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Table 42 presents a product profile of Dymista.

Table 42: Product Profile – Dymista	
Molecule (Brand)	Azelastine hydrochloride/fluticasone propionate (Dymista)
Launch Date	US – 2012; 5EU – 2013; Japan – preregistered, expected launch in 2012
Therapeutic Class	H1 receptor antagonist and corticosteroid
Alternative Brand Names	Dygaro (Italy); Azeflu (France); Dymolin (Germany); Dylastine (Germany, Spain); Dyvistanil (Germany); Synaze (France, Spain); Xatalin (France); Dymol (Spain), Nycena (Italy)
Developer	Cipla
Marketing Partner	Meda
Primary Indication	The relief of symptoms of SAR and PAR in patients age 12 years and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief, when each drug alone is not considered sufficient
Formulation and Dosing	Intranasal spray; recommended dose is one spray per nostril twice daily in adults and adolescents age ≥12 years.
Primary Patent or Exclusivity Expiry	2023–2026 (US, 5EU)
Source: GlobalData; Dymista package insert, 2015; USPTO, 2015	

6.5.1.2 Efficacy

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

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

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Table 43: Efficacy of Dymista

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

NCT01165138; Meltzer et al., 2014

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

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

AZE = azelastine

6.5.1.3 Safety

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

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

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

Table 44: Safety of Dymista

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

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

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6.5.1.4 SWOT Analysis

Table 45 provides a SWOT analysis of Dymista.

Table 45: Dymista SWOT Analysis, 2014

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

Source: GlobalData; Dymista package insert, 2015

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

6.5.1.5 Forecast

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

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

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

Source: GlobalData
CAGR = Compound Annual Growth Rate

6.6 Decongestants

6.6.1 Overview

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

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

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

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

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

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

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

EU Key Opinion Leader

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

EU Key Opinion Leader

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

US Key Opinion Leader

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

EU Key Opinion Leader

6.7 Intranasal Anticholinergics

6.7.1 Overview

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

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

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

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

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

EU Key Opinion Leader

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

US Key Opinion Leader

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

EU Key Opinion Leader

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

EU Key Opinion Leader

6.8 Leukotriene Receptor Antagonists

6.8.1 Overview

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

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

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

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

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

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

Competitive Assessment

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

EU Key Opinion Leader

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

US Key Opinion Leader

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

EU Key Opinion Leader

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

EU Key Opinion Leader

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

Japanese Key Opinion Leader

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6.9 Cromones

6.9.1 Overview

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

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

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

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

EU Key Opinion Leader

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

US Key Opinion Leader

Competitive Assessment

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

EU Key Opinion Leader

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

EU Key Opinion Leader

6.10 Thromboxane A2 Receptor Antagonists

6.10.1 Overview

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

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

Japanese Key Opinion Leader

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

Japanese Key Opinion Leader

6.11 T_H2 Cytokine Inhibitors

6.11.1 Overview

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

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

Japanese Key Opinion Leader

7 Unmet Need and Opportunity

7.1 Overview

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

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

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

Unmet Need and Opportunity

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

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

Table 47: Unmet Need and Opportunity in AR

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

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

7.2 Pharmacist Education

7.2.1 Unmet Need

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

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

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

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

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

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

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

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

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

EU Key Opinion Leader, 2014

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

EU Key Opinion Leader

7.2.2 Gap Analysis

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

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

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

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

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

EU Key Opinion Leader, 2014

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

EU Key Opinion Leader, 2014

7.2.3 Opportunity

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

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

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

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

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

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

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

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7.3 Patient Compliance With Intranasal Corticosteroids and Antihistamines

