.0	74.7	74.3	73.8	97.8	97.2	96.5	95.9	95.5	
Total	**7,181.3**	**6,612.4**	**6,719.6**	**6,579.9**	**6,689.9**	**6,887.1**	**6,937.4**	**7,047.0**	**7,109.0**	**7,196.7**	**7,265.3**	**0.1**

Source: GlobalData

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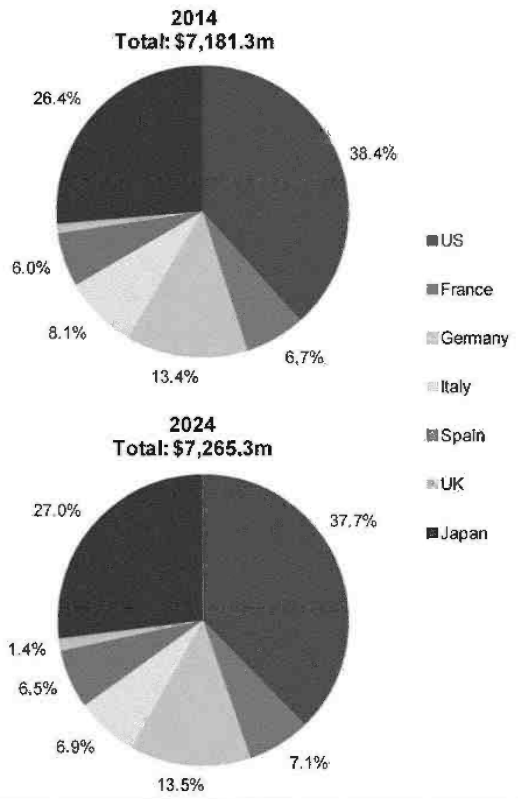
Figure 9 illustrates the global sales for AR by region during the forecast period.

Figure 9: Global Sales for AR by Region, 2014–2024



Source: GlobalData

10.1.2 Drivers and Barriers – Global Issues

Table 64 presents the drivers and barriers in the global AR market during the forecast period.

Table 64: Global AR Market – Drivers and Barriers, 2014–2024

Drivers	Barriers
Rising Pollen Counts and Extended Pollen Seasons, in Tandem with Global Warming, Will Increase the Severity and Prevalence of AR Globally	The leading brands for AR treatment are facing generic erosion.
Restricted Healthcare Spending in Europe Has Incentivized Partnerships to Deliver AITs to the US and Japanese Markets	Increasing pressures for cost-effectiveness will limit the pricing of new products, and in some cases, prevent their reimbursement.
The uptake of novel causative therapy options will temper AR market decline due to generic erosion	Variable weather patterns, and hence pollen counts, have thwarted the efforts of drug manufacturers developing new treatments for AR. The introduction of controversial environmental exposure chambers has not been a successful substitute for conventional AR clinical trials, and many drugs have failed late-stage clinical development, owing to abnormal pollen counts at the time of the trial.
	An increasing push for patients to self-medicate using OTC drugs will decrease the prescription AR drug market size.

Source: GlobalData

10.1.2.1 Driver: Rising Pollen Counts and Extended Pollen Seasons, in Tandem with Global Warming, Will Increase the Severity and Prevalence of AR Globally

The prevalence of allergic diseases worldwide is rising dramatically in both developed and developing countries. These diseases currently affect between 10% and 30% of the global population. Studies indicate that the prevalence rates of allergies are increasing worldwide. According to the European Academy of Allergy and Clinical Immunology (EAACI), 50% of Europeans will suffer from an allergy by 2027 (Papadopoulos et al., 2012).

Global climate change is evidenced by an increasing average earth temperature, increasing anthropogenic greenhouse gas levels, and elevated pollen levels. Pollutants of interest include carbon dioxide (CO_2), ozone (O_3), and nitrous oxide (NO_2), because they can enhance the allergic response and lead to increased symptoms of allergic respiratory diseases. Heightened CO_2 levels stimulated pollen production via photosynthesis and increased growth in multiple plant species investigated (Lin and Zacharek, 2012). Allergen patterns are also changing in response to climate change, and air pollution can modify the allergenic potential of poliens, especially under specific weather conditions.

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The prevalence of asthma and allergic diseases has increased dramatically during the past few decades (D'Amato et al., 2013). This is evidenced by the change in the prevalence of AR in the US population, from 10% in 1970 to 30% in 2000. It has been postulated that the changing environment, particularly the trend of global warming, may lead to increased pollen exposure and expanded environments for the growth of numerous plant species. An increase in the growing season, with earlier flowering and possible increased airborne pollen counts, could be the consequences of the increasing average earth temperature.

Ragweed, a plant previously native to South and North America, is a leading and increasingly common cause of AR. In the recent National Health and Nutrition Examination Survey III (NHANES III) (1988–1994), 26.2% of the US population was sensitized to ragweed, the third most common allergen after HDMs (27.5%) and perennial rye grass (26.9%). This prevalence increased from 10% of the US population in NHANES II (1976–1980). Ragweed is also a major allergen in Canada. In a series of 3,371 atopic patients, Boulet and colleagues discovered that 44.9% were sensitized to ragweed. Ragweed has expanded and is now becoming an increasingly common species globally. It is particularly problematic in Europe, where it is thought to have been introduced as a result of importing raw plant materials.

Pollen seasons are set to last longer and to become increasingly more intense. If pollen seasons are going to overlap more frequently, the severity of symptoms experienced by polysensitized patients is set to increase.

Japanese pollen counts have grown five-fold over the past three decades, with the primary culprits being the afforestation policy that was started to provide a steady supply of domestic lumber, and global warming. In addition, particle-laden smog, known as PM2.5, comes from the Gobi Desert, where the yellow dust picks up dirt and pollen from China and carries it over to South Korea and Japan. Increasing pollution from this region is contributing to the AR problem in Japan.

10.1.2.2 Driver: Restricted Healthcare Spending in Europe Has Incentivized Partnerships to Deliver AITs to the US and Japanese Markets

The global economic downturn in 2008, and the ensuing slow recovery, has negatively impacted European healthcare expenditures. As a result of the mandatory austerity measures imposed in the EU, there has been a perceptible decline in the allergen extract market, which accounts for a substantial proportion of the worldwide immunotherapy market. Over the forecast period, tempered growth is expected in the immunotherapy market in Europe. ALK-Abello and Stallergenes, the

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global market leaders in AIT, have begun to explore new underserved markets. By partnering with companies in the US and Japan — ALK with Merck and Torii, and Stallergenes with Greer and Shionogi — both companies are aiming to expand and deliver their AIT portfolios outside Europe. The US is a large market that is currently underserved in terms of AIT, with SC allergen extracts being the only FDA-licensed therapy available in 2013. The Japanese immunotherapy market is currently non-existent. Despite having a large population with AR, fewer than 6,000 patients in Japan were treated with SIT in 2013. Cedartolen, a sublingual liquid containing the standardized Japanese cedar pollen allergen, was evaluated in randomized controlled trials and was subsequently approved in 2014. As a condition of its approval, prescribing physicians must undergo an online training course. This will increase physician awareness of novel developments in AITs, an unmet need in this field. The approval of SITs with clinically-proven efficacy will bolster the credibility of this therapy type in Japan, which saw a rapid decline in previous decades due to the advent of more convenient symptomatic therapies with a rapid onset of action. Within the 10-year forecast period, three tablet formulations of Japanese cedar pollen and HDM will be launched in Japan. Torii has been the sole player in this market since SIT became available in Japan in the 1960s. However, Shionogi, in partnership with Stallergenes, is set to enter the SIT market in Japan. Shionogi's brand power and extensive marketing base in Japan will put the company in a strong position in this field. In view of these developments, the extremely small SIT-treated population in Japan is set to increase by 10-fold during the forecast period.

10.1.2.3 The uptake of novel causative therapy options will temper AR market decline due to generic erosion

One of the few remaining unmet needs in the AR market is for a causative therapy that is capable of providing long-term relief of symptoms. The allergen-specific immunotherapy (SIT) market is the clinical development of a new generation of tablet formulations, moving away from the standard SCIT injections and sublingual immunotherapy (SLIT) drops. Tablet formulations that have been evaluated according to a standardized stepwise algorithm in dose-finding studies and double-blind, placebo-controlled efficacy trials have gained marketing authorization (MA) via the traditional routes. These products will continue to add legitimacy to immunotherapy as an important treatment option for patients with AR. ALK-Abello and Stallergenes will lead the way by introducing their relevant allergens in tablet form into the Japanese and US markets through licensing partners. Japan, a market previously not widely treated with SIT, is set to see a new range of standardized, clinically-evaluated products containing the two most prevalent allergens: HDM and Japanese

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cedar pollen. These treatment options will include AIT formulations that were previously unavailable in the market. Advancements in SIT, particularly the advent of tablet formulations, will increase the use of immunotherapy among the pediatric population. The introduction of AITs will drive growth in the AR market, due to their high cost relative to the standard subcutaneous (SC) allergen extracts, thereby decreasing the negative impact of the growing genericized market.

10.1.2.4 Barrier: The Leading Brands for AR Treatment are Facing Generic Erosion

All of the AR blockbuster drugs are facing generic erosion over the forecast period. Singulair lost its marketing exclusivity in 2012 in the US market, and in the European markets in 2013, and further sales losses are expected as Singulair generics enter the Japanese market in 2016. The generic erosion of last blockbuster in the AR space, Nasonex, is also imminent. Despite the fact that there are several drugs within the INCS class with patent protection, numerous generic manufacturers have fought and won the right to launch early generic versions of these branded drugs prior to their patent expiries. Overall, the main therapies for AR will face significant decreases in sales during the forecast period, which will slow the growth of the global AR market.

10.1.2.5 Barrier: Increasing Pressures for Cost-Effectiveness

Across the major markets, there is a trend where pharmaceutical companies are required to prove the cost-effectiveness of their products prior to being granted reimbursement authority approval. In the US, the free-pricing of pharmaceuticals is still common. However, in the 5EU and Japan, drugs must be priced in line with the reimbursement authorities' expectations in order to be covered by the national health insurance plans. In many cases, the national pricing watchdogs must deem drugs as being cost-effective in order for them to be reimbursed. Pipeline products entering the global market will have to show a clear added benefit and competitive advantage in order to ensure a successful launch. In addition, austerity measures in the EU, and the Affordable Care Act (ACA) in the US, will force third-party payers to shift to generics in order to cover the increased need for AR drugs.

10.1.2.6 Barrier: Variable Weather Patterns Hamper New Drug Development

Clinical trials evaluating novel AR treatments are complicated by several factors, including variable allergy testing methods and pollen counts, as well as variations in the timing and intensity of exposure to seasonal allergens. In addition, patients can be allergic to various allergens, and be exposed to various geographic regions and varying pollen levels, with potential exposure to numerous allergens and pollutants. In addition, there is a changeable weather pattern, which

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further complicates the assessment of immunotherapies, as the treatment must be initiated prior to the onset of the pollen season. Therefore, subjects are enrolled into trials of AR treatments based on their symptoms during the previous pollen season, which may vary over consecutive years and pollen seasons.

Variable weather patterns, and hence pollen counts, have thwarted the efforts of drug manufacturers that are developing new treatments for AR. This includes Nuvo Research's WF10, which failed to demonstrate a statistically significant reduction in nasal symptoms in a repeat Phase II trial. The company reported that the cold and wet allergy season in Germany during the trial could have potentially reduced the nasal symptoms for all patients, thereby impacting the difference in symptoms between the investigational and placebo arms. ALK's grass immunotherapy tablet also failed to show significant improvements in the symptom scores when assessed in a repeat trial following three successful trials with identical study designs. The company offered a number of possible explanations for this failure, including high pre-seasonal symptom levels and the lack of a relationship between the pollen count and the symptom score in the presence of a significant immunological response, suggesting that the reported symptoms were not principally attributable to grass pollen exposure (Murphy et al., 2013).

Environmental exposure chambers are used to achieve controlled pollen counts, and have been used to assess several AR drugs, including AHs, such as Allegra and Claritin. However, the use of this method has been criticized, as it does not reflect the "real-world" experience of AR patients. Further validation will be required before it gains acceptance by the European Medicines Agency (EMA) and the FDA as a sufficient method for assessing AR drug efficacy and safety. This will affect the launch of new AR candidates, and could discourage drug companies from pursuing the development of pipeline candidates in this space.

10.1.2.7 An increasing push for patients to self-medicate using OTC drugs will decrease the prescription AR drug market size.

In an attempt to retain a revenue stream from branded generics, companies have sought a successful strategy to convert their AR prescription drugs to OTC status, known as the Rx-to-OTC switch, transferring these products to their respective consumer care units. The most recent examples of this are the Food and Drug Administration's (FDA's) approval of OTC status for Sanofi's Nasacort Allergy 24HR (triamcinolone intranasal) and GSK's Flonase (fluticasone propionate), the first INCS to be available OTC in the US. This is set to have a large impact on the

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prescription drug treatment rate, as patients are incentivized to self-diagnose and self-medicate using the growing number of OTC options. Direct-to-consumer (DTC) advertising, increased co-payments on prescription AR drugs, and stretched healthcare resources, as well as the increasingly competitive cost of OTC-equivalent options, will all further the progressively increasing trend for AR patients to seek treatment independently.

10.2 United States

10.2.1 Forecast

In 2014, the base year of the forecast period, AR sales in the US were around $2.8 billion. GlobalData anticipates that these numbers will shrink through 2024 (not accounting for inflation) to $2.7 billion. As in the global markets, this decrease will be fueled mainly by the patent expiries of numerous INCS, and the launch of the first OTC INCS in US pharmacies. Despite the fact that the prevalence of AR patients is set to increase over the forecast period, only one drug will be launched during this time, which is expected to face stiff competition upon entry and capture little market share. The approval of novel immunotherapy options, including tablet formulations and AIT products with ultra-short courses of SC injections, is expected to bolster the US AR market, dampening the effect of the eroding symptomatic prescription drug market. Although the target patient pool for these immunotherapies will be relatively limited, as they will target only specific subpopulations of severe AR patients who have exhausted all other treatment options, they will fulfill some of the major unmet needs for the treatment of patients with severe AR who do not respond to conventional treatment with INCS and AH therapies. The high cost of these immunotherapies and the expected necessity of their use in certain patient subpopulations will make up for their lack of a large patient share, and they will all reach high sales figures by 2024.

The approval of novel immunotherapy options, including tablet formulations and AIT products with ultra-short courses of SC injections, is expected to bolster the US AR market, dampening the effect of the eroding symptomatic prescription drug market.

