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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:

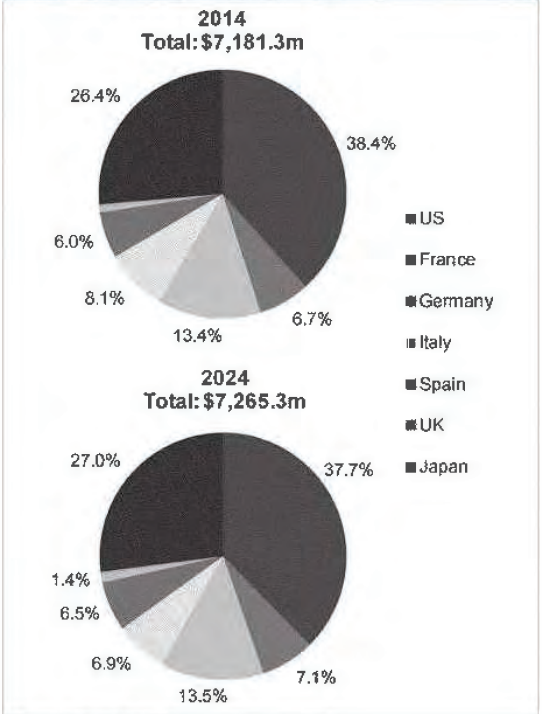
- The introduction of several AIT tablets: Merck's Grastek (grass), Ragwitek (ragweed), and Mitizax (house dust mite [HDM]) tablets, as well as Greer's Oralair (grass) in the US. These new products overcome the inconvenience of conventional subcutaneous immunotherapies (SCITs).
- The increasing global 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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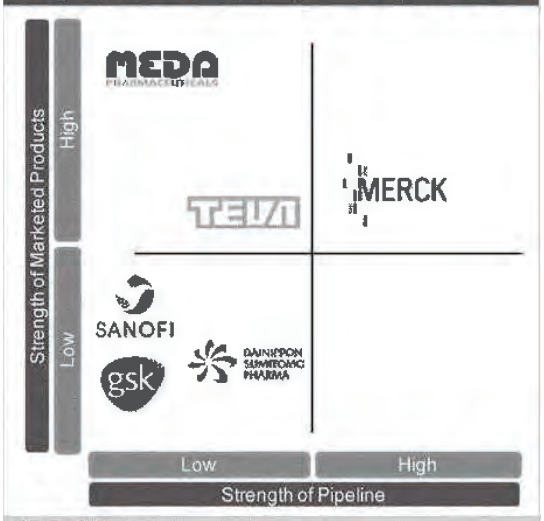
The figure below provides an analysis of the company portfolio gap in AR during the forecast period.

Company Portfolio Gap Analysis in AR, 2014–2024



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 oral 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

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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).

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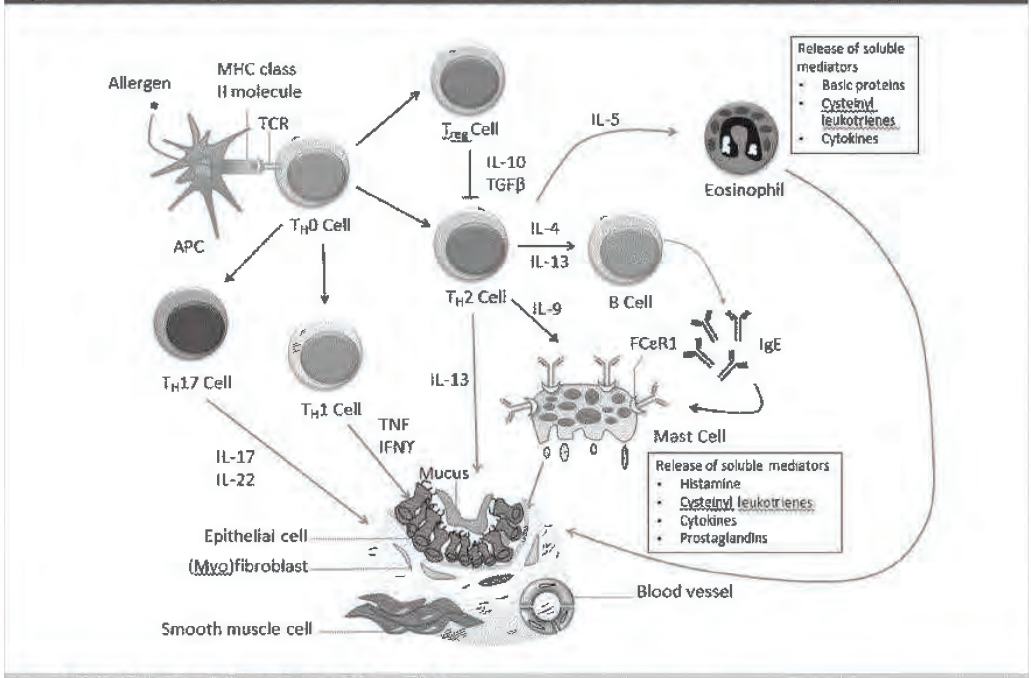
Figure 1 illustrates the immunological mechanisms involved in the early- and late-phase response to an inhaled allergen in a sensitized individual.