7.3.1 Unmet Need

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

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

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

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

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

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

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

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

Japanese Key Opinion Leader, 2014

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

US Key Opinion Leader, 2014

7.3.2 Gap Analysis

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

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

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

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

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

US Key Opinion Leader, 2014

7.3.3 Opportunity

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

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

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

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

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

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

Japanese Key Opinion Leader, 2014

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

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

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

US Key Opinion Leader, 2014

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

US Key Opinion Leader, 2014

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

US Key Opinion Leader, 2014

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

US Key Opinion Leader, 2014

Unmet Need and Opportunity

7.4 More Convenient and More Patient-Friendly Immunotherapies

7.4.1 Unmet Need

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

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

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

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

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

EU Key Opinion Leader

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

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

EU Key Opinion Leader

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

EU Key Opinion Leader

7.4.2 Gap Analysis

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

Unmet Need and Opportunity

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

US Key Opinion Leader

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

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

US Key Opinion Leader

Unmet Need and Opportunity

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

US Key Opinion Leader

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

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

EU Key Opinion Leader

7.4.3 Opportunity

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

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

Unmet Need and Opportunity

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

7.5 Primary Care Physician Education

7.5.1 Unmet Need

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

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

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

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

Unmet Need and Opportunity

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

EU Key Opinion Leader, 2014

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

Japanese Key Opinion Leader, 2014

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

Japanese Key Opinion Leader, 2014

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

Japanese Key Opinion Leader, 2014

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

US Key Opinion Leader, 2014

Unmet Need and Opportunity

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

EU Key Opinion Leader, 2014

7.5.2 Gap Analysis

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

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

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

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

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

EU Key Opinion Leader

Unmet Need and Opportunity

7.5.3 Opportunity

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

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

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

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

Unmet Need and Opportunity

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

EU Key Opinion Leader

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

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8 Pipeline Assessment

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

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

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

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

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

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

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

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

EU Key Opinion Leader, 2014

8.1 Promising Drugs in Clinical Development

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

Table 48: Late-Stage Pipeline for AR, 2014

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

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

8.1.1 S-555739

8.1.1.1 Overview

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

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

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

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

Table 49 presents a product profile of S-555739.

Table 49: Product Profile – S-555739

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

Source: GlobalData

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8.1.1.2 Efficacy

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

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

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

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

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

Source: GlobalData

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

8.1.1.3 Safety

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

8.1.1.4 Dosing and Formulation

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

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8.1.1.5 Potential Commercial Positioning

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

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

8.1.1.6 Potential Clinical Positioning

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

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

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

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

8.1.1.7 SWOT Analysis

Table 51 provides a SWOT analysis of S-555739.

Table 51: S-555739 SWOT Analysis, 2014

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

Source: GlobalData

8.1.1.8 Forecast

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

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

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

Source: GlobalData
CAGR = Compound Annual Growth Rate

8.1.2 HP-3060

8.1.2.1 Overview

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

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

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

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

Table 53 presents a product profile of HP-3060.

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

Source: GlobalData

8.1.2.2 Efficacy

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

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

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

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8.1.2.3 Safety

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

8.1.2.4 Dosing and Formulation

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

8.1.2.5 Potential Commercial Positioning

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

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

8.1.2.6 Potential Clinical Positioning

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

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

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

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

8.1.2.7 SWOT Analysis

Table 54 provides a SWOT analysis of HP-3060.

Table 54: HP-3060 SWOT Analysis, 2014

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

Source: GlobalData

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8.1.2.8 Forecast

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

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

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

Source: GlobalData
CAGR = Compound Annual Growth Rate

9 Current and Future Players

9.1 Overview

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

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

There is an extremely sparse pipeline for new AR treatments.

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

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

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

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

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

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

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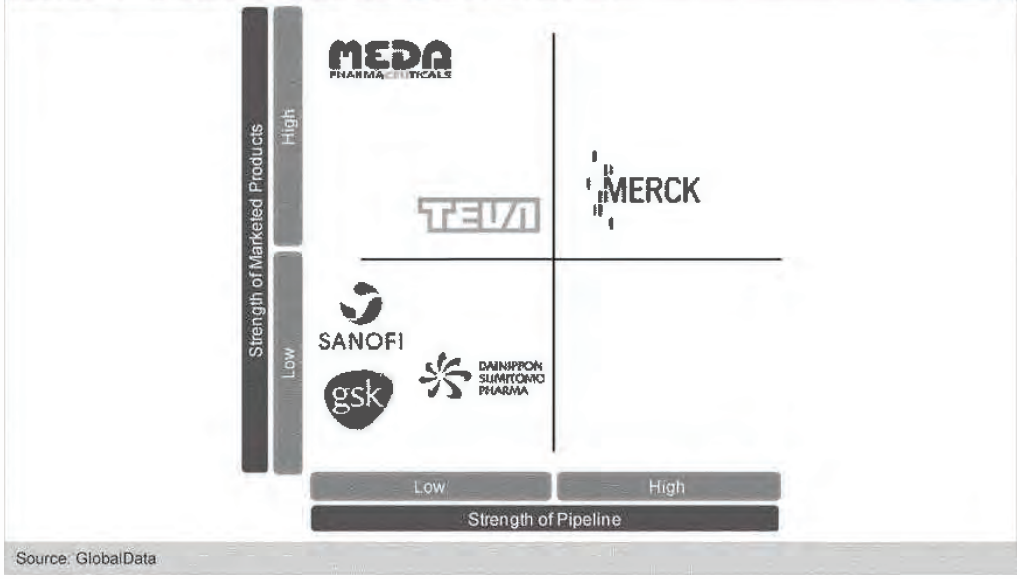
Figure 8 provides an analysis of the company portfolio gap in AR during the forecast period.