Merck's Nasonex, an INCS, is the market leader of the US AR space, with sales of $686m in 2014 from the AR indication alone. However, Nasonex will lose its dominant position in the US market during the forecast period, and its sales will shrink at a negative CAGR of 35.4% to $8.8m by 2024. The second best-selling AR therapy drug class in the US is intranasal AHs, which include Meda Pharmaceuticals' Astepro and Alcon's Patanase, with combined sales of $429m in 2014. Astepro's US formulation patent is due to expire in 2028. However, some companies, such as Perrigo, have already developed generic versions of the drug. After extensive litigation, Perrigo's azelastine hydrochloride nasal spray received FDA approval in May 2014. In addition, Apotex's AB-rated generic version of Alcon's Patanase was approved by the FDA in October 2014. The generic

entrants into this market are set to decrease the annual cost of this therapy considerably, and will negatively affect the sales of intranasal AHs in the coming years, bringing them down to $184m in 2024. In addition, the approval of Meda's first-in-class Dymista, which contains Astepro's active ingredient, azelastine, in combination with an INCS, will compete for market share with the intranasal AHs.

The INCS are, by far, the largest AR drug class, with sales of $1.6 billion in 2014. Regarding the INCS space, the significant number of patent expiries and the launch of a new class of combination INCS and intranasal AHs is set to impact the market considerably, reducing the average ACOT and decreasing the patient share for this drug class. However, the greatest major change is the entry of OTC INCS following the Rx-to-OTC transition of Nasacort and Flonase in 2014 and 2015, respectively.

Premature generic entry into the INCS space is common. For example, the patent for AstraZeneca's Rhinocort Aqua expires in 2017. However, a generic version of the drug manufactured by Apotex entered the market in May 2014. Furthermore, Zetonna/Omnaris and Veramyst generics are entering the market in 2017 and 2016, respectively. Veramyst was approved in both the US and EU in 2007, and has patent protection until 2021 and 2023 in the US and EU, respectively. However, Sandoz, challenged the patents for Veramyst, and submitted an ANDA with a Paragraph IV Certification in November 2011. Although GSK subsequently initiated a lawsuit against Sandoz, the two companies reached a settlement that allowed Sandoz to enter the US market with a generic competitor in Q3 2016 or earlier, under certain circumstances. Sales of Veramyst are expected to decline from $66.0m in 2014 to $2.2m to 2024, as they will be eroded by numerous generic alternatives, with similar efficacy and safety profiles.

The HFA dry-mist INCS class, which includes Qnasl and Zetonna, has a relatively small patient share, owing to patient dissatisfaction with the device and the relatively high cost of these therapies compared with generics. Qnasl launched in 2012, and received pediatric approval in December 2014. The drug is protected by various patents in the US that expire between 2014 and 2027, and it generated approximately $45.8m in sales in 2014. Should Teva successfully defend the patents for Qnasl, it will be the only remaining INCS with patent protection in 2024, generating modest sales of $68.9m in a market saturated with generics. Similarly, the second HFA INCS, Takeda and Sunovion's Zetonna, which launched in 2012, posted weak sales of $24m in 2013. GlobalData anticipates that a generic equivalent of Zetonna will be launched in 2017, alongside an aqueous generic version of Omnaris, which will contain the same active ingredient, ciclesonide. The

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ciclesonide franchise generated $47m for Sumitomo Dainippon Pharma in 2014. Following the entry of generic competition, this figure is set to decline to approximately $10m by 2024.

A key contributing factor to the large size of the INCS drug class in terms of revenue is its position in the ARIA guidelines, where it is listed as the first-line therapy for patients with persistent and moderate to severe AR, who represent the vast majority of AR patients. However, in 2013, INCS were available only by prescription in the US. In 2014, the first INCS, Nasacort, transitioned to OTC status, followed closely by Flonase, which was launched OTC in US pharmacies in 2015. This is set to decrease the number of patients seeking INCS from a physician. As a result, INCS drug class market size will become stagnant, generating $892m by 2024, at a CAGR of 0% during the forecast period.

The marketed branded product with the most growth potential is Meda's Dymista, which is currently approved for AR in the US. As a first-in-class drug, GlobalData expects Dymista to dominate the branded segment of the INCS/AH FDC market in the US, as it is the first intranasal combination AR treatment to be approved in the US. Sales of the drug will reach $84m in 2024, which will help Meda to recover revenues lost as a result of the generic erosion of Astepro.

Weak growth is expected for the LRAs and anticholinergic agents during the forecast period. After the dip in sales caused by the Singulair patent expiry in 2012, the generics of these drug classes are not expected to bring any changes to the treatment landscape.

The AR pipeline products with the highest growth potential are Merck's grass, HDM, and ragweed AITs — Grastek, Mitizax, and Ragwitek, respectively — and Greer Laboratories' Oralair. With their once-daily regimen, AITs have a competitive advantage over the SC immunotherapies. In addition, they are administered at home, which may significantly improve patient compliance and adherence to the lengthy treatment regimen. GlobalData estimates that US sales of the AIT drug class will grow to $628m in 2024 (the individual drug sales are provided in GlobalData's Allergen Immunotherapy OpportunityAnalyzer report, published in 2014 [GlobalData, 2014]).

Another pipeline drug, SI-555739, is a PGD2 receptor antagonist, and has a unique mechanism of action compared with the other marketed and pipeline AR products in the US. However, it faces stiff competition in a market with flagging giants and a wave of generics set to enter the arena over the next five years. GlobalData estimates that sales of S-555739 will reach $173m in 2023, despite the fact that the drug will be launched late, in 2017.

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Table 65 presents the sales forecasts for AR products in the US from 2014–2024.

Table 65: Sales Forecasts ($m) for AR in the US, 2014–2024

Year	2014	2015	[illegible]	[illegible]	[illegible]	[illegible]	2020	2021	[illegible]	[illegible]	[illegible]	[illegible]
Oral H1Ahs	241.2	242.6	244.1	245.5	247.0	248.6	250.1	251.7	253.3	254.9	256.3	0.6%
Intranasal H1Ahs	429.1	224.1	217.1	218.4	211.2	195.6	188.2	189.4	190.6	183.1	184.1	-8.1%
INCS	1,809	1,310	1,272	955	911	896	892	897	880	884	892	0
Nasonex	686.5	331.4	333.4	89.9	22.5	11.3	11.4	11.5	11.5	8.7	8.8	-35.4%
Nasonex, generic	0.0	89.8	90.1	123.1	130.3	144.2	151.7	152.7	153.7	154.6	155.5	
Qnasl	45.8	48.0	50.2	52.5	54.7	57.0	59.4	61.7	64.1	66.6	68.9	4.2%
Zetonna	24.6	29.7	37.4	10.0	9.1	8.6	8.2	7.7	8.3	8.8	8.9	-9.7%
Zetonna, generic	0.0	0.0	0.0	7.8	8.6	9.0	9.4	9.7	10.4	11.5	12.7	0
Omnaris	22.2	14.9	13.9	7.5	5.0	2.5	2.6	2.6	2.6	1.3	1.3	-24.6%
Omnaris, generic	0.0	0.0	0.0	1.5	2.2	2.5	2.5	2.4	2.4	2.3	2.3	
Veramyst	66.4	54.3	42.0	25.4	17.0	8.6	4.3	2.2	2.2	2.2	2.2	-28.9%
Veramyst, generic	0.0	0.0	9.4	9.5	9.5	9.6	9.6	9.7	9.8	9.8	9.9	
Dymista	41.4	67.4	67.8	74.4	74.9	75.4	75.8	82.7	83.2	83.7	84.2	7.3%
LRAs	203.6	204.7	206.0	207.2	208.4	209.8	211.1	212.4	213.7	215.1	216.3	0.6%
Anticholinergic drugs	54.2	54.5	54.8	55.1	55.5	55.8	56.2	56.5	56.9	57.2	57.5	0.6%
Decongestants	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8	0.6%
SITs	173.3	225.1	366.1	444.2	543.8	683.4	706.7	764.0	798.3	841.1	869.2	17.5%
SI-555739	0.0	0.0	0.0	55.4	111.4	140.2	141.1	147.6	160.0	172.5	173.4	
Total	2754.6	2331.3	2430.2	2257.7	2365.5	2507.4	2526.3	2604.5	2638.2	2694.9	2736.1	-0.1%

Source: GlobalData
CAGR = Compound Annual Growth Rate.

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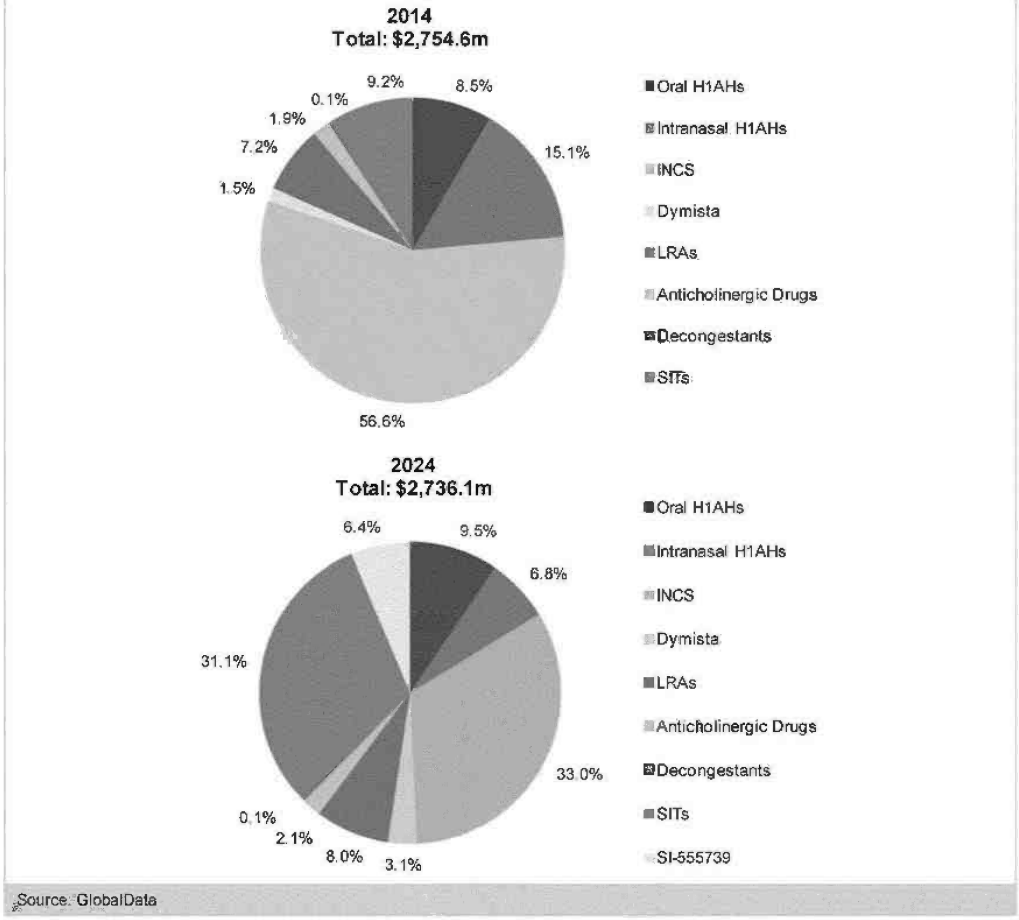
Figure 10 illustrates the sales for AR in the US by drug class during the forecast period.

Figure 10: Sales for AR in the US by Drug Class, 2014–2024



Source: GlobalData

10.2.2 Key Events

Table 66 lists the key events impacting the sales for AR in the US during the forecast period.

Table 66: Key Events Impacting Sales for AR in the US, 2014–2024

Year	Event	Level of Impact	Type of Impact
2014	Nasonex patent expiry	High	↓↓↓
2014	Astepro patent expiry	Low	↓
2014	Patanase patent expiry	Low	↓
2014	Grastek approval	High	↑↑
2014	Ragwitek approval	High	↑↑
2014	Oralair approval	High	↑↑
2016	Veramyst generic entry	Low	↓
2017	Zetonna patent expiry	Low	↓
2017	Omnaris patent expiry	Low	↓
2017	S-555739 launch	Low	↑
2016	SAIL Short Ragweed Sublingual Liquid approval	Low	↑
2016	HDM AIT approval	High	↑↑

Source: GlobalData

10.2.3 Drivers and Barriers

Table 67 presents the drivers and barriers of the AR market in the US during the forecast period.

Table 67: AR Market – Drivers and Barriers in the US, 2014–2024

Drivers	Barriers
The ACA will lead to AR market growth in the US.	The approval of OTC INCS Will Increase the Patient Flow to Pharmacies and Lower the Prescription Drug Treatment Rate
The rising prevalence of AR in the US will stimulate the market growth.	The FDA's September 2013 draft guidance may spur the production of additional generic AR medications.

Source: GlobalData

The ACA requires that all Americans carry health insurance , by 2014, or otherwise pay a tax penalty. Under this act, many patients with allergies or asthma in the US are more likely to obtain cost-effective and much-needed preventive, primary, and specialty care services.

10.2.3.1 Driver: The ACA Will Lead to AR Market Growth

The US has been trying to overhaul its healthcare policy through the ACA. The ACA requires that all Americans carry health insurance by 2014, or otherwise pay a tax penalty. Under this act, many patients with allergies or asthma in the US are more likely to obtain cost-effective and much-needed preventive, primary, and specialty care services. In addition, patients who do not have

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employer-provided health insurance can buy private health insurance plans, which cannot charge more for pre-existing conditions, and parents can purchase health benefits for children without being denied coverage or having to pay significantly more due to pre-existing conditions.

A key provision of the ACA involving asthma and allergies is that health insurance companies cannot arbitrarily cancel an individual's health insurance due to a chronic illness, such as asthma, or the frequent use of expensive treatments, such as immunotherapy. In addition, under this act, doctor-recommended allergy and asthma screenings and tests must be covered by all healthcare plans at no extra cost to patients. The entire US AR market will be driven by this healthcare reform, particularly the use of generic drugs, as pricing pressures will increase.

10.2.3.2 Driver: The Rising Prevalence of AR in the US Will Stimulate Market Growth

According to GlobalData epidemiologists, about one in seven people in the US has been diagnosed with AR at some point in their life, or about 43 million people. In addition, this rate appears to be on the rise, and in 2024, this number will reach over 46 million. This increase of the AR prevalence in the US will strongly drive the growth of this market, as the AR patient pool will increase, leading to higher consumption of medications used to treat the disease.

10.2.3.3 Barrier: The approval of OTC INCS Will Increase the Patient Flow to Pharmacies and Lower the Prescription Drug Treatment Rate

Nasacort and Flonase are the first two INCS to be approved in the US for OTC use, becoming available in pharmacies in 2014 and 2015, respectively. As INCS are the recommended first-line treatment for persistent and moderate to severe AR, this Rx-to-OTC switch will bring added convenience for AR patients, as they will no longer have to visit and to pay to see a doctor in order to receive treatment. In addition, this will decrease the burden that allergies impose on PCPs. However, the expected decrease in the physician visitation rate will lead to a decrease in the AR diagnosis rate, and the number of prescribed treatments. This will occur not only with the OTC versions of AHs and INCS, but also eventually with the current prescription-only AR drugs, such as LRAs, mast cell stabilizers, and immunotherapies. Many medical insurance companies will no longer cover Nasacort AQ on health plans, and it is likely in the future that other prescription INCS will no longer be covered. The advent of OTC INCS and AHs, the use of which is supported by insurance companies, will inevitably drive the patient flow to self-diagnosis and treatment via community pharmacies. This will significantly dampen the growth of the prescription AR drug market.