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

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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

Disease Overview

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.

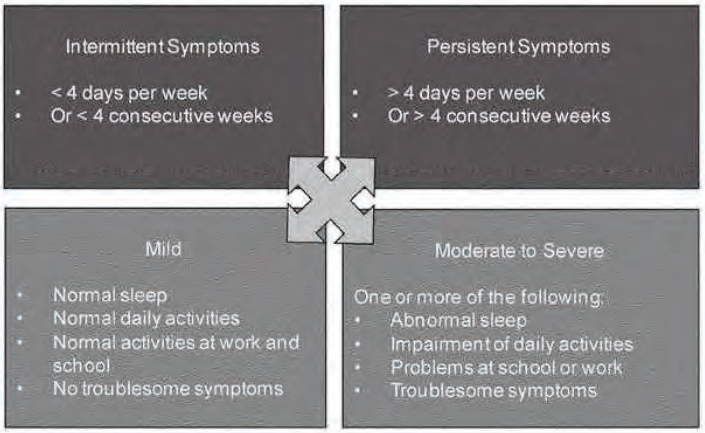
3.3.2 ARIA Classification of AR

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.

Disease Overview

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.

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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

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(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

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

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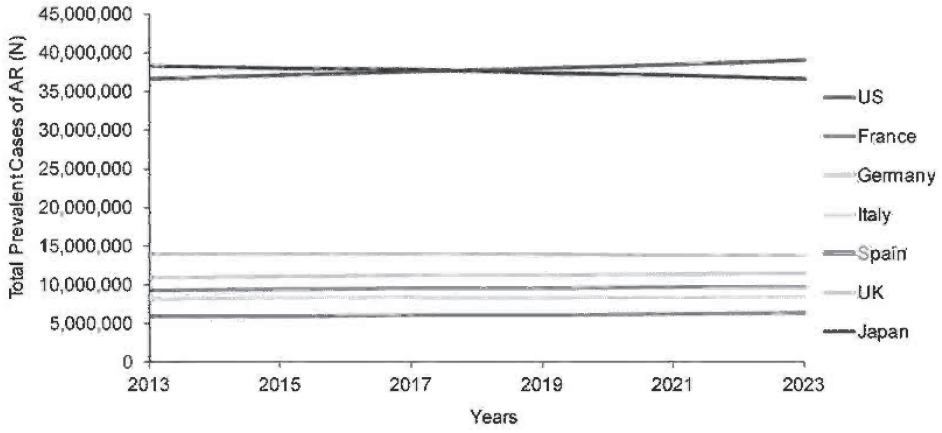
Figure 3: 7MM, Total Prevalent Cases of AR, Both Sexes, Age ≥18 Years, N, 2013–2023