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



Source: GlobalData

9.2 Trends in Corporate Strategy

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

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

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

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

9.3 Major Companies

9.3.1 Merck & Co.

9.3.1.1 Overview

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 57: Merck's AR Portfolio Assessment, 2014

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

Source: GlobalData; Merck & Co., 2014

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9.3.2 GlaxoSmithKline

9.3.2.1 Overview

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

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

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

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

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

Table 58: GSK's AR Portfolio Assessment, 2014

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

Source: GlobalData, GSK, 2014

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9.3.3 Sumitomo Dainippon Pharma

9.3.3.1 Overview

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

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

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

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

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

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

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

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

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

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

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

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

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

Source: GlobalData; AstraZeneca, 2014

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9.3.4 Sanofi

9.3.4.1 Overview

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

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

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

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

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

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

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

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

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

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

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

Table 60: Sanofi's AR Portfolio Assessment, 2014

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

Source: GlobalData; Sanofi, 2014

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9.3.5 Teva

9.3.5.1 Overview

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

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

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

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

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

Table 61: Teva's AR Portfolio Assessment, 2014

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

Source: GlobalData; Teva; 2015

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9.3.6 Meda AB

9.3.6.1 Overview

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

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

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

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

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

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

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

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

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

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

Table 62: Meda's AR Portfolio Assessment, 2014

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

Source: GlobalData; Meda; 2014

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10.1 Global Markets

10.1.1 Forecast

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

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

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

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

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

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

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

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

Year	2014	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2023	2024	CAGR (2014–2024) (%)
Oral H1Ahs	1261.0	1262.1	1263.6	1264.3	1264.4	1264.2	1263.9	1263.4	1262.7	1261.8	1263.4	-0.0%
Intranasal H1Ahs	621.7	416.7	409.7	410.9	403.4	387.4	379.7	380.5	381.3	373.3	374.3	-0.0%
INCS	3293.3	2807.1	2736.1	2378.9	2299.9	2281.9	2265.3	2259.6	2227.8	2218.5	2215.9	-0.0%
Erizas capsule	141.6	141.0	140.5	139.8	138.9	138.1	137.2	136.3	135.4	134.5	133.6	0.0
Nasacort	11.1	11.1	11.1	5.6	1.1	0.6	0.6	0.6	0.6	0.6	0.6	-0.3
Nasacort, generic	0.0	0.0	0.0	3.0	6.1	6.1	6.1	6.1	6.1	6.2	6.2	
Nasonex	915.3	411.0	388.7	87.5	31.4	20.1	20.1	20.1	20.1	17.2	17.2	-0.3
Nasonex, generic	8.5	225.9	239.2	274.5	281.1	307.3	316.9	320.0	320.2	320.3	320.8	
Omnaris	22.2	14.9	13.9	7.5	5.0	2.5	2.6	2.6	2.6	1.3	1.3	-0.2
Omnaris, generic	0.0	0.0	0.0	1.5	2.2	2.5	2.5	2.4	2.4	2.3	2.3	
Qnasl	45.9	48.0	50.2	52.5	54.7	57.0	59.4	61.7	64.1	66.6	66.9	0.0
Veramyst (Avamys/ Allermist)	200.4	195.3	180.4	163.6	160.3	148.9	141.6	139.1	138.8	138.4	138.4	0.0
Veramyst, generic	0.0	0.0	9.4	9.5	9.5	9.6	9.6	9.7	9.8	9.8	9.9	
Zetonna	24.6	29.7	37.4	10.0	9.1	8.6	8.2	7.7	8.3	8.8	8.9	-0.1
Zetonna, generic	0.0	0.0	0.0	7.8	8.6	9.0	9.4	9.7	10.4	11.5	12.7	
Anticholinergic drugs	80.3	72.5	72.9	73.3	73.6	74.0	74.4	74.8	75.1	75.5	70.4	0.0
Decongestants	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8	0.0
Mast cell stabilizers (cromones)	1.8	1.8	1.8	1.8	1.8	1.8	1.7	1.7	1.7	1.7	1.7	0.0
TAX2 antagonists (Baynas)	83.0	82.7	82.4	82.0	74.1	66.3	65.8	58.2	57.8	57.4	57.1	0.0
T_H2 cytokine inhibitors (IPD®)	22.1	22.0	22.0	21.9	21.7	21.6	21.5	21.3	21.2	21.0	20.9	0.0
LRAs (all markets)	681.2	687.3	670.0	586.1	591.1	596.1	595.4	595.7	595.8	601.4	602.5	0.0
Singulair	223.4	222.4	175.0	4.8	3.5	2.3	1.1	1.1	0.9	0.8	0.6	-0.4
Montelukast	0.0	0.0	28.5	113.6	118.6	123.4	122.5	121.9	121.1	125.7	125.2	