10.2.3.4 Barrier: The FDA's September 2013 Draft Guidance May Spur the Production of Additional Generic AR Medications

The key branded AR drugs have been subjected to numerous patent challenges, with generic manufacturers attempting to launch equivalent drugs ahead of the expiration of the branded drugs' marketing exclusivity. These companies successfully applied to the FDA to launch Omnaris and Veramyst generics prior to their respective patent expirations. In September 2013, the FDA issued a draft guidance, which may eventually spur the production of additional generic AR medications. As per the new guidance, generic manufacturers only need to submit bioequivalence data, rather than data from costly and time-consuming clinical trials (FDA, 2013). As a result, generic versions of Zetonna, Omnaris, and Veramyst might enter the market as early as 2016, resulting in a decline in the sales of the branded INCS drugs.

10.3 5EU

10.3.1 Forecast

In 2014, the base-year of the forecast period, sales of AR products in the 5EU totaled $2.53 billion. GlobalData estimates these numbers to grow slightly by 0.1% per year through 2024 (not accounting for inflation) to $2.56 billion. As in the global markets, this decline will be fueled mainly by the patent expiry of two key INCS, Merck's Nasonex and Sanofi's Nasacort. The 5EU AR market will remain stagnant, with no major events occurring over the 10-year forecast period. There are no pipeline AR products set to launch in the 5EU during this time.

The patent expiries of the best-selling prescription INCS, Nasonex and Nasacort, will be the events that have the most negative impact on the 5EU AR market during the forecast period. Nasonex generated $46.2m in sales in 2014, which are expected to decline to $2.2m in 2024, as the drug is set to experience strong erosion following the launch of generics across the 5EU in 2014. Nasacort, which had modest sales of $11m in 2014, will see its sales diminish to under $1m in 2024, due to generic competition beginning in 2017. At the end of the forecast period, in 2014 there will be no branded AR drugs, as GSK's Veramyst lose market exclusivity in 2024. The 5EU market has had a wealth of OTC INCS for over two decades, as these are common products with strong patient familiarity and with major brands on the pharmacy shelves. Therefore, GlobalData does not anticipate that the transition of any additional INCS to OTC status will have any impact.

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The AR market in the 5EU experienced a dip in sales caused by Singulair's patent expiry in 2013, with generics being launched across Europe in Q1 2013. Prior to the expiry, Singulair was a blockbuster drug, generating $1.7 billion annually in non-US sales (including sales for other indications, such as asthma).

The marketed branded product with the most growth potential is Meda's Dymista, which is currently approved for AR in the US. As a first-in-class drug, GlobalData expects Dymista to dominate the branded segment of the 5EU INCS/AH FDC market, as it is the first intranasal combination treatment to be approved for the 5EU AR market. The drug will attain $72m in sales in 2024, which will help Meda recover revenues lost as a result of the generic erosion of Astepro.

In 2014, sales of AITs in the 5EU markets were $840.0m. In the 5EU, the AR immunotherapy market is currently diverse, with several allergen manufacturers distributing SCIT, SLIT, and AITs across the different markets. SIT is currently prescribed predominantly on a named-patient basis, in which an allergen product is prepared according to a customized prescription for an individual patient, which is known as a named patient product (NPP). A handful of allergen products have obtained marketing authorization (MA) in the 5EU through the standard approval process. However, in Germany, which is the largest SIT market in Europe, under the Therapie-Allergene-Verordnung (TAV), allergen extracts must now obtain an MA according to the European Directive 2001/83/EC. This includes all NPPs derived from grass pollen, early-flowering tree pollen, HDMs, and bee and wasp venom, regardless of whether the allergen is produced as a single-allergen preparation or is included in mixtures (Eichler and Soriano, 2011). The new regulations required companies to submit a Marketing Authorization Application (MAA) to the relevant German authorities by December 2010, and numerous clinical trials are currently ongoing. Due to a large influx of MAAs, the German authorities have not set a timeline to respond to each manufacturer. Similar regulations are set to be introduced in Spain and Italy.

In recent years, poor economic conditions have led to a decreased market size for AITs in the 5EU. Austerity measures have led to new legislation being introduced to restrict the pricing and reimbursement of medicines. Therefore, in some locations, such as certain parts of Italy, AIT is no longer partially or fully-reimbursed, and patients faced with economic hardships are declining immunotherapy. The drug treatment rate during the forecast period (approximately 2.4%) is low because of the high price and inconvenience of AIT, and is set to remain low until novel formulations are approved.

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GlobalData expects that the allergy immunotherapy market in the 5EU will reach $932.6m in 2024, at a CAGR of 1.0% during the forecast period. A large number of smaller allergen manufacturers are expected to experience a moderate decline in patient share, owing to an increase in dominance by the larger players in a difficult market environment. Generally speaking, allergen extract manufacturers are streamlining their product portfolios, as it is not economically viable to clinically evaluate products that are only used by niche patient populations; this trend will lead to a decline in the sales of SCIT in the 5EU. The slightly positive growth in the allergy immunotherapy market in the 5EU will largely be contributed by ALK's and Stallergenes' tablet portfolios, with CAGRs of 9.7% and 4.59%, respectively, over the 10-year forecast period. Overall, however, it will not offset the declining symptomatic therapies market.

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Table 68 presents the sales forecasts for AR products in the 5EU during 2014–2024.

Table 68: Sales Forecasts ($m) for AR in the 5EU, 2014–2024

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014–2024) (%)
Oral H1AHs	561.5	563.1	564.8	566.3	567.6	568.7	569.6	570.4	571.0	571.4	573.6	0.2%
Intranasal H1Ahs	100.9	101.2	101.5	101.8	102.1	102.4	102.6	102.7	102.9	103.0	103.4	0.2%
INCS	752.2	578.4	556.7	548.6	525.4	517.3	509.7	504.5	496.3	488.0	481.0	-4.4%
Nasonex	46.2	20.8	14.5	4.7	2.4	2.4	2.4	2.3	2.3	2.3	2.2	-26.1%
Nasonex, generic	8.5	22.9	25.8	28.8	28.8	31.8	34.8	37.7	37.8	37.8	38.9	16.1%
Nasacort	11.1	11.1	11.1	5.6	1.1	0.6	0.6	0.6	0.6	0.6	0.6	-25.8%
Nasacort, generic	0.0	0.0	0.0	3.0	6.1	6.1	6.1	6.1	6.1	6.2	6.2	
Avamys (Veramyst)	58.5	55.9	63.5	63.7	69.2	66.7	64.2	64.3	64.4	64.5	64.8	1.0%
Dymista	72.0	102.5	141.9	157.9	158.3	180.4	186.8	209.0	231.2	253.3	276.3	14.4%
Cromones	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5%
LRAs	177.5	183.8	184.4	184.9	185.4	185.8	186.2	186.5	186.8	187.0	187.7	0.6%
Anticholinergic drugs	26.1	18.0	18.1	18.1	18.2	18.2	18.2	18.2	18.3	18.3	12.9	-6.8%
SITs	843.2	853.2	860.8	869.1	879.9	888.0	896.9	905.9	914.8	923.7	932.6	1.0%
Total	**2,658.1**	**2,521.3**	**2,543.4**	**2,552.8**	**2,544.8**	**2,568.7**	**2,578.5**	**2,608.7**	**2,632.7**	**2,656.3**	**2,679.6**	**0.1%**

Source: GlobalData
CAGR = Compound Annual Growth Rate

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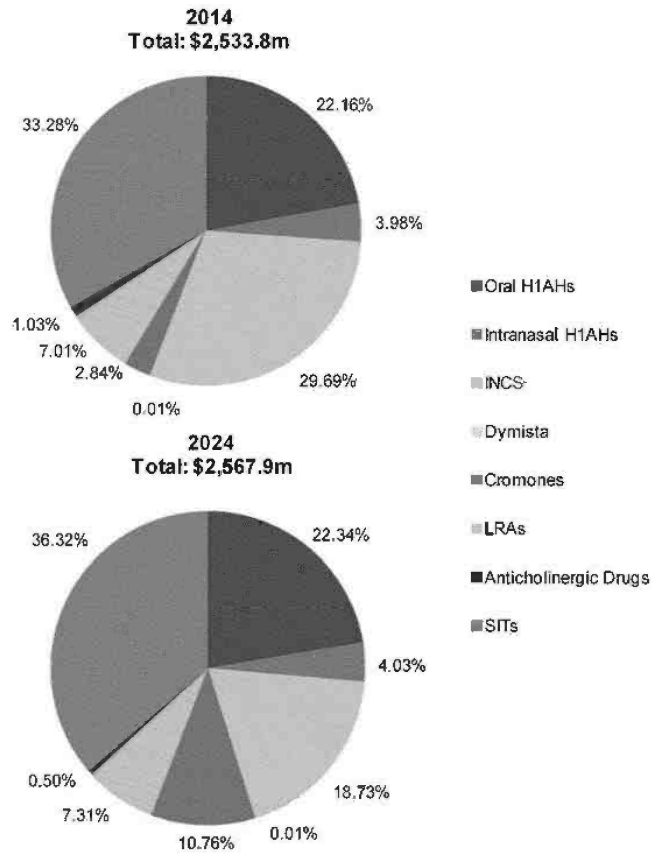
Figure 11 illustrates the sales for AR in the 5EU by drug class during the forecast period.

Figure 11: Sales for AR in the 5EU by Drug Class, 2014-2024



Source: GlobalData

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10.3.2 Key Events

Table 69 lists the key events impacting the sales for AR in the 5EU during the forecast period.

Table 69: Key Events Impacting Sales for AR in the 5EU, 2014–2024

Year	Event	Level of Impact	Type of Impact
2014	Nasonex patent expiry	Low	↓
2017	Nasacort patent expiry	Low	↓
2016–2024	AIT launches	Low	↑

Source: GlobalData

10.3.3 Drivers and Barriers

Table 70 presents the drivers and barriers of the AR market in the 5EU during the forecast period.

Table 70: AR Market – Drivers and Barriers in the 5EU, 2014

Drivers	Barriers
The EAACI allergy awareness campaign will increase AR awareness.	Poor economic conditions in the 5EU have led to a decreased market size for AITs.
High healthcare expenditures in France will fuel AR market growth.	Government Drug Pricing and Reimbursement Restrictions in France are Likely to Stifle the Growth of the AR Market
The new planning directive in Germany will boost pharmaceutical sales.	The French Act N°2011-2012 poses an obstacle to the growth of the AR market.
The Italian government reimburses almost all expensive and novel medicines.	Mandatory drug rebates in Germany will stifle the growth of the AR market.
The Agenzia Italiana del Farmaco (AIFA) and the Istituto Superiore di Sanità (ISS) agreements will facilitate and encourage an increase in the number of AR clinical trials in Italy.	The Therapy Allergen Ordinance (Therapie-Allergene-Verordnung [TAV]) directive in Germany will stifle the growth of the AR market.
The implementation of electronic medical records will improve patients' access to healthcare services, and will drive the growth of the Spanish AR market,	Government Drug Pricing Restrictions in Spain May Limit the Uptake of New Branded Agents
Massive immigration during the past few years will lead to an increase in the demand for pharmaceuticals in Spain.	Government drug pricing restrictions in Spain may limit the uptake of more expensive products.
The "Patent Box" will provide relief for manufacturers of branded drugs for AR in the UK.	Reforms promoting the use of generics will slightly stifle the growth of the Spanish AR market.
	Uncertainty regarding how the proposed value-based pricing (VBP) system will impact market access for novel AR therapies in the UK.
	Drug price cuts will stifle the growth of the AR market in the UK.
	The decline in foreign direct investment (FDI) in the UK will stifle innovation in the AR space.

Source: GlobalData

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10.3.3.1 Driver: EAACI Initiative to Increase AR Awareness

AR experts across Europe launched a new partnership in June 2014 to tackle Europe's high AR prevalence. The EEACI's Allergy Awareness Campaign aims to help the community better understand allergy sufferers' symptoms, how greatly allergy impacts QoL, how severe and costly AR can be, and how early diagnosis of the disease is important to improve its management. The EAACI hopes that this campaign, which focuses on education about allergy prevention, early diagnosis, and correct management, patients and their families will be able to achieve better control of their allergies and improve their QoL. Another objective of the campaign is to increase the resources allocated by health ministries to better manage the allergy epidemic. The EACCI will roll out the campaign in phases running from 2014 through 2015, and will highlight the individual causes of various allergies (including AR, anaphylaxis, asthma, and food and skin allergies) as well as their treatments, such as AIT. This campaign will also tackle several barriers in AR treatment, such as inadequate organization of healthcare services, limited availability of drugs to treat severe AR, lack of training and education for clinicians, and poor adherence to treatment. As a result, not only will this initiative improve the QoL of people with AR, but it will also inevitably lead to better treatment, which will in turn, lead to a larger patient pool and stimulate growth of the AR market.

The EEACI's Allergy Awareness Campaign aims to help the community better understand allergy sufferers' symptoms, how greatly allergy impacts QoL, how severe and costly AR can be, and how early diagnosis of the disease is important to improve its management.

10.3.3.2 Driver: High Healthcare Expenditures in France Will Fuel AR Market Growth

In 2007, healthcare expenditures in France accounted for 11.2% of the country's Gross Domestic Product (GDP), which increased to 12% in 2011 (GlobalData, 2013b). In 2005, per-capita healthcare expenditures were $3,294, and increased at a CAGR of 3.8% to $3,974 in 2010. The country's robust social healthcare system is supported by universal insurance coverage, which means that patient out-of-pocket expenditures are very low. Access to medicines includes public reimbursement of expensive and novel drug therapies for acute and chronic disease conditions. These high healthcare expenditures are fueling the growth of the AR market. In addition, patients in France benefit from relatively quick access to innovative drugs for life-threatening diseases with high unmet need through the Temporary Authorization for Use (Autorisations Temporaires d'Utilisation) program. This program allows these drugs to be used in hospitals even before they are registered, which may boost the sales of the AR immunotherapies in development, even before they reach the market.

10.3.3.3 Driver: The New Planning Directive in Germany Will Boost Pharmaceutical Sales

The Federal Joint Committee (G-BA) has defined a new version of its Planning Directive, which came into effect on January 1, 2013. This new directive will ensure the uniform and demand-based availability of physicians and GPs across Germany (GlobalData, 2013c). As a result of the implementation of the Planning Directive, the availability of GPs and physicians has increased in rural areas. The uniform availability of the healthcare personnel will ensure patient access to healthcare facilities and treatment, and will contribute to the growth of the AR market in Germany.