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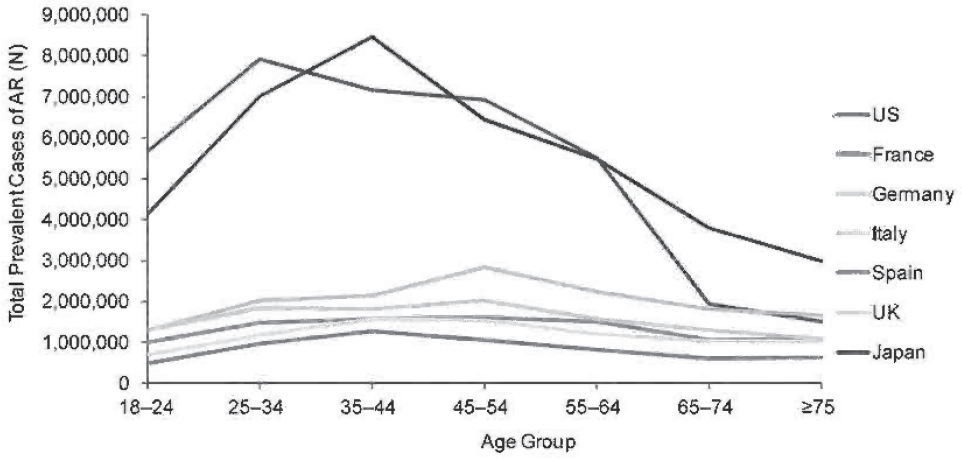
Figure 4: 7MM, Age-Specific Total Prevalent Cases of AR, Both Sexes, N, 2013



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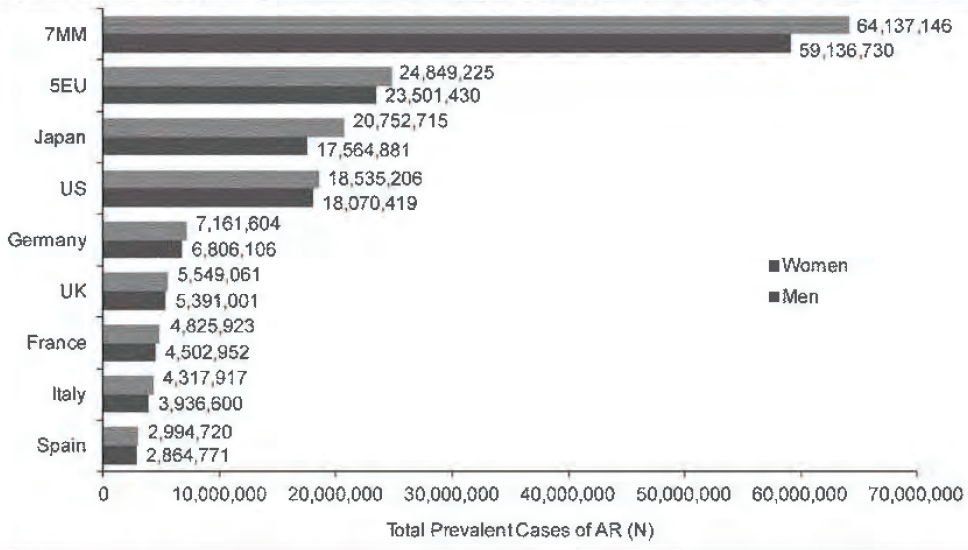
Figure 5: 7MM, Sex-Specific Total Prevalent Cases of AR, Ages ≥18 Years, N, 2013



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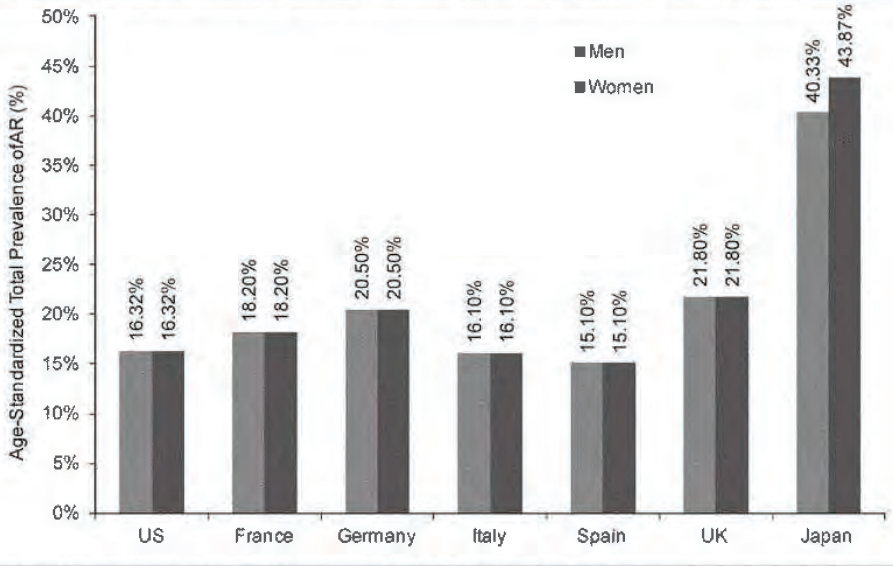
was due to the use of prevalence percentages that were measured for both sexes for the forecast. In Japan, the sex-specific total prevalence was used for the forecast.