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

Source: GlobalData

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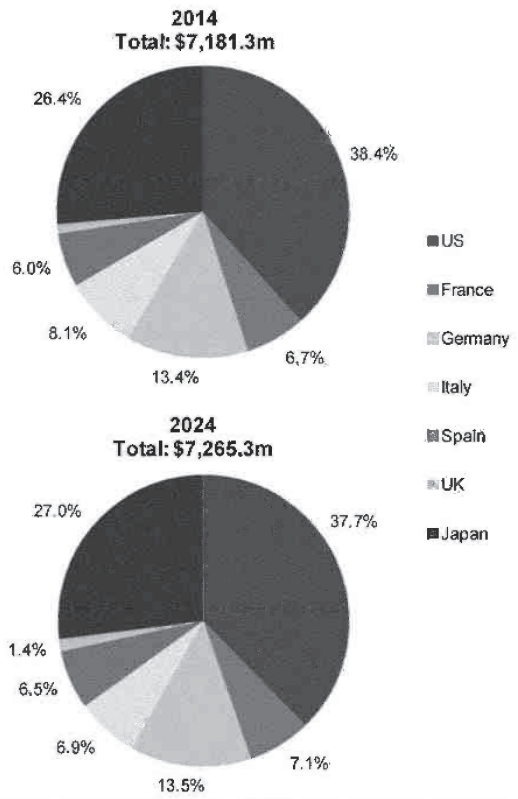
Figure 9 illustrates the global sales for AR by region during the forecast period.

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



Source: GlobalData

Market Outlook

10.1.2 Drivers and Barriers – Global Issues

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

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

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

Source: GlobalData

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

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

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

Allergen patterns are also changing in response to climate change, and air pollution can modify the allergenic potential of pollens, especially under specific weather conditions.

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

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

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

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

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

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

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

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

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

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

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

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

10.1.2.5 Barrier: Increasing Pressures for Cost-Effectiveness

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

10.1.2.6 Barrier: Variable Weather Patterns Hamper New Drug Development

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

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

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

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

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

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

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

10.2 United States

10.2.1 Forecast

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Year	2014	2015	[illegible]	[illegible]	[illegible]	[illegible]	2020	2021	[illegible]	[illegible]	[illegible]	[illegible]
Oral H1Ahs	241.2	242.6	244.1	245.6	247.0	248.6	250.1	251.7	253.3	254.9	256.3	0.6%
Intranasal H1Ahs	429.1	224.1	217.1	218.4	211.2	195.6	188.2	189.4	190.6	183.1	184.1	-8.1%
INCS	1,809	1,310	1,272	955	911	896	892	897	880	884	892	0
Nasonex	686.5	331.4	333.4	89.9	22.5	11.3	11.4	11.5	11.5	8.7	8.8	-35.4%
Nasonex, generic	0.0	89.8	90.1	123.1	130.3	144.2	151.7	152.7	153.7	154.6	155.5	
Qnasl	45.8	48.0	50.2	52.5	54.7	57.0	59.4	61.7	64.1	66.6	68.9	4.2%
Zetonna	24.6	29.7	37.4	10.0	9.1	8.6	8.2	7.7	8.3	8.8	8.9	-9.7%
Zetonna, generic	0.0	0.0	0.0	7.8	8.6	9.0	9.4	9.7	10.4	11.5	12.7	0
Omnaris	22.2	14.9	13.9	7.5	5.0	2.5	2.6	2.6	2.6	1.3	1.3	-24.6%
Omnaris, generic	0.0	0.0	0.0	1.5	2.2	2.5	2.5	2.4	2.4	2.3	2.3	
Veramyst	66.4	54.3	42.0	25.4	17.0	8.6	4.3	2.2	2.2	2.2	2.2	-28.9%
Veramyst, generic	0.0	0.0	9.4	9.5	9.5	9.6	9.6	9.7	9.8	9.8	9.9	
Dymista	41.4	67.4	67.8	74.4	74.9	75.4	75.8	82.7	83.2	83.7	84.2	7.3%
LRAs	203.6	204.7	206.0	207.2	208.4	209.8	211.1	212.4	213.7	215.1	216.3	0.6%
Anticholinergic drugs	54.2	54.5	54.8	55.1	55.5	55.8	56.2	56.5	56.9	57.2	57.5	0.6%
Decongestants	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8	0.6%
SITs	173.3	225.1	366.1	444.2	543.8	683.4	708.7	764.0	798.3	841.1	869.2	17.5%
SI-555739	0.0	0.0	0.0	55.4	111.4	140.2	141.1	147.6	160.0	172.5	173.4	
Total	2754.6	2331.3	2430.2	2257.7	2365.5	2507.4	2526.3	2604.5	2638.2	2694.9	2736.1	-0.1%

Source: GlobalData
CAGR = Compound Annual Growth Rate.