10.3.3.4 Driver: The Italian Government Reimburses Almost all Expensive and Novel Medicines

The Italian government provides universal healthcare coverage to the country's population. It reimburses almost all expensive and novel medicines, which increases patient compliance and the number of prescriptions written, and drives the pharmaceutical market in Italy. Reimbursement of medicines will be particularly relevant with regard to AITs that are in late-stage development for AR, and will be a major factor in increasing patient compliance and access to medicines, which will both drive the AR market in Italy.

10.3.3.5 Driver: The AIFA and ISS Agreements Will Facilitate and Encourage Increased Number of Clinical Trials in Italy

In 2012, the AIFA, the ISS, and the Italian Association for the Development of Biotechnology signed an agreement to encourage early-phase clinical trials for new drugs (AIFA, press release, October 4, 2012). As a result, the time of evaluation for clinical trial applications was reduced to 45 days. This policy will drive the early launch of new medicines in the Italian market, revive research, and attract investment. Facilitation of greater numbers of clinical trials of early-stage drugs will encourage the development of much needed next-generation and personalized therapies for AR.

10.3.3.6 Driver: Implementation of Electronic Medical Records Will Improve Patients' Access to Healthcare Services and Will Drive the Growth of the Spanish AR Market

The Spanish government has invested in the implementation of electronic medical record and the use of information and communication technology to integrate the services provided by public hospitals with those of the National Health System (Sistema Nacional de Salud [SNS]) (GlobalData, 2013e). E-prescriptions were introduced in 2005 for patients with chronic diseases who make regular visits to primary health centers to renew their prescriptions. The introduction of

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e-health services allows patients to make an appointment with and get a prescription from physicians online. Doctors can also access all medical records, including the laboratory test results, of patients in any SNS hospital, which helps improve treatment. These initiatives have improved patients' access to healthcare services and reduced their travel time, consequently improving compliance, and driving the healthcare sector. Overall, pharmaceutical sales in the AR market in Spain will be driven by the e-health services.

10.3.3.7 Driver: Massive Immigration in the Past Few Years Will Lead to an Increase in the Demand for Pharmaceuticals in Spain

Spain has experienced massive immigration in the past few years, and has the second highest number of immigrants in Europe. According to the Spanish government, there were 4.5 million foreign residents in 2007. The increasing immigration is one of the reasons for the increase in the demand for pharmaceuticals (GlobalData, 2013e). This driver will be reflected in the overall growth of the AR market in Spain.

10.3.3.8 Driver: "Patent Box" Will Provide Relief for Manufacturers of Branded AR Drugs in the UK

In order to bring business into the UK to generate revenue, the government established the Patent Box policy as Part of the Finance Bill, which began at the end of 2012 (GlobalData, 2013h). This policy will provide tax relief for companies that manufacture patent-protected goods in the UK, and is indirectly aimed at attracting drug companies. The corporate tax rate of 20% is decreased to 10% for companies that qualify. This will bolster the overall presence of the pharmaceutical market in the UK. Consequently, the AR market in the UK will also see stronger growth compared with other European countries.

10.3.3.9 Barrier: Poor Economic Conditions in the 5EU Have Led to a Decreased Market Size for AITs

Poor economic conditions in the 5EU have led to decreased market size for AITs in recent years. Austerity measures have led to new legislation being introduced to restrict the pricing and reimbursement of medicines. Therefore, in some locations, such as certain parts of Italy, AIT is no longer partially or fully-reimbursed, and patients faced with economic hardships are declining immunotherapy. The drug treatment rate for AR during the forecast period will be low (approximately 2.4%) because of the high price and inconvenience of AIT, and is set to remain low until novel formulations are approved.

10.3.3.10 Barrier: Government Drug Pricing and Reimbursement Restrictions in France are Likely to Stifle the Growth of the AR Market

In France, the Economic Committee for Health Products (Comité Economique des Produits de Santé [CEPS]) monitors drug prices and it revises those that it deems too high, based on a clinical evaluation performed by the Haute Autorité de Santé (HAS). This could hurt new biologic products in late development for AR, as the CEPS may deem these drugs too expensive and as not having any advantages over the currently available therapies. The CEPS expects to help lower the budget deficit by cutting the prices of branded and generic drugs. It also determines which products should be fully- or partially reimbursed by public insurers, with the level of reimbursement being based on the medical worth of the product. Also, as in its neighboring EU countries, the French government imposes price cuts on pharmaceuticals from private companies. Price cutting due to competition among manufacturers is likely to impact the overall growth of the AR market (GlobalData, 2013b). These price-cutting strategies were implemented partly as a result of the sovereign-debt crisis.

10.3.3.11 Barrier: The French Act N°2011-2012 Poses an Obstacle to the Growth of the AR Market

The French Act N°2011-2012, formulated by the National Assembly, gave the National Safety Agency for Drug and Health Products (Agence Nationale de sécurité du Médicament et des produits de santé, ANSM) the power to require the MA holder of a medicinal product to carry out post-authorization safety and effectiveness analyses. To be listed as a reimbursable medication, a medicinal product must have been clinically tested against other existing therapeutic strategies (indication by indication). This requirement applies to applications filed on or after January 1, 2012. This could hurt many biologic therapies in development for AR, as it might not be easy to prove that one of these therapies is more effective than the other.

10.3.3.12 Barrier: Mandatory Drug Rebates in Germany will Stifle the Growth of AR Market

In 2003, the German government required pharmaceutical companies to pay a 6% rebate to the SHI funds. In 2004, the government again increased the mandatory rebate to 16% in order to provide immediate savings to the health fund system, while reference pricing was being developed. This 16% mandatory rebate is still applicable and is stifling the growth of the AR market as a whole, since it acts as a discouraging factor for pharmaceutical manufacturers.

10.3.3.13 Barrier: The TAV Directive in Germany Will Stifle the Growth of the AR Market

Germany's Federal Ministry of Health issued a TAV directive in November 2008, requiring all manufactured human pharmaceutical products, including AITs, to receive MA according to the European Directive 2001/83/EC, as amended by the EMA. Under the TAV, each product's MA must be obtained through a standard drug development procedure, including large-scale, multicenter, randomized, placebo-controlled clinical trials in adults and children. However, with regard to AITs, this requirement only applies to the most prevalent allergens. It also requires official batch testing of all bulk allergen extracts manufactured.

The relevant regulatory documents had to be submitted to the Paul-Ehrlich-Institut (PEI) by December 1, 2010. However, the PEI has not yet responded to all the applications. Until the MAs have been issued, the PEI has afforded the allergen manufacturers a transition period until 2017 to prepare the relevant documentation and to complete the clinical data on safety and efficacy in randomized controlled trials for the final MAs, provided that the companies have notified the PEI regarding their intention to complete a full application. During this time, the companies are able to sell and distribute their products (Allergy Therapeutics, press release, November 28, 2010). There is no set timeline for the PEI to respond to the MAAs. The PEI has shown a preference for single-allergen vaccines, and it is expected that specific allergen mixes will only be used in clinical practice for rare allergies.

In 2010, 60% of SIT products in Germany were marketed NPPs, without an MA in the meaning of Directive 2001/83/EC. Under the new TAV, all immunotherapy products containing the most prevalent allergens must have received an MA by 2017. This includes all NPPs derived from grass pollen, early-flowering tree pollen, HDMs, and bee and wasp venom, regardless of whether the allergen is produced as a single-allergen preparation or included in mixtures (Eichler and Soriano, 2011). All MAAs must be submitted to the relevant German authorities by December 1, 2010. As Germany represents the largest revenue stream for immunotherapy products, any delays in the registration of these products may limit SIT sales in Germany.

The TAV represents a significant financial challenge for allergen manufacturers marketing products in Germany, which is the largest AIT market.

The TAV represents a significant financial challenge for allergen manufacturers marketing products in Germany, which is the largest AIT market. It will not be economical for each manufacturer to register all of the required products in their portfolio in line with the TAV requirements, due to the associated costs and time required for preparing an application and conducting potentially lengthy clinical trials in both children and adults.

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The EU member states are at different stages in their efforts to comply with this directive. Similar regulations are set to be rolled out in Spain and Italy in the near future. However, through the European Union Mutual Recognition Procedure (MRP), companies who gain MA in Germany can apply for approval in other EU member states. Smaller national companies that have not applied for registration of their products in Germany will need to do so once the directive has been enforced in the relevant country.

10.3.3.14 Barrier: Government Drug Pricing and Reimbursement Controls In Italy May Limit the Uptake Of More Expensive Agents

Italy provides government-funded universal health insurance coverage, and the Italian government is trying to promote the use of generic drugs over the more expensive branded medications. The strict pricing of drugs through negotiations and external and internal reference pricing is a major challenge for the launch of innovative molecules (GlobalData, 2013d). Another attempt by the Italian government to reduce healthcare costs is a pay-to-perform measure on new drugs, which was implemented in 2007. Under this program, the government may cut drug prices by up to 40% after launch. After a two-year review of performance to assess whether the drug provides a health benefit based on its efficacy, the price may be increased or lowered. This plan may hinder the market entry and penetration of all drugs in development for AR (Tonareili, 2011).

10.3.3.15 Barrier: Government Drug Pricing Restrictions in Spain May Limit the Uptake of New Branded Agents

The Spanish government has adopted two pricing strategies, both of which ultimately present a barrier to the pharmaceutical market (GlobalData, 2013e). The first is the generic reference pricing strategy, which is comparable to that in the other EU markets. Under this strategy, drug prices are based on the price of the least expensive comparable drug available. The second methodology entails the application of a 7.5% discount on branded drugs that are financed by the Spanish National Health System. As a result of these strategies, pharmaceutical companies take a loss when generics are allowed to enter the market. Thus, the government's control of drug pricing will stifle the growth of the AR market in Spain.

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10.3.3.16 Barrier: Reforms Promoting the Use of Generics Will Slightly Stifle the Growth of the Spanish AR Market

In 2011, the Spanish government introduced reforms to promote the use of generics. Doctors were mandated to state the active ingredient on the prescription instead of a brand name, and pharmacists were strictly required to dispense the cheapest medicine available containing the active ingredient (GlobalData, 2013e). These measures have led to an increase in the sale of generics. The share of generics in the SNS' total pharmaceutical bill increased from 20.9% in 2007 to 38.9% in 2011 in terms of volume, and from 9.2% in 2007 to 14.4% in 2011 in terms of value. This has reduced pharmaceutical companies' revenue. As a result of these reforms, the AR space in Spain could see an increase in use of generic versions of Pulmicort, Advair, and Symbicort.

10.3.3.17 Barrier: Uncertainty Regarding How the Proposed VBP System Will Impact Market Access for Novel AR Therapies in the UK

The NICE is often cited as being ineffective as a result of its tendency to focus almost exclusively on the cost-effectiveness of various treatment options, rather than on their clinical benefit. This system means that the best, most effective drugs do not always become available in the UK. The proposed introduction of a VBP system by the UK government has been met with uncertainty by drug manufacturers, with questions as to how the system would appraise drugs; weight them by innovation, unmet need, and the severity of disease; and determine prices for them (GlobalData, 2013f). This system may benefit the patient in that there may be greater access to novel therapies. However, this system is sure to affect the sales of branded drugs in the UK, as these drugs may not get approved for pricing and reimbursement in a timely fashion, which will result in the delayed uptake of novel AR therapies.

10.3.3.18 Barrier: Drug Price Cuts Will Stifle the Growth of the AR Market in the UK

Price cuts have led to a decline in the value of the pharmaceutical market in the UK. It fell to $24.1 billion in 2012 from $27.1 billion in 2008, due to price cuts on branded medicines of 3.9% in 2009 and 1.9% in 2010, in order to reduce NHS expenditures (GlobalData, 2013f). In June 2013, the Department of Health announced plans to cut prices by 10–20% on branded medicines that are not covered in the voluntary Pharmaceutical Price Regulation Scheme. These price cuts will adversely affect the revenues of manufacturers of branded medicines in the UK, and therefore, the growth of the AR market in the UK will be stifled.

10.3.3.19 Barrier: The Decline in FDI in the UK Will Stifle Innovation in the AR Space

Capital investment in the UK declined by 0.8% between 2010 and 2012 to 14.3% of GDP, which is less than in other EU countries, such as France and Germany, where it was 19.9% and 17.2% of GDP, respectively (GlobalData, 2013f). The global economic slowdown, the Eurozone crisis, and the UK government's deficit reduction program have all hindered the economic recovery, resulting in a decline in FDI. This will be reflected negatively in the R&D investment that is needed for the development of novel AR therapies.

10.4 Japan

10.4.1 Forecast

Sales of AR products in Japan were $1.89 billion in 2014. GlobalData forecasts this figure to grow by 0.4% per year through 2024 (not accounting for inflation) to $1.96 billion. As in the global markets, the growth in the Japanese AR market will be fueled mainly by the uptake of the new AITs, and will be offset by the patent expiry of the best-selling AHs in 2013, and Merck's INCS, Nasonex, in 2017. In 2013, the Japanese cedar pollen count was considerably higher compared to 2012, resulting in a peak in the sales of anti-allergy medications. The forecast for Japan is based on consistent pollen levels; however, they are highly variable from one year to the next, which will ultimately have an effect on the OTC and prescription AR market in this country.

Japan had the largest oral AH market globally in 2014, with sales of $458m. The current version of the Japanese guidelines for the treatment of AR recommends monotherapy with AHs or LRAs as a first-line therapy, while the combination of two products, an AH and an INCS, or three products, with the addition of an LRA, can be prescribed, depending on the type of illness and severity. Prior to 2013, Allegra was the best-selling AH in Japan, followed by Allelock with Xyzal, and Alesion and Talion competing for the third most commonly used AH. However, several of the most popular AHs in Japan are due to lose patent protection during the forecast period. Allegra lost patent protection in February 2013, and Allelock lost its protection in December 2012. It is expected that the introduction of generics will decrease the daily cost of therapy of this drug class, but is not expected to alter the patient share, as there were numerous AHs available in Japan, both generic and OTC, prior to the start of the forecast period. The AH market size in Japan is due to decline to $433.3m in 2024.

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The INCS market in Japan is set to decline by 1%, from $931m in sales in 2014 to $843m in 2024. The most significant factor contributing to the decline of this market during the forecast period is the patent expiry of the leading branded INCS, Nasonex, in 2017, which will experience a decline in annual sales from $183m in 2014 to around $6m in 2024, following the launch of generic versions of the drug.

The blockbuster LRA, Singulair, has experienced significant generic erosion in the US and EU markets since its patent expiry. Singulair still has patent protection until 2016 in Japan. However, following the launch of generics, the LRA market in Japan is set to decline at a CAGR of negative 4%, from $300m in 2014 to $198m in 2024.