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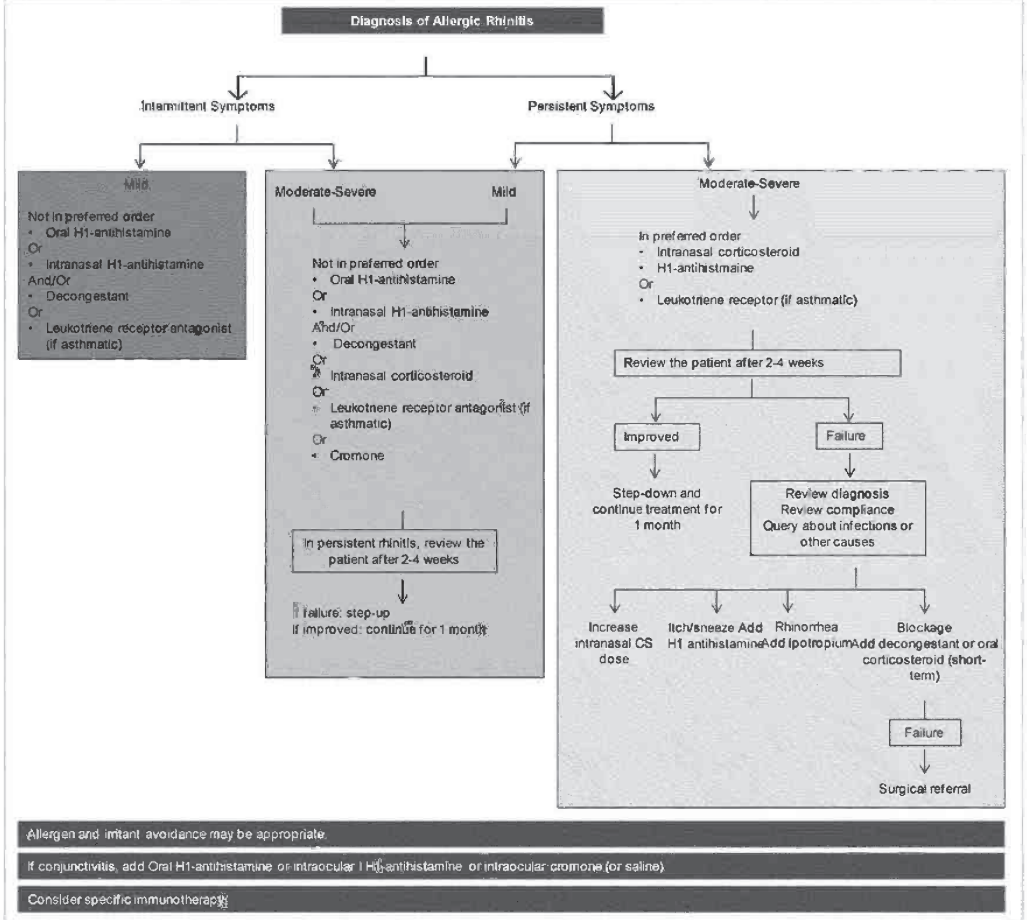
Figure 7: Algorithm Used for the Management of AR in the 7MM*



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 2013; Brozek 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	

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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

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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,

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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

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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

Competitive Assessment

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. 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.

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.

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