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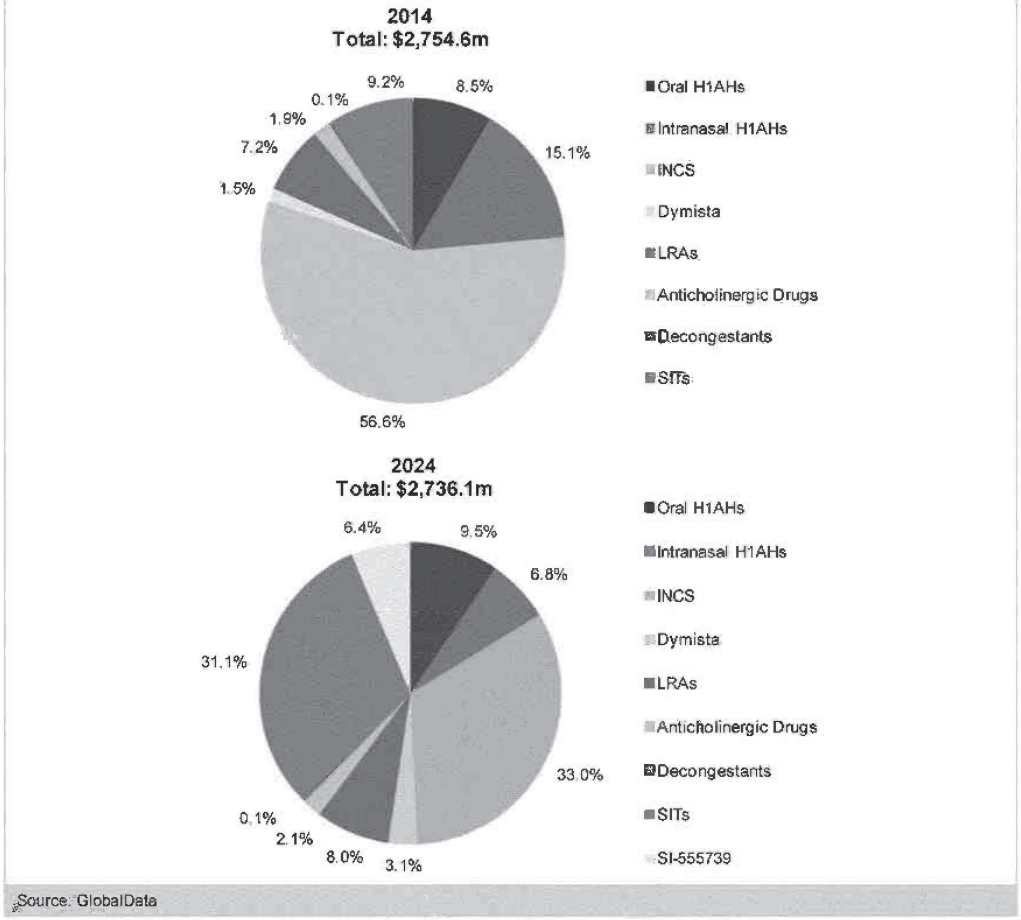
Figure 10 illustrates the sales for AR in the US by drug class during the forecast period.