In 2014, the AIT drug treatment rate in Japan was very low, despite the large AR prevalent population. Allergen extracts have been available in Japan since 1963, and were prescribed more frequently in the past, albeit still modestly, when taking into account the size of overall AR population. The advent of symptomatic therapies that can provide an immediate reduction in nasal symptoms, such as the second-generation AHs, resulted in a significant decrease in the use of AIT in Japan. In addition to the standard barriers to immunotherapy (needle phobia, high cost, and inconvenience), the lack of allergen standardization, HDM-specific allergen extracts, and clinically demonstrable efficacy or long-term symptom relief have also contributed to the decline in SIT sales in Japan.

In 2013, there was only one allergen extract manufacturer in Japan, Torii, which had exclusivity on the SCIT market. The approval of Torii's Japanese cedar pollen immunotherapy, Cedartolen, an SLIT liquid, will represent an opportunity to fulfill a significant unmet need in the Japanese market. However, after initial talks with regulatory officials, Cedartolen failed to secure a place on the NHI reimbursement list. Cedartolen was placed on the reimbursement list, and subsequently launched on the Japanese market in October 8th 2014.

The launch of Cedartolen is expected to contribute to an increase in both the drug treatment rate and sales of Torii's SLIT portfolio in Japan. However, Torii's launch of a highly-anticipated AIT containing Japanese cedar pollen is expected to largely take the cedar pollen AR market share. As both products will be marketed by Torii, GlobalData expects the company to drive sales of the AIT formulation. AITs are expected to be more expensive, but are also easier to store and transport, than SLIT. Torii's SLIT portfolio is forecast to reach sales of $13.88m in 2018, at a CAGR of

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35.62%. This is a modest figure, as it is anticipated that allergists and patients alike will prefer the newer AIT formulations over inconvenient SCITs and SLITs.

The introduction of two HDM AITs by Shionogi and Torii via partnerships with the European manufacturers, Stallergenes and ALK, respectively, will significantly bolster the failing Japanese AIT market and increase the drug treatment rate. Currently, Japanese patients with HDM-induced AR are treated with house dust extract, which contains a number of components in addition to HDMs at an unstandardized concentration. Therefore, an HDM allergen tablet that contains a regulated HDM extract, whose efficacy has been demonstrated in a randomized controlled clinical trial, represents a large shift in the treatment of this allergy. Torii's HDM tablet is expected to enter the market H1 2016, and is expected have a 4% patient share. It is expected to generate sales of $1.32m in 2016, and reach $20.7m by 2018.

The introduction of two HDM AITs by Shionogi and Torii via partnerships with the European manufacturers, Stallergenes and ALK, respectively, will significantly bolster the failing Japanese AIT market and increase the drug treatment rate.

Shionogi will be the new entrant in a market that has been dominated by one player, Torii, for decades. This represents a unique situation; in addition, the launch of the company's HDM tablet at the same time as Torii's HDM AIT in H1 2016 will dampen the sales of this drug. However, Shionogi's HDM tablet is still expected to generate sales of $1.98m in 2016, which will increased to $12.28m in 2018.

Austerity measures and other regulations implemented in Europe have led AIT manufacturers to target Japan. The high prevalence of AR in Japan represents a significant market opportunity for AITs. The advent of novel sublingual formulations and the entry of a new drug into the market, Cedartolen, are set to increase the drug-treated population. As a result, GlobalData projects that immunotherapy sales in Japan will reach $110m in 2024, at a CAGR of 39.4%.

In addition to the launch of new AITs, Japan is set to have two pipeline products enter the market within the forecast period: Shionogi's S-555739 and Hisamitsu Pharmaceutical's HP-3060. S-555739 is expected to be launched in 2017, and gain respectable sales of $114m in 2024 in a saturated generic market. The transdermal treatment, HP-3060, is also expected to be launched in 2017. Despite its unknown active ingredient, this product is expected to be used specifically in the elderly and younger pediatric population. Given that HP-3060 is likely to compete directly compete with generic oral and intranasal AHs (which are widely available in syrup formulations for patients with a distaste for tablets), this product is expected to have a relatively low daily cost of therapy. Nonetheless, due to the popularity of transdermal preparations in Japan, the drug will generate sales of approximately $96m in 2024.

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Table 71 presents the sales forecasts for AR products in Japan from 2014–2024.

Table 71: Sales Forecasts ($) for AR in Japan, 2014–2024

Year	2014	2015	[illegible]	[illegible]	[illegible]	2019	2020	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Oral H1AHs	458.3	456.3	454.8	452.5	449.8	446.9	444.1	441.3	438.4	435.4	433.6	-0.6%
Intranasal H1AHs	91.8	91.4	91.1	90.6	90.1	89.5	88.9	88.4	87.8	87.2	86.8	-0.6%
INCS	532.4	530.2	528.4	525.7	522.6	519.3	516.0	512.7	509.3	505.9	503.7	-0.6%
Erizas capsule	141.6	141.0	140.5	139.8	138.9	138.1	137.2	136.3	135.4	134.5	133.9	-0.6%
Nasonex	182.5	58.8	40.8	13.0	6.5	6.4	6.4	6.3	6.3	6.2	6.2	-28.7%
Nasonex, generic	0.0	113.4	123.3	122.7	121.9	131.3	130.4	129.6	128.7	127.9	127.3	
Allermist	75.5	75.2	74.9	74.5	74.1	73.6	73.1	72.7	72.2	71.7	71.4	-0.6%
Singulair	223.4	222.4	175.0	4.6	3.5	2.3	1.1	1.1	0.9	0.8	0.8	-43.2%
Montelukast sodium	0.0	0.0	28.5	113.6	118.6	123.4	122.6	121.9	121.1	125.7	125.2	
Generic pranlukast	76.7	76.4	76.1	75.7	75.3	74.8	74.3	73.8	73.4	72.9	72.6	-0.6%
Mast cell stabilizers	1.8	1.8	1.8	1.8	1.8	1.8	1.7	1.7	1.7	1.7	1.7	-0.6%
TXA2 receptor antagonists	83.0	82.7	82.4	82.0	74.1	66.3	65.8	58.2	57.8	57.4	57.1	-3.7%
T_H2 cytokine inhibitors	22.1	22.0	22.0	21.9	21.7	21.6	21.5	21.3	21.2	21.0	20.9	-0.6%
SJ-555739	0.0	0.0	0.0	49.7	74.1	98.2	97.5	109.0	113.1	114.8	114.3	
HP-3060	0.0	0.0	0.0	74.7	74.3	73.8	97.8	97.2	96.5	95.9	95.5	
SITs	4.0	8.9	21.5	32.3	40.1	51.4	62.1	73.4	85.3	98.0	110.3	39.4%
Total	1893.0	1880.4	1860.9	1875.2	1887.3	1918.6	1940.7	1944.9	1949.2	1956.8	1961.3	0.4%

Source: GlobalData
CAGR = Compound Annual Growth Rate

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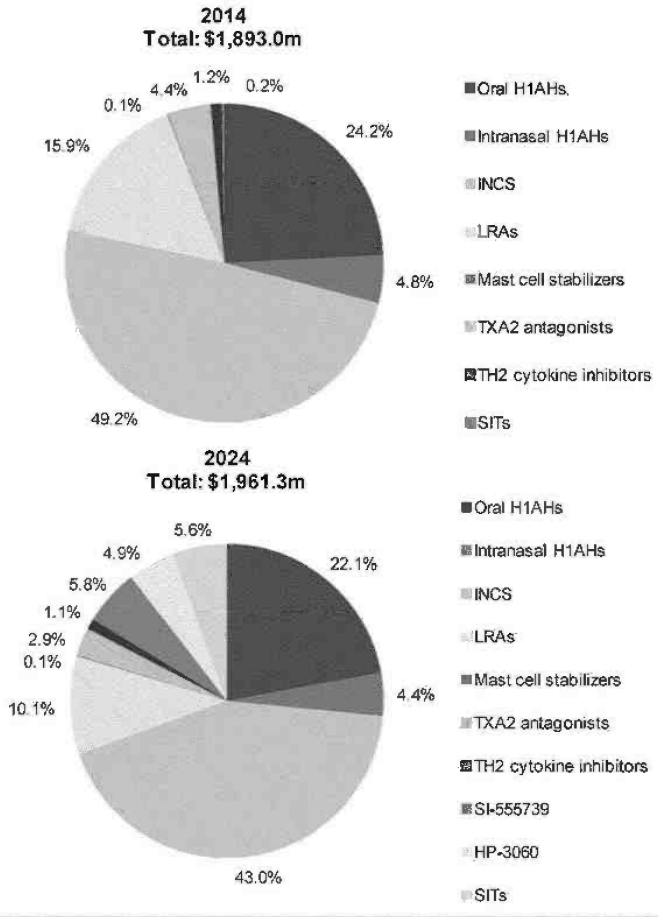
Figure 12 illustrates the sales for AR in Japan by drug class during the forecast period.

Figure 12: Sales for AR in Japan by Drug Class, 2014–2024



Source: GlobalData

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10.4.2 Key Events

Table 72 lists the key events impacting sales for AR in Japan during the forecast period.

Table 72: Key Events Impacting Sales for AR in Japan, 2014–2024

Year	Event	Level of Impact	Type of Impact
2015	Nasonex patent expiry	High	↓↓↓
2016	Singulair patent expiry	High	↓↓↓
2017	S-555739 launch	Medium	↑
2017	HP-3060 launch	Medium	↑
2014	Cedartolen added to the NHI reimbursement list	High	↑↑
2015	Torii HDM SCIT approval	Low	↑
2016	HDM AIT approval (Torii via a licensing agreement with ALK)	High	↑↑
2016	HDM AIT approval (Shionogi via a licensing agreement with Stallergenes)	High	↑
2017	Japanese cedar pollen AIT approval (Torii via a licensing agreement with ALK)	High	↑↑↑

Source: GlobalData

10.4.3 Drivers and Barriers

Table 73 presents the drivers and barriers of the AR market in Japan during the forecast period.

Table 73: AR Market – Drivers and Barriers in Japan, 2014–2024

Drivers	Barriers
Japanese pharmaceutical companies will have enhanced opportunities through increased partnerships with US and EU companies.	Japanese language requirements for regulatory submissions slow the approval process for non-Japanese pharmaceutical companies.
The decreased timeline for drug approval may allow faster access to novel AR therapies.	Pricing Reforms in Japan Will Increase the Use of Generics in the AR Space
Increased pollen counts and pollution will increase the intensity and duration of the allergy season in Japan. The rising prevalence AR in Japan will stimulate the growth of this market.	Physician preference for surgical interventions for patients with AR will negatively impact the drug treatment rate
The launch of novel AITs, in addition to two first-in-class AR pipeline drugs, during the forecast period will temper the effects of generic erosion.	Pricing Reforms in Japan Will Increase the Use of Generics in the AR Space

Source: GlobalData

Increased pollen counts and pollution will increase the intensity and duration of the allergy season in Japan. The rising prevalence AR in Japan will stimulate the growth of this market.

10.4.3.1 Driver: Japanese Pharmaceutical Companies Will Have Enhanced Opportunities Through Increased Partnerships with US and EU Companies

Recent activity related to M&As has provided US and European pharmaceutical companies with enhanced opportunities to partner with Japanese companies. Japanese pharmaceutical companies can gain from the pipelines of the US and European companies, as well as compete globally, while the US and European companies can extend their business into the Japanese market. For example, Shionogi and Torii, through partnerships with European manufacturers, Stallergenes and ALK, are developing and launching novel AITs, which helps the drugs' success in this territory.

10.4.3.2 Driver: The Decreased Timeline for Drug Approval May Allow Faster Access to Novel AR Therapies

The Special Zone for Innovative Technology project was started in 2008 to overcome factors inhibiting the development of innovative technologies in Japan (GlobalData, 2013g). As a result, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) altered its longstanding policy of requiring separate and additional clinical trials in Japanese patients for drug approval. The new policy allows for global clinical data to be used in the Japanese approval process, as long as safety studies are conducted in Japanese patients. The PMDA has also increased its review staff and established a committee that reviews drugs approved elsewhere to make recommendations for fast-track approval in Japan. The hope is that such changes will decrease the regulatory timeframe for drug approval in the world's second-largest pharmaceutical market. This will be important for upcoming drugs in the AR development pipeline, as they will likely be able to hit the market earlier.

10.4.3.3 Driver: Increased Pollen Counts and Pollution Will Increase the Intensity and Duration of the Allergy Season in Japan

Japanese pollen counts have grown fivefold over the past three decades. A primary cause of these rising pollen levels is the afforestation policy for cedar, cypress, and birch trees, which was introduced in the post-World War II era to provide a steady supply of domestic lumber. There are estimated to be 4.5 billion cedar trees in Japan. In addition to the increasingly prevalent Japanese tree pollen, Asian dust events occur, where smog laden with fine particles that are less than 2.5 micrometers in diameter, known as PM2.5, enters Japan from inland China — for example, from the Gobi Desert, where the yellow dust picks up dirt and pollen and carries it to South Korea and Japan via the westerly winds. Increasing pollution from this region is contributing to the AR problem in Japan. Furthermore, studies have shown that pollen levels in Japan are rising in tandem with

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global warming. Scientists have suggested that rising temperatures have helped plant growth in Japan.

10.4.3.4 Driver: The launch of novel AITs, in addition to two first-in-class AR pipeline drugs, during the forecast period will temper the effects of generic erosion.

The Japanese immunotherapy market is currently non-existent. Despite having a large population with AR, less than 6,000 patients were treated with SIT in 2013. Cedartolen, a sublingual liquid containing the standardized Japanese cedar pollen allergen, was evaluated in randomized controlled trials and subsequently approved in 2014. As a condition of approval, prescribing physicians must undergo an online training course. This will increase physician awareness of novel developments in allergen immunotherapies, an unmet need in the field of allergen immunotherapy. The approval of SITs with clinically proven efficacy will bolster the credibility of this therapy type in Japan, which has seen a rapid decline in previous decades, due to the advent of more convenient symptomatic therapies with a rapid onset of action. Within the five-year forecast period, three tablet formulations for Japanese cedar pollen and HDM will be launched in Japan. Torii has been the sole player in this market since SIT became available in Japan in the 1960s. However, Shionogi, in partnership with Stallergenes, is set to enter the SIT market in Japan. Their brand power and extensive marketing base in Japan will place them strongly in this field. Taken together, the extremely small SIT-treated population is set to increase ten-fold in the period between 2013 and 2018.

10.4.3.5 Barrier: Japanese Language Requirements for Regulatory Submissions Slow the Approval Process for Non-Japanese Pharmaceutical Companies

Japanese drug regulatory processes require that foreign drug applications be submitted in the Japanese language. This requirement poses a problem for foreign firms attempting to gain regulatory and intellectual property rights in Japan (GlobalData, 2013g). This policy not only slows the approval process for new drugs coming into the country, but also creates a barrier to patient access to novel therapies, thus making drug access in Japan a time-consuming process. This affects those companies requiring Japanese marketing partners more than those that have already established entry in Japan. This hurdle may be overcome by entering into an agreement with Japanese companies to co-develop and co-commercialize AR pharmaceuticals in Japan.

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10.4.3.6 Barrier: Reference Pricing and Comparator Pricing in Japan Could Present a Challenge for the Launch of New Drugs in the AR Space

The Japanese government strictly regulates drug prices through biennial pricing reviews, reference pricing, and comparator pricing in order to reduce healthcare expenditures (GlobalData, 2013g). The prices for new pharmaceuticals are determined by the MHLW, based on the comparator pricing system. Under this system, prices are set based on similarly-priced drugs already on the market that have the same or similar efficacy and side effect profiles. This could be a challenge for the launch of innovative molecules and stifle the growth of the Japanese AR market. Furthermore, the government can order repricing for classes of drugs if it determines that it is appropriate under the applicable rules.

10.4.3.7 Barrier: Pricing Reforms in Japan Will Increase the Use of Generics in the AR Space

Under the 2014 Japanese drug pricing reforms, a three-bracket price-grouping rule for listed generics was introduced. Under the new regulations, listed generics with the same APIs, formulations, and specifications were placed into three price brackets, based on their market prices. This resulted in products in the same bracket receiving a uniform NHI price, which was based on the weighted-average of their market prices. According to the plans for the 2016 pricing reform, the Central Social Insurance Medical Council is in talks to create a single NHI price for generics with the same APIs, formulations, and specifications. In 2013, the MHLW set a target that generics account for 60% of the market by the end of 2017. There is pressure for the government to set a higher goal as soon as possible. The Z2 rule introduced as part of the 2014 reform reduces the NHI prices of long-listed products, or off-patent brand-name drugs with slow generic penetration by up to 2%.

10.4.3.8 Barrier: Physician preference for surgical interventions for patients with AR will negatively impact the drug treatment rate

Surgical interventions, such as, laser turbinectomy resection, vidian neurotomy, and posterior nasal neurotomy are part of the treatment algorithm in Japan for AR, and are commonly used to treat patients with airborne allergies with nasal obstruction. An increase in physician preference for surgical interventions for patients with AR will decrease the drug treatment rate in the long term.

Appendix

11 Appendix

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Appendix

11.2 Abbreviations

Table 74: Abbreviations	
7MM	seven major markets (US, France, Germany, Italy, Spain, and UK)
AAAI	American Academy of Allergy, Asthma, and Immunology
ACA	Affordable Care Act
ACOT	annual cost of therapy
AGR	Annual Growth Rate
AH	antihistamine
AIFA	Agenzia Italiana del Farmaco
AIT	allergen immunotherapy
ANCOVA	analysis of covariance
ANDA	Abbreviated New Drug Application
ANOVA	analysis of variance
ANS	aqueous nasal spray
ANSM	Agence Nationale de sécurité du Médicament et des produits de santé
APC	antigen-presenting cell
API	active pharmaceutical ingredient
AQ	aqueous
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ASK	Allergic Schoolchildren in Kyoto study
AUC	area under the curve
AZE	azelastine
BBB	blood-brain barrier
BDP	beclomethasone dipropionate
BKC	benzalkonium chloride
BLA	Biologics License Application
BSACI	British Society for Allergy & Clinical Immunology
CAGR	Compound Annual Growth Rate
CDC	Centers for Disease Control and Prevention
CEPS	Comité Economique des Produits de Santé
CFC	chlorofluorocarbon
CI	Confidence Interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disorder
COX	cyclooxygenase
$CysLTR_1$	cysteinyl leukotriene receptor 1
DP1	D prostanoid 1

Appendix

DP2	D prostanoid 2
DTC	direct-to-consumer
EAACI	European Academy of Allergy and Clinical Immunology
ECG	electrocardiogram
ECHRS	European Community Respiratory Health Survey
EEC	environmental exposure chamber
EFA	European Federation of Allergy and Airway Diseases
EMA	European Medicines Agency
ENT	ear, nose and throat specialist
ER	extended-release
EU	European Union
FCεRI	high-affinity IgE receptor
FDA	US Food and Drug Administration
FDC	fixed-dose combination
FDI	foreign direct investment
FP	fluticasone propionate
FY	fiscal year
GA2LEN	Global Allergy and Asthma European Network
GAP	Grazax Asthma Prevention
G-BA	Federal Joint Committee
GCSE	General Certificate of Secondary Education
GDP	Gross Domestic Product
GP	General Practitioner
GSK	GlaxoSmithKline
H1AH	H1 antihistamine
HAS	Haute Autorité de Santé
HDM	house dust mite
HFA	hydrofluoroalkane
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal axis
HRQoL	health-related quality of life
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
INAH	Intranasal antihistamine
INCS	intranasal corticosteroid
IFNγ	interferon-gamma
IPD®	suplatast tosilate

Appendix

ISAAC	International Study of Asthma and Allergies in Childhood
ISS	Istituto Superiore di Sanità
iTNSS	instantaneous total nasal symptom score
ITT	intent-to-treat
J&J	Johnson & Johnson
JPMA	Japan Pharmaceutical Manufacturers Association
JPY	Japanese yen
KOL	key opinion leader
LRA	leukotriene receptor antagonist
LTD-4	cysteinyl leukotriene D4
M&As	mergers and acquisitions
MA	marketing authorization
MAA	Marketing Authorization Application
MAST	multiple allergen simultaneous test
MDI	metered-dose inhaler
MHC	major histocompatibility complex
MHLW	Ministry of Health, Labour and Welfare
MRP	Mutual Recognition Procedure
NAR	non-allergic rhinitis
NHANES	National Health and Nutrition Examination Survey
NHI	National Health Insurance
NHIS	National Health Interview Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNSS	non-nasal symptoms score
NPP	named patient product
NSS	nasal symptoms score
OR	Odds Ratio
OTC	over-the-counter
P&G	Proctor & Gamble
PAR	perennial allergic rhinitis
PCP	primary care physician
PD	pharmacodynamic
PEI	Paul-Ehrlich-Institut
PGD2	prostaglandin D2
PgP	P glycoprotein
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PMPRB	Patented Medicines Prices Review Board

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POM	pharmacist-only medicine; proof of mechanism
PRR	Prevalence Rate Ratio
QoL	quality of life
R&D	research and development
RAST	radioallergosorbent test
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
rTNSS	reflective total nasal symptom score
Rx	prescription
SaKK	Sanofi-aventis KK
S&B	Section and Board (UEMS)
SAR	seasonal allergic rhinitis
SC	subcutaneous
SCIT	subcutaneous immunotherapy
SCUAD	severe chronic upper airway disease
SE	Standard Error
SEAIC	Spanish Society of Allergology and Clinical Immunology
SEK	Swedish Krona
SGA	second-generation antihistamine
SHI	Statutory Health Insurance
SIDRIA	Italian Studies of Respiratory Diseases in Childhood and the Environment
SIT	specific immunotherapy
SLIT	sublingual immunotherapy
sNDA	supplemental New Drug Application
SNS	Sistema Nacional de Salud
SWOT	strengths, weaknesses, opportunities, threats
TAV	Therapie-Allergene-Verordnung
TCM	Traditional Chinese Medicine
TCR	T-cell receptor
TDDS	Transdermal Drug Delivery System technology
TGA	third-generation antihistamine
TGF-β	transforming growth factor-beta
T_H	T helper cell
T_H1	T helper 1 cell
T_H2	T helper 2 cell
TNF	tumor necrosis factor
TNSS	total nasal symptom score
TRAE	treatment-related adverse events
T_{reg}	regulatory T cells
TSS	Total Symptoms Score

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TXA2	thromboxane A2
UEMS	European Union of Medical Specialists
USCB	United States Census Bureau
USPTO	United States Patent and Trademark Office
VBP	value-based pricing
WAO	World Allergy Organization
WHO	World Health Organization

Source: GlobalData

Appendix

11.3 Methodology

GlobalData's dedicated research and analysis teams consist of experienced professionals with marketing, market research, and consulting backgrounds in the pharmaceutical industry, and advanced statistical expertise.

GlobalData adheres to the codes of practice of the European Pharmaceutical Marketing Research Association (EphMRA, ephmra.org).

All GlobalData databases are continuously updated and revised. The following research methodology is followed for all databases and reports.

11.4 Forecasting Methodology

GlobalData uses a patient-based forecast to determine the market size for therapeutic indications. Estimates for the 2014 market for AR in the 7MM (US, France, Germany, Italy, Spain, UK, and Japan) are based on a number of sources, including KOL interviews, prescriber surveys, company reports, press releases, published articles, proprietary databases and general news media.

For asthma, the total patient share exceeds 100% when patients are prescribed more than one drug. The estimated number of compliant days for each drug is determined from prescriber surveys, KOL interviews and internal estimated compliance rates based on the drug's profile.

GlobalData's proprietary forecast model does not account for inflation and is in 2014 dollars. The following paragraphs outline the underlying assumptions for the forecast.

11.4.1 Pediatric Allergic Rhinitis Population

GlobalData's forecast for the allergen-specific immunotherapy market includes both the pediatric and adult populations. The methodology used by GlobalData epidemiologists to estimate the size of the adult AR population in each of the countries under study is described in the Epidemiology section of this report. To estimate the size of the pediatric AR population, the following country-specific methodologies were used.

11.4.1.1 US

GlobalData epidemiologists obtained the age-specific total prevalence of AR in the US from a nationally-representative study that provided the total prevalence of AR in the US in 1993. The study was divided into two parts. In the first part, the study investigators sent a screening

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questionnaire to 15,000 randomly selected households across the US. The researchers screened the household members for the number of days in the past 12 months during which they experienced symptoms of sneezing, runny nose, stuffy nose, itchy eyes, or watery eyes (Nathan et al., 1997). The researchers also screened the household members for doctor-diagnosed hay fever, rhinitis, persistent stuffy nose or head, or allergies involving the eyes, nose, or throat in the past 12 months. Around 10,000 households responded to the first part of the study, representing 22,285 people from across the US. In the second part of the study, the investigators sent a follow-up questionnaire to a sample of 1,450 persons, who responded affirmatively to having symptoms for >7 days within the past year, either singly or consecutively. In the follow-up questionnaire, the participants were asked to select the term that best described their symptoms. If the participants replied affirmatively to the options "seasonal allergy" or "an allergy I have all the time," then they were termed as having AR (Nathan et al., 1997).

To construct the epidemiological forecast for the total prevalent cases of AR in the US, GlobalData epidemiologists used data on the total prevalence of AR from the 1993 study by Nathan and colleagues. Although the study provided the 12-month prevalence, and not the lifetime prevalence, GlobalData epidemiologists selected the study, as epidemiological studies report that both prevalence measures are comparable for AR in children (Austin et al., 1999; Kusunoki et al., 2009). However, the study researchers only provided the overall age-specific total prevalence of AR. Because the researchers reported that there is no difference in the sex-specific total prevalence of AR, GlobalData epidemiologists applied the overall (both sexes) age-specific total prevalence of AR to both sexes to obtain the age- and sex-specific total prevalence of AR in the US (Nathan et al., 1997). Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (1993) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in the US for each year to forecast the total prevalent cases of AR in the US from 2013–2023 (Nathan et al.,1997; USCB, 2012).

11.4.1.2 France

GlobalData epidemiologists obtained the total prevalence of AR among children ages 13–14 years in France from cross-sectional surveys conducted in 2002 in Languedoc Roussillon, France. These surveys used the ISAAC protocol to collect information from randomly selected schools. The first survey consisted of 3,383 participants, and the second survey consisted of 1,642 participants. The

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questionnaires were the French version of the ISAAC core questionnaire, and were completed by the children themselves (Annesi-Maesano et al., 2009).

To construct the epidemiological forecast for the total prevalent cases of AR in France, GlobalData epidemiologists used data on the total prevalence of AR from the study by Annesi-Maesano and colleagues. The study researchers provided the total prevalence of AR in children ages 13–14 years in France, which was applied to age group 10–14 years. Additionally, as there were no data on the prevalence of AR in other age groups (0–4 years, 5–9 years, and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age groups 0–4 years, 5–9 years, and 15–17 years was the same as the prevalence in the age group 13–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2002) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in France in each year to forecast the total prevalent cases of AR in France from 2013–2023 (Annesi-Maesano et al., 2009; USCB, 2012).

11.4.1.3 Germany

Due to the lack of total prevalence data for AR in children in Germany, GlobalData epidemiologists assumed that the total prevalence of AR in children in Germany was the same as that in France (Annesi-Maesano et al., 2009).

Due to the scarcity of total prevalence data for AR in children in Germany, GlobalData epidemiologists assumed that the age- and sex-specific total prevalence of AR in Germany were the same as that in France. GlobalData epidemiologists kept the age- and sex-specific prevalence proportions of AR constant throughout the forecast period due to the lack of historical data necessary to forecast future trends. GlobalData epidemiologists then applied the age- and sex-specific total prevalence proportions of AR to the respective age- and sex-specific population estimates in each year to forecast the total prevalent cases of AR in Germany from 2013–2023 (Annesi-Maesano et al., 2009; USCB, 2013).

11.4.1.4 Italy

GlobalData epidemiologists obtained the age-specific total prevalence of AR in Italy from a study by Galassi and colleagues. This study was a part of the ISAAC study, and was designed

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specifically to study the prevalence of AR and other allergic conditions in children ages 6–7 years and 13–14 years under a project called the Italian Studies of Respiratory Diseases in Childhood and the Environment (SIDRIA). Phase I of SIDRIA was conducted between October 1994 and May 1995, and Phase II of SIDRIA was conducted between January and May 2002, in Turin, Milan, Trent, Emilia-Romagna, Florence, Empoli, Siena, and Rome. During Phase I of the study, 16,115 questionnaires were filled out by the parents of the children ages 6–7 years, and 19,723 questionnaires were filled out by adolescents ages 13–14 years. Similarly, during the Phase II of the study, 11,287 questionnaires were filled out by the parents of the children ages 6–7 years, and 10,267 questionnaires were filled out by adolescents ages 13–14 years. The questionnaires consisted of ISAAC core questions on AR (Galassi et al., 2006).

To construct the epidemiological forecast for the total prevalent cases of AR in Italy, GlobalData epidemiologists used data on the self-reported total prevalence of AR from the study by Galassi and colleagues. Although the study provided the 12-month prevalence, and not the lifetime prevalence, GlobalData epidemiologists selected the study, as other epidemiological studies report that both prevalence measures are comparable for AR in children (Austin et al., 1999; Kusunoki et al., 2009). The study researchers provided the self-reported total prevalence of AR in children ages 6–7 years and 13–14 years in Italy, which was applied to the age groups 5–9 years and 10–14 years, respectively. Additionally, as there were no data on the prevalence of AR in the other age groups (0–4 years and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age group 0–4 years was the same as the prevalence in the age group 5–9 years, and that the prevalence in the age group 15–17 years was the same as the prevalence in the age group 10–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2002) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Italy in each year to forecast the total prevalent cases of AR in Italy from 2013–2023 (Galassi et al., 2006; USCB, 2012).