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



Source: GlobalData

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10.2.2 Key Events

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

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

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

Source: GlobalData

10.2.3 Drivers and Barriers

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

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

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

Source: GlobalData

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

10.2.3.1 Driver: The ACA Will Lead to AR Market Growth

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

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

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

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

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

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

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

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

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

10.3 5EU

10.3.1 Forecast

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

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

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

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

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

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

Market Outlook

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

Market Outlook

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

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

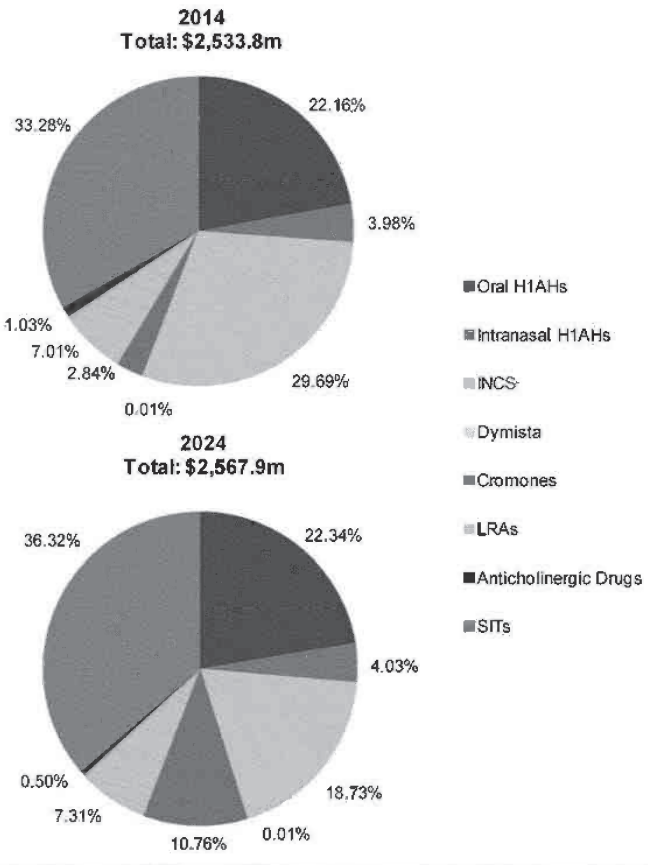
Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	CAGR (2014-2024) (%)
Oral H1AHs	561.5	563.1	564.8	566.3	567.6	568.7	569.6	570.4	571.0	571.4	573.6	0.2%
Intranasal H1Ahs	100.9	101.2	101.5	101.8	102.1	102.4	102.6	102.7	102.9	103.0	103.4	0.2%
INCS	752.2	578.4	556.7	548.6	525.4	517.3	509.7	504.5	496.3	488.0	481.0	-4.4%
Nasonex	46.2	20.8	14.5	4.7	2.4	2.4	2.4	2.3	2.3	2.3	2.2	-26.1%
Nasonex, generic	8.5	22.9	25.8	28.8	28.8	31.8	34.8	37.7	37.8	37.8	38.9	16.1%
Nasacort	11.1	11.1	11.1	5.6	1.1	0.6	0.6	0.6	0.6	0.6	0.6	-25.8%
Nasacort, generic	0.0	0.0	0.0	3.0	6.1	6.1	6.1	6.1	6.1	6.2	6.2	
Avamys (Veramyst)	58.5	65.9	63.5	63.7	69.2	66.7	64.2	64.3	64.4	64.5	64.8	1.0%
Dymista	72.0	102.5	141.9	157.9	158.3	180.4	186.8	209.0	231.2	253.3	276.3	14.4%
Cromones	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5%
LRAs	177.5	183.8	184.4	184.9	185.4	185.8	186.2	186.5	186.8	187.0	187.7	0.6%
Anticholinergic drugs	26.1	18.0	18.1	18.1	18.2	18.2	18.2	18.2	18.3	18.3	12.9	-6.8%
SITs	843.2	853.2	860.8	869.1	879.9	888.0	896.9	905.9	914.8	923.7	932.6	1.0%
Total	**2,658.1**	**2,521.3**	**2,543.4**	**2,552.8**	**2,544.8**	**2,568.7**	**2,578.5**	**2,608.7**	**2,632.7**	**2,656.3**	**2,679.8**	**0.1%**

Source: GlobalData
CAGR = Compound Annual Growth Rate

Market Outlook

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

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



Source: GlobalData

Market Outlook

10.3.2 Key Events

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

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

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

Source: GlobalData

10.3.3 Drivers and Barriers

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

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

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

Source: GlobalData

Market Outlook

10.3.3.1 Driver: EAACI Initiative to Increase AR Awareness

AR experts across Europe launched a new partnership in June 2014 to tackle Europe's high AR prevalence. The EEACI's Allergy Awareness Campaign aims to help the community better understand allergy sufferers' symptoms, how greatly allergy impacts QoL, how severe and costly AR can be, and how early diagnosis of the disease is important to improve its management. The EAACI hopes that this campaign, which focuses on education about allergy prevention, early diagnosis, and correct management, patients and their families will be able to achieve better control of their allergies and improve their QoL. Another objective of the campaign is to increase the resources allocated by health ministries to better manage the allergy epidemic. The EACCI will roll out the campaign in phases running from 2014 through 2015, and will highlight the individual causes of various allergies (including AR, anaphylaxis, asthma, and food and skin allergies) as well as their treatments, such as AIT. This campaign will also tackle several barriers in AR treatment, such as inadequate organization of healthcare services, limited availability of drugs to treat severe AR, lack of training and education for clinicians, and poor adherence to treatment. As a result, not only will this initiative improve the QoL of people with AR, but it will also inevitably lead to better treatment, which will in turn, lead to a larger patient pool and stimulate growth of the AR market.

The EEACI's Allergy Awareness Campaign aims to help the community better understand allergy sufferers' symptoms, how greatly allergy impacts QoL, how severe and costly AR can be, and how early diagnosis of the disease is important to improve its management.