11.4.1.5 Spain

GlobalData epidemiologists estimated the total prevalence of AR among children ages 10–11 years in Spain from a cross-sectional study, which was carried out as part of ISAAC Phase II in 2001. The study included 1,143 children in 29 schools in Almeria, Spain, whose parents were

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administered questionnaires prepared on the basis of the ISAAC protocol. Additionally, the skin prick test was also conducted to test for a positive reaction to allergens. The current and past prevalence of AR was estimated by a positive response to the question, "Has your son/daughter sneezed or ever sneezed, or has he/she had a runny or blocked nose without having a cold or influenza during the last 12 months?" (Batlles-Garrido et al., 2010).

To construct the epidemiological forecast for the total prevalent cases of AR in Spain, GlobalData epidemiologists used data on the self-reported total prevalence of AR from the study by Battles-Garrido and colleagues. Although the study provided the 12-month prevalence, and not the lifetime prevalence, GlobalData epidemiologists selected the study, as other epidemiological studies report that both prevalence measures are comparable for AR in children (Austin et al., 1999; Kusunoki et al., 2009). The study researchers provided the self-reported total prevalence of AR in children ages 10–11 years in Spain, which was applied to the age group 10–14 years. Additionally, as there were no data on the prevalence of AR in the other age groups (0–4 years, 5–9 years, and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age groups 0–4 years, 5–9 years, and 15–17 years was the same as the prevalence in the age group 13–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2001) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Spain in each year to forecast the total prevalent cases of AR in Spain from 2013–2023 (Battles-Garrido et al., 2010; USCB, 2012).

11.4.1.6 UK

GlobalData epidemiologists obtained the total prevalence of AR among children ages 12–14 years in the UK from a survey that was carried out as part of the ISAAC study conducted by Anderson and colleagues during the years 1995 and 2002. The researchers conducted the study in England, Scotland, Wales, and the offshore islands of Guernsey, Isle of Man, and Jersey in the UK. The researchers administered 15,083 questionnaires during 1995, and 15,755 questionnaires during 2002, among secondary school children ages 12–14 years. The questionnaire was adopted from the ISAAC protocol, and all the questionnaires were filled out by the children themselves (Anderson et al., 2004).

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To construct the epidemiological forecast for the total prevalent cases of AR in the UK, GlobalData epidemiologists used data on the total prevalence of AR from the study by Anderson and colleagues. The study researchers provided the total prevalence of AR in children ages 12–14 years in the UK, which was applied to the age group 10–14 years. Additionally, as there were no data on the prevalence of AR in the other age groups (0–4 years, 5–9 years, and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age groups 0–4 years, 5–9, years, and 15–17 years was the same as the prevalence in the age group 13–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2002) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in the UK in each year to forecast the total prevalent cases of AR in the UK from 2013–2023 (Anderson et al., 2004; USCB, 2012).

11.4.1.7 Japan

GlobalData epidemiologists obtained data on the prevalence of AR in Japan from a population-based survey called the Allergic Schoolchildren in Kyoto (ASK) study conducted in Kyoto, Japan during 2006. The study enrolled 13,215 schoolchildren ages 7–15 years from 30 schools, whose parents were administered questionnaires prepared on the basis of the ISAAC questionnaire, which was validated by the Study Group of Epidemiology of Allergic Diseases established by the Japanese MHLW (Kusunoki et al., 2009).

To construct the epidemiological forecast for the total prevalent cases of AR in Japan, GlobalData epidemiologists used data on the total prevalence of AR from the study by Kusunoki and colleagues. The study researchers provided the sex-specific total prevalence of AR in children ages 7–15 years in Japan, which was applied to the age groups 5–9 years, 10–14 years, and 15–17 years. Additionally, as there were no data on the prevalence of AR for the age group 0–4 years, GlobalData epidemiologists assumed that the prevalence in the age group 0–4 years was the same as the prevalence in the age group 5–9 years in both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2006) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Japan in each year to

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forecast the total prevalent cases of AR in Japan from 2013–2023 (Kusunoki et al., 2009; USCB, 2012).

11.4.2 Diagnosed AR Patients

The total AR population includes both undiagnosed and diagnosed patients. GlobalData multiplied the total AR population by a diagnosis rate obtained from our prescriber surveys to determine the diagnosed patient population. The diagnosis rate was modified in order to account for the fact that the AR prevalence numbers represent the lifetime AR prevalence.

11.4.3 Percentage of Drug-Treated Patients

The drug treatment rates for AR were obtained from GlobalData's survey of high-prescribing physicians and KOL interviews. This number will remain constant during the forecast period in the 7MM (US, France, Germany, Italy, Spain, UK, and Japan).

11.4.4 Drugs Included in Each Therapeutic Class

Due to the large number of drugs in each therapeutic class, the lists below are not exhaustive, but rather, a representation of the drugs considered.

Antihistamines

AHs include, but are not limited to:

US: Generic versions of brompheniramine, cetirizine hydrochloride, fexofenadine hydrochloride, levocetirizine, loratadine, acrivastine, and desloratadine

Europe: Illaxten (bilastine), Mizollen (mizolastine), Rupafin (rupatadine fumarate), and generic versions of fexofenadine, levocetirizine, loratadine, cetirizine hydrochloride, acrivastine, and desloratadine

Japan: Generic versions of epinastine hydrochloride, cetirizine hydrochloride, bepotastine besilate, fexofenadine hydrochloride, olopatadine hydrochloride, loratadine, and levocetirizine

Intranasal Antihistamines

The INAHs include, but are not limited to, Livostin and generic versions of azelastine and olopatadine.

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Intranasal Corticosteroids

Veramsyt/Avamys (fluticasone furoate), Omnaris (ciclesonide), Zetonna (ciclesonide) Qnasl (beclomethasone dipropionate) Erizas (dexamethasone cipecilate), and generic versions of beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, and flunisolide

Intranasal Corticosteroid/Antihistamine

Dymista

Leukotriene Receptor Antagonists

Singulair and generic versions of montelukast sodium

Anticholinergics

Generic versions of ipratropium bromide

Decongestants

Generic versions of pseudoephedrine, phenylephrine, and oxymetazoline

Mast cell stabilizers

Sodium cromoglycate

Thromboxane A2 receptor antagonist

Baynas (ramatroban)

TH2 cytokine inhibitor

Suplatast tosilate (IPD®)

Subcutaneous immunotherapy

Includes extracts manufactured by:

US: ALK-Abello A/S, Allergy Laboratories, Greer Laboratories and Jubilant Hollister-Steir Laboratories LLC

EU: ALK-Abello A/S, Stallergenes, Allergy Therapuetics, HAL Allergy, Merck KGaA, Leti, and other smaller companies

Japan: Torii Pharmaceuticals

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Sublingual immunotherapy

Includes extracts manufactured by:

US: Greer

EU: ALK-Abello A/S, Stallergenes, Allergy Therapuetics, HAL Allergy, Merck KgaA, Leti, and other smaller companies

Japan: Torii

Allergen immunotherapy tablets

Includes extracts manufactured by:

US: Merck (including Grastek, Ragwitek, and Mitizax) and Greer (Oralair)

EU: ALK-Abello A/S, Stallergenes, Allergy Therapuetics, HAL Allergy, Leti, and other smaller companies

Japan: Torii and Shionogi

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11.4.5 Launch and Patent Expiry Dates

Table 75 lists the key launch dates of the currently available AR therapies.

Table 75: Key Launch Dates of the Currently Available AR Therapies

Product	US	5EU	Japan
Allegra (fexofenadine)	1996	1997	2000
Allelock (olopatadine)	N/A	N/A	2001
Astelin (azelastine)	1996	2000	-
Astepro (azelastine hydrochloride)	2009	2013	N/A
Baynas (ramatroban)	N/A	N/A	2000
Beconase (beclomethasone)	1976	1975	-
Benadryl (diphenhydramine)	1946	-	1998
Clarinex (desloratadine)	2002	2001	Phase III
Claritin (loratadine)	1993	1988	2002
Dymista (azelastine/fluticasone propionate)	2012	2013	N/A
Flonase (fluticasone propionate)	1995	-	-
Ilaxten (bilastine)	N/A	2011	Phase II
Nasacort (triamcinolone acetonide)	1991	1997	2013
Nasalcrom (sodium cromoglycate)	1997	-	-
Nasonex (mometasone furoate)	1997	1997	N/A
Omnaris (ciclesonide)	2008	N/A	N/A
Patanase (olopatadine hydrochloride)	2008	N/A	N/A
Qnasl (beclomethasone diproprionate)	2012	N/A	2002
Rhinocort (budesonide)	1994	-	1986
Singulair (montelukast sodium)	1998	2001	2008
Suplatast tosilate (IPD®)	N/A	N/A	1995
Talion (bepotastine)	N/A	N/A	2000
Veramyst (fluticasone furoate)	2007	2008	2009
Xyzal (levocetirizine dihydrochloride)	2007	2001	N/A
Zetonna (ciclesonide)	2008	N/A	N/A
Zyrtec (cetirizine hydrochloride)	1996	1989	1998
Zyrtec-D (cetirizine hydrochloride and pseudoephedrine hydrochloride)	2001	-	-
S-555739	2018	N/A	2017
HP-3060	N/A	N/A	2017

Source: GlobalData

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Table 76 lists the key loss of exclusivity dates of the currently available AR therapies.

Table 76: Key Loss of Exclusivity Dates of the Currently Available AR Therapies

Product	US	5EU	Japan
Astepro (azelastine)	2028	-	2025
Baynas (ramatroban)	N/A	N/A	2016
Dymista (azelastine/fluticasone propionate)	2026	2023	
Flonase (fluticasone propionate)	2004	2005	-
Ilaxten (bilastine)	2017	2022	2017
Nasonex (mometasone furoate)	2018	2014	2016
Patanase (olopatadine hydrochloride)	2011	N/A	N/A
Qnasl (beclomethasone diproprionate)	2017	N/A	N/A
Singulair (montelukast sodium)	2012	2013	2016
Veramyst (fluticasone furoate)	2021	2023	2025
Zetonna (ciclesonide)	2017	2016	2016
Omnaris (ciclesonide)	2017	2016	2016

Source: GlobalData

11.4.6 1General Pricing Assumptions

GlobalData uses national formularies to gather pricing information and recognizes that the prices presented in formularies can differ, representing prices at different stages in the supply chain. As such, when ex-factory wholesale prices are not available, GlobalData uses conversion formulas, which remove taxes, and/or pharmacy and wholesale margins, in order to obtain estimated ex-factory wholesale prices for each country.

Currency conversion to US dollars utilized the 2014 yearly average from OANDA (www.oanda.com).

The following references were used as price sources, backing-out formulas, and discount rates for each market covered in this report to estimate ex-factory wholesale pricing:

- US: prices were obtained from Thomson Reuter's Red Book.
- France: prices were obtained from Ministry of Social Affairs and Health (Ministère des Affaires Sociales et de la Santé)
- Germany: prices were obtained from the Rote List, and conversion formulas were determined based on information from the Patented Medicine Prices Review Board (PMPRB) (2013).

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- Italy: prices were obtained from the Italian Medicines Agency (Agenzia Italiana del Farmaco, l'Informatore Farmaceutico), and conversion formulas were determined based on information from the PMPRB (2013).
- Spain: prices were obtained from the Spanish Agency for Medicines and Products (Agencia Española de Medicamentos y Productos, Organización Farmacéutica Colegial).
- UK: prices were obtained from the British National Formulary (BNF) and conversion formulas were determined based on information from the European Parliament (2011) and National Institute for Health and Care Excellence (NICE) (2014).
- Japan: prices were obtained from SSRI's NHI drug price database (April 2012). Conversion formulas were determined based on information from the Japan Pharmaceutical Manufacturers Association (JPMA) (2012) and *The Wall Street Journal* (Mochizuki, 2014).

11.4.7 Individual Drug Assumptions

Oral antihistamine assumptions:

- Clinical Positioning: GlobalData expects that AHs will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 140 in the US and 200 in the 5EU and Japan.
- ACOT: Treatment with oral AHs costs: US ($92.40); France ($38.00); Germany ($66.00); Italy ($37.00); Spain ($63.00); UK ($14.00); Japan ($139.00).
- Compliance: Oral AHs' average compliance rate, according to GlobalData's primary research, is estimated to be: US (63%); EU (73%); Japan (64%).

Intranasal antihistamine assumptions:

- Clinical Positioning: GlobalData expects that intranasal antihistamines will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 240 in the US and 200 in the 5EU and Japan.
- ACOT: Treatment with intranasal antihistamines costs: US ($269.00); France ($32.00); Germany ($48.00); Italy ($32.00); Spain ($48.00); UK ($80.00); Japan ($144.00). The ACOT

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for the US will decrease upon the patent expiry of two key drugs, Astepro and Patanase, to ($224.00).

- Compliance: INAHs' average compliance rate, according to GlobalData's primary research, is estimated to be: US (44%); EU (48%); Japan (33%).

Intranasal corticosteroid assumptions:

- Clinical Positioning: GlobalData expects that INCS will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment with INCS costs: US ($304.00); France ($39.00); Germany ($66.00); Italy ($125.00); Spain ($57.00); UK ($35.00); Japan ($224.00).
- Compliance: INCS' average compliance rate, according to GlobalData's primary research, is estimated to be: US (60%); EU (59%); Japan (67%).

Nasonex assumptions:

- Clinical Positioning: GlobalData expects that Nasonex will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment with Nasonex costs: US ($152.00); France ($24.00); Germany ($48.00); Italy ($68.00); Spain ($32.00); UK ($32.00);
- Compliance: Nasonex's average compliance rate, according to GlobalData's primary research, is estimated to be: US (60%); EU (59%)

Qnasl assumptions:

- Clinical Positioning: GlobalData expects that Qnasl will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200 in the US .
- ACOT: Treatment with Qnasl costs: US ($912.00);
- Compliance: Qnasl's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

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Zetonna assumptions:

- Clinical Positioning: GlobalData expects that Zetonna will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200 in the US .
- ACOT: Treatment with Zetonna costs: US ($1,176.00);
- Compliance: Zetonna's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Omnaris assumptions:

- Clinical Positioning: GlobalData expects that Omnaris will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200 in the US .
- ACOT: Treatment with Omnaris costs: US ($1,176.00)
- Compliance: Omnaris' average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Veramyst assumptions:

- Clinical Positioning: GlobalData expects that Veramyst will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment with Veramyst costs: US ($992.00); France ($56.00); Germany ($56.00); Italy ($144.00); Spain ($96.00); UK ($56.00); Japan ($304.00)
- Compliance: Veramyst's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Dymista assumptions:

- Clinical Positioning: GlobalData expects that Dymista will be used for all AR severities as a medication to provide quick relief of AR symptoms.