10.3.3.2 Driver: High Healthcare Expenditures in France Will Fuel AR Market Growth

In 2007, healthcare expenditures in France accounted for 11.2% of the country's Gross Domestic Product (GDP), which increased to 12% in 2011 (GlobalData, 2013b). In 2005, per-capita healthcare expenditures were $3,294, and increased at a CAGR of 3.8% to $3,974 in 2010. The country's robust social healthcare system is supported by universal insurance coverage, which means that patient out-of-pocket expenditures are very low. Access to medicines includes public reimbursement of expensive and novel drug therapies for acute and chronic disease conditions. These high healthcare expenditures are fueling the growth of the AR market. In addition, patients in France benefit from relatively quick access to innovative drugs for life-threatening diseases with high unmet need through the Temporary Authorization for Use (Autorisations Temporaires d'Utilisation) program. This program allows these drugs to be used in hospitals even before they are registered, which may boost the sales of the AR immunotherapies in development, even before they reach the market.

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10.3.3.3 Driver: The New Planning Directive in Germany Will Boost Pharmaceutical Sales

The Federal Joint Committee (G-BA) has defined a new version of its Planning Directive, which came into effect on January 1, 2013. This new directive will ensure the uniform and demand-based availability of physicians and GPs across Germany (GlobalData, 2013c). As a result of the implementation of the Planning Directive, the availability of GPs and physicians has increased in rural areas. The uniform availability of the healthcare personnel will ensure patient access to healthcare facilities and treatment, and will contribute to the growth of the AR market in Germany.

10.3.3.4 Driver: The Italian Government Reimburses Almost all Expensive and Novel Medicines

The Italian government provides universal healthcare coverage to the country's population. It reimburses almost all expensive and novel medicines, which increases patient compliance and the number of prescriptions written, and drives the pharmaceutical market in Italy. Reimbursement of medicines will be particularly relevant with regard to AITs that are in late-stage development for AR, and will be a major factor in increasing patient compliance and access to medicines, which will both drive the AR market in Italy.

10.3.3.5 Driver: The AIFA and ISS Agreements Will Facilitate and Encourage Increased Number of Clinical Trials in Italy

In 2012, the AIFA, the ISS, and the Italian Association for the Development of Biotechnology signed an agreement to encourage early-phase clinical trials for new drugs (AIFA, press release, October 4, 2012). As a result, the time of evaluation for clinical trial applications was reduced to 45 days. This policy will drive the early launch of new medicines in the Italian market, revive research, and attract investment. Facilitation of greater numbers of clinical trials of early-stage drugs will encourage the development of much needed next-generation and personalized therapies for AR.

10.3.3.6 Driver: Implementation of Electronic Medical Records Will Improve Patients' Access to Healthcare Services and Will Drive the Growth of the Spanish AR Market

The Spanish government has invested in the implementation of electronic medical record and the use of information and communication technology to integrate the services provided by public hospitals with those of the National Health System (Sistema Nacional de Salud [SNS]) (GlobalData, 2013e). E-prescriptions were introduced in 2005 for patients with chronic diseases who make regular visits to primary health centers to renew their prescriptions. The introduction of

e-health services allows patients to make an appointment with and get a prescription from physicians online. Doctors can also access all medical records, including the laboratory test results, of patients in any SNS hospital, which helps improve treatment. These initiatives have improved patients' access to healthcare services and reduced their travel time, consequently improving compliance, and driving the healthcare sector. Overall, pharmaceutical sales in the AR market in Spain will be driven by the e-health services.

10.3.3.7 Driver: Massive Immigration in the Past Few Years Will Lead to an Increase in the Demand for Pharmaceuticals in Spain

Spain has experienced massive immigration in the past few years, and has the second highest number of immigrants in Europe. According to the Spanish government, there were 4.5 million foreign residents in 2007. The increasing immigration is one of the reasons for the increase in the demand for pharmaceuticals (GlobalData, 2013e). This driver will be reflected in the overall growth of the AR market in Spain.

10.3.3.8 Driver: "Patent Box" Will Provide Relief for Manufacturers of Branded AR Drugs in the UK

In order to bring business into the UK to generate revenue, the government established the Patent Box policy as Part of the Finance Bill, which began at the end of 2012 (GlobalData, 2013h). This policy will provide tax relief for companies that manufacture patent-protected goods in the UK, and is indirectly aimed at attracting drug companies. The corporate tax rate of 20% is decreased to 10% for companies that qualify. This will bolster the overall presence of the pharmaceutical market in the UK. Consequently, the AR market in the UK will also see stronger growth compared with other European countries.

10.3.3.9 Barrier: Poor Economic Conditions in the 5EU Have Led to a Decreased Market Size for AITs

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

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10.3.3.10 Barrier: Government Drug Pricing and Reimbursement Restrictions in France are Likely to Stifle the Growth of the AR Market

In France, the Economic Committee for Health Products (Comité Economique des Produits de Santé [CEPS]) monitors drug prices and it revises those that it deems too high, based on a clinical evaluation performed by the Haute Autorité de Santé (HAS). This could hurt new biologic products in late development for AR, as the CEPS may deem these drugs too expensive and as not having any advantages over the currently available therapies. The CEPS expects to help lower the budget deficit by cutting the prices of branded and generic drugs. It also determines which products should be fully- or partially reimbursed by public insurers, with the level of reimbursement being based on the medical worth of the product. Also, as in its neighboring EU countries, the French government imposes price cuts on pharmaceuticals from private companies. Price cutting due to competition among manufacturers is likely to impact the overall growth of the AR market (GlobalData, 2013b). These price-cutting strategies were implemented partly as a result of the sovereign-debt crisis.

10.3.3.11 Barrier: The French Act N°2011-2012 Poses an Obstacle to the Growth of the AR Market

The French Act N°2011-2012, formulated by the National Assembly, gave the National Safety Agency for Drug and Health Products (Agence Nationale de sécurité du Médicament et des produits de santé, ANSM) the power to require the MA holder of a medicinal product to carry out post-authorization safety and effectiveness analyses. To be listed as a reimbursable medication, a medicinal product must have been clinically tested against other existing therapeutic strategies (indication by indication). This requirement applies to applications filed on or after January 1, 2012. This could hurt many biologic therapies in development for AR, as it might not be easy to prove that one of these therapies is more effective than the other.

10.3.3.12 Barrier: Mandatory Drug Rebates in Germany will Stifle the Growth of AR Market

In 2003, the German government required pharmaceutical companies to pay a 6% rebate to the SHI funds. In 2004, the government again increased the mandatory rebate to 16% in order to provide immediate savings to the health fund system, while reference pricing was being developed. This 16% mandatory rebate is still applicable and is stifling the growth of the AR market as a whole, since it acts as a discouraging factor for pharmaceutical manufacturers.

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10.3.3.13 Barrier: The TAV Directive in Germany Will Stifle the Growth of the AR Market

Germany's Federal Ministry of Health issued a TAV directive in November 2008, requiring all manufactured human pharmaceutical products, including AITs, to receive MA according to the European Directive 2001/83/EC, as amended by the EMA. Under the TAV, each product's MA must be obtained through a standard drug development procedure, including large-scale, multicenter, randomized, placebo-controlled clinical trials in adults and children. However, with regard to AITs, this requirement only applies to the most prevalent allergens. It also requires official batch testing of all bulk allergen extracts manufactured.

The relevant regulatory documents had to be submitted to the Paul-Ehrlich-Institut (PEI) by December 1, 2010. However, the PEI has not yet responded to all the applications. Until the MAs have been issued, the PEI has afforded the allergen manufacturers a transition period until 2017 to prepare the relevant documentation and to complete the clinical data on safety and efficacy in randomized controlled trials for the final MAs, provided that the companies have notified the PEI regarding their intention to complete a full application. During this time, the companies are able to sell and distribute their products (Allergy Therapeutics, press release, November 28, 2010). There is no set timeline for the PEI to respond to the MAAs. The PEI has shown a preference for single-allergen vaccines, and it is expected that specific allergen mixes will only be used in clinical practice for rare allergies.

In 2010, 60% of SIT products in Germany were marketed NPPs, without an MA in the meaning of Directive 2001/83/EC. Under the new TAV, all immunotherapy products containing the most prevalent allergens must have received an MA by 2017. This includes all NPPs derived from grass pollen, early-flowering tree pollen, HDMs, and bee and wasp venom, regardless of whether the allergen is produced as a single-allergen preparation or included in mixtures (Eichler and Soriano, 2011). All MAAs must be submitted to the relevant German authorities by December 1, 2010. As Germany represents the largest revenue stream for immunotherapy products, any delays in the registration of these products may limit SIT sales in Germany.

The TAV represents a significant financial challenge for allergen manufacturers marketing products in Germany, which is the largest AIT market.

The TAV represents a significant financial challenge for allergen manufacturers marketing products in Germany, which is the largest AIT market. It will not be economical for each manufacturer to register all of the required products in their portfolio in line with the TAV requirements, due to the associated costs and time required for preparing an application and conducting potentially lengthy clinical trials in both children and adults.

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The EU member states are at different stages in their efforts to comply with this directive. Similar regulations are set to be rolled out in Spain and Italy in the near future. However, through the European Union Mutual Recognition Procedure (MRP), companies who gain MA in Germany can apply for approval in other EU member states. Smaller national companies that have not applied for registration of their products in Germany will need to do so once the directive has been enforced in the relevant country.

10.3.3.14 Barrier: Government Drug Pricing and Reimbursement Controls In Italy May Limit the Uptake Of More Expensive Agents

Italy provides government-funded universal health insurance coverage, and the Italian government is trying to