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- Treatment days: The number of treatment days per year for all AR patients is 260 in the US and 200 in the 5EU .
- ACOT: Treatment with Dymista costs: US ($146.00); France ($144.00); Germany ($176.00); Italy ($208.00); Spain ($144.00); UK ($176.00)
- Compliance: Dymista's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Leukotriene receptor antagonist assumptions:

- Clinical Positioning: GlobalData expects that LRAs will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 260 in the US and 200 in the 5EU .
- ACOT: Treatment with LRAs costs: US ($304.00); France ($124.00); Germany ($124.00); Italy ($60.00); Spain ($134.00); UK ($36.00); Japan (Singulair: $466.00)
- Compliance: LRAs' average compliance rate, according to GlobalData's primary research, is estimated to be: US (60%); EU (54%); Japan (32%).

Decongestant assumptions:

- Clinical Positioning: GlobalData expects that decongestants will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 27.
- ACOT: Treatment for 365 days with decongestants costs: US ($16.20).
- Compliance: Decongestants' average compliance rate, according to GlobalData's primary research, is estimated to be: 47%

Mast cell stabilizers assumptions:

- Clinical Positioning: GlobalData expects that mast cell stabilizers will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with mast cell stabilizers costs: Japan ($32.00).

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- Compliance: Mast cell stabilizers' average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Thromboxane A2 receptor antagonist (Baynas) assumptions:

- Clinical Positioning: GlobalData expects that Baynas will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with Baynas costs: Japan ($532.00).
- Compliance: Baynas' average compliance rate, according to GlobalData's primary research, is estimated to be 70%.

TH2 cytokine inhibitors (suplatast tosilate, IPD®) assumptions:

- Clinical Positioning: GlobalData expects that suplatast tosilate, IPD®, will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with suplatast tosilate, IPD®, costs: Japan ($234.00).
- Compliance: Suplatast tosilate, IPD®'s average compliance rate, according to GlobalData's primary research, is estimated to be 60%.

S-555739 assumptions:

- Clinical Positioning: GlobalData expects that S-555739 will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with S-555739 costs: US ($1,056.00); Japan ($532.00).
- Compliance: S-555739 average compliance rate, according to GlobalData's primary research, is estimated to be 60%.

HP-3060 assumptions:

- Clinical Positioning: GlobalData expects that HP-3060 will be used for all AR severities as a medication to provide quick relief of AR symptoms.

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- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with HP-3060 costs: Japan ($400.00).
- Compliance: HP-3060's average compliance rate, according to GlobalData's primary research, is estimated to be 80%. Subcutaneous Immunotherapy:

US

- Clinical positioning: GlobalData estimated that 100% of patients treated with SIT will receive SCIT in 2018. This is because, despite the approval of AITs, it is thought that they will be prescribed as second-line treatments to SCIT, or to those who have refused SCIT, owing to the lack of financial incentives for US allergists, and their single-allergen composition.
- Average ACOT: Based on KOL guidance, prices obtained directly from several manufacturers, and a 2014 research paper by Dranitsaris and Ellis that analyzed the direct and indirect costs of SIT, suggesting that the average cost of an allergen extract administered as a SCIT is $200 per year, based on an estimated three-year treatment course and a high dropout rate of over 50% in Year 1. (Dranitsaris and Ellis, 2014)
- Compliance: We assumed a compliance rate of 40%, based KOL insight, due to the undesirable nature of injections and the frequent clinic visits required.

5EU

- Clinical positioning: GlobalData estimates that the use of SCIT will decline within the forecast period.
- ACOT: Based on KOL guidance suggesting that the average cost of an allergen extract administered as a SCIT is $1,050 per year.
- Compliance: We assumed a compliance rate of 51%, based on KOL insight and a survey of patients receiving SCIT in Germany from 2005–2007, published in Current Medical Research Opinion (Sieber et al., 2011).

Japan

- Clinical positioning: KOL insight suggested that in 2014, approximately 10% of prescription drug-treated Japanese AR patients received SCIT, most commonly for HDM allergy. GlobalData estimated that only 1% of patients receiving SIT will receive SCIT in 2018. The

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launch of two AITs containing the standardized HDM extract will largely take the patient share of HDM-allergic AR patients, due to their increased convenience, as they can be administered at home and are preferable to injections for most patients, especially children.

- ACOT: Based on KOL guidance and secondary research suggesting that the average cost of an allergen extract administered as an SCIT is $1,224 per year.
- Compliance: We assumed a compliance rate of 40%, based KOL insight, due to the undesirable nature of injections and the frequent hospital visits required for each treatment.

Sublingual Immunotherapy Drops:

US

- Clinical positioning: GlobalData estimated that 0.9% of SIT-treated AR patients will be treated with Greer's SAIL short ragweed sublingual liquid in 2018, following its estimated launch in 2016. This slow uptake will be tempered by the launch of Ragwitek in 2014, a tablet containing the short ragweed allergen, marketed by Merck in collaboration with ALK-Abello.
- Treatment days: SAIL is a once-daily sublingual drop therapy used for 8–16 weeks pre-seasonally and during the entire ragweed pollen season.
- ACOT: Based on the ex-manufacturer price of sublingual therapies in the 5EU, SAIL was assigned a price of $513.20 per year.
- Compliance: We assumed a compliance rate of 70%, based on KOL insight and a survey of patients receiving SLIT in Germany from 2005–2007 published in Current Medical Research Opinion (Sieber et al., 2011).

5EU

- Clinical positioning: GlobalData estimated that the SLIT market will decline slightly over the forecast period, as physicians would prescribe a tablet over a liquid drop in patients prescribed allergen immunotherapy sublingually.
- ACOT: Based on KOL guidance suggesting that the average cost of an allergen extract administered as a SLIT is $513.20 per year.

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- Compliance: We assumed a compliance rate of 70%, based on KOL insight and a survey of patients receiving SLIT in Germany from 2005–2007 published in Current Medical Research Opinion (Sieber et al., 2011).

Japan

- Clinical positioning: KOL insight suggested that in 2014, approximately 90% of SIT-treated Japanese patients received SLIT; most patients receive SLIT for seasonal allergies, predominantly Japanese cedar pollen. GlobalData estimated that this patient share will decrease to 40% by 2018, primarily due to the launch of a sublingual AIT containing the cedar pollen allergen.
- ACOT: Based on KOL guidance and secondary research, GlobalData assumed that the average cost of an allergen extract administered as an SLIT is $1,224 per year.
- Compliance: We assumed a compliance rate of 50%, based KOL insight, due to the inconvenience of this treatment option and its delayed onset of action compared with the symptomatic therapies.

Allergen Immunotherapy Tablets:

US

- Clinical positioning: GlobalData estimates that 6.1% of the SIT drug-treated population will be treated with an AIT by 2018.
- Treatment days: Oralair, a once-daily tablet, was used as a benchmark. Treatment should start four months before grass pollen is expected to appear, and be continued until the end of the pollen season (usually 2–6 months). On average, we assumed that Oralair would be taken for eight months a year. Grazax (Grastek), a once-daily tablet, should be initiated at least four months before the start of the pollen season, and be continued year-round for up to three years. The grass pollen season, on average, begins around April in the US. On average, we assumed that Grazax would be taken for 12 months a year. Based on these two products, we determined that tablet formulations would be used for 10 months each year.
- Average cost of therapy: Based on the ex-manufacturer price of Grazax and Oralair in the 5EU, allergen immunotherapy tablets were assigned an average annual cost of ($2685.00), (ex-factory wholesale price).

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- Compliance: We assumed a compliance rate of 70%, based on the convenience of Grazax and Oralair compared with other SIT formulations and its once-daily dosing.

5EU

- Clinical positioning: GlobalData estimates that 10% of the SIT drug-treated population will be treated with either a tablet by 2018.
- Treatment days: Oralair, a once-daily tablet, was used as a benchmark. Treatment should start four months before grass pollen is expected to appear and be continued until the end of the pollen season (usually 2–6 months). On average, we assumed that Oralair would be taken for eight months a year. Grazax (Grastek), a once-daily tablet, should be initiated at least four months before the start of the pollen season and be continued year round for up to three years. The grass pollen season on average begins in April in the 5EU. On average, we assumed that Grazax would be taken for 12 months a year. Based on these two products we averaged that tablet formulations would be used for 10 months each year.
- Average ACOT: Based on the ex-manufacturer price of Grazax and Oralair in the 5EU, AIT tablets were assigned an average annual cost of ($1,206.50), (ex-factory wholesale price).
- Compliance: We assumed a compliance rate of 70%, based on the convenience of Grazax and Oralair compared with other SIT formulations, and its once-daily dosing.

Japan

- Clinical positioning: GlobalData estimates that 59% of the SIT drug-treated population will be treated with either a Torii or a Shionogi tablet by 2018.
- Average ACOT: Using the average annual cost of Grazax and Oralair in the 5EU ($1,206.50), a ratio was applied to the ACOT for SCITs in Japan and the 5EU. The price for an AIT in Japan was extrapolated, generating an ACOT of $1,407, which was applied to both Torii and Shionogi's pipeline tablets.
- Compliance: We assumed a compliance rate of 70%, based on convenience of AIT compared with other SIT formulations, and its potential once-daily dosing.

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11.4.8 Generic Erosion

The prices of drugs with expiring patents are decreased during our forecast to account for generic competition. The percentage of branded prescriptions shifting to generics is adjusted to reflect the overall strength of the generic drug market in each country.

11.4.9 Pricing of Pipeline Agents

- S-555739 is priced similarly to the branded TXA2 receptor antagonist, Baynas, as it will be used for the third-line treatment of patients with chronic refractory AR, targeting a related pathway with specific biological and clinical features.
- HP-3060 is priced at a 40% premium over the class of INCS therapies, including multiple generic products, due to its more convenient transdermal administration. This will be a first-in-class product on the Japanese market, where there is a preference for patch formulations, particularly among elderly and pediatric patients.

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11.5 Physicians and Specialists Included in This Study

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President Elect INTERASMA-Global Asthma Association

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Appendix

High-Prescribing Physician Survey

In addition to the KOLs cited above, high-prescribing physicians (non-KOLs), including allergists and PCPs, represented the seven markets covered in this report. All of the non-KOL responses were obtained through an electronic survey created by the report authors in collaboration with the GlobalData primary research team. The survey was launched in October 2014, and was completed in November 2014.

Table 77 provides a summary of the high prescribers surveyed for this report, by country.

Table 77: High-Prescribing Physicians (non-KOLs) Surveyed, by Country

Country	Total Number of Physicians Surveyed
US	20
France	15
Germany	10
Italy	16
Spain	16
UK	9
Japan	10

Source: GlobalData

Appendix

11.6 About the Authors

11.6.1 Analyst

Claire Gibson, PhD, Managing Analyst, Oncology

Claire Gibson, PhD, is an Oncology Healthcare Managing Analyst at GlobalData in London. Claire's previous academic research experience in the biomedical field included the formulation of extended-release drug formulations containing small molecules. Prior to working at GlobalData, she was an analyst at Q Chip, a Cardiff-based biotechnology company, evaluating metabolic disorders. Claire received a BBSRC CASE award to complete an industrially-led PhD in stem cell and regenerative medicine at Cardiff University, sponsored by Q Chip. Here, she developed a novel microfluidics-generated microcarrier technology to isolate, rapidly expand, and differentiate mesenchymal stem cells. Prior to this, she completed a BSc in Biochemistry from the School of Biomedical Sciences, Cardiff University. In addition to her academic career, Claire also worked within the NHS in prescription services, and also ran several healthcare screening programs.

11.6.2 Therapy Area Director

Valentina Gburcik, PhD, Director, Cardiovascular and Metabolic Disorders

Valentina Gburcik, PhD, is the Director of Cardiovascular and Metabolic Disorders at GlobalData in London. Valentina has previously produced reports and forecasting models for the type 2 diabetes, microvascular complications of diabetes, and gout markets. Valentina's previous academic research experience in the biomedical field included the molecular and systems biology approach to diabetes and obesity. She also participated in the development of a novel nanoparticle-based system for the delivery of nucleic acids and drugs into cells, which led her to co-author a patent application, and co-found Tecrea Ltd., a spinoff company based in London's Bioscience Innovation Centre. Previously, in parallel with her academic research, she worked part-time as a Business Development/Project Manager for the biotech company, Imuthes Ltd., in London. Valentina received her PhD in Biological Sciences from the Department of Cell Biology, University of Geneva, where she worked on the mechanisms of drug resistance in breast cancer. During that time, she also obtained a Certificate in Entrepreneurship from CTI – Venture Challenge Program, Switzerland. Previously, she obtained her BSc degree in Biochemistry from the Faculty of Chemistry, University of Belgrade.

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11.6.3 Epidemiologist

Lizzy Sunny, PhD, Project Manager, Epidemiology

Lizzy Sunny, PhD, currently serves as Project Manager of the Epidemiology Division at GlobalData in Hyderabad, India. Dr. Sunny has worked with various national-level cancer registries, academic institutions, and pharmaceutical consulting companies around the globe. She is experienced in the design and execution of many large-scale population-based epidemiological studies, including breast cancer screening studies, and in analyzing epidemiology research data. During her career, she has published several research articles in various international peer-reviewed journals, and has written several reports and monographs related to cancer epidemiology. Additionally, she has worked for top pharmaceutical companies in the US and Europe on epidemiology consulting projects. She has received large project grants from national and international organizations, and has headed various national-level epidemiology projects in India. Dr. Sunny holds a Master's degree in Science from MG University, India; a Doctoral Programs in Public Health (DPPH) degree from Tampere School of Public Health at Tampere University, Finland; and a PhD in Epidemiology from Tampere University, Finland. She completed her post-doctoral research in clinical cancer epidemiology at Gothenburg University in Sweden.

11.6.4 Global Head of Healthcare

Jim Coutcher, MS, Global Head of Healthcare

Jim Coutcher, MS, is Global Head of Healthcare for GlobalData in Boston, managing the Medical and Pharmaceutical arms of the business. Jim has more than 20 years' experience in the pharmaceutical industry, in which time he has focused on both the preclinical and clinical aspects of drug development. He began his career in the laboratories of Pfizer, where he was involved in preclinical research for diabetes, diabetic complications and obesity. After more than 10 years in research, he transitioned into positions in sales and marketing for ALPCO Diagnostics; consulting for CNS, CVMD, immunology and oncology projects for Citeline, and business development for KCAS. Jim received his B.A. in Chemistry from Boston University and an MS in Neuropharmacology from the University of South Florida.

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11.7 About GlobalData

GlobalData is a leading global provider of business intelligence in the healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports, and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

GlobalData has offices in New York, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

11.8 Disclaimer

The facts of this report are believed to be correct at the time of publication, but cannot be guaranteed. Please note that the findings, conclusions and recommendations that GlobalData delivers will be based on information gathered in good faith from both primary and secondary sources, whose accuracy we are not always in a position to guarantee. As such, GlobalData can accept no liability whatsoever for actions taken based on any information that may subsequently prove to be incorrect.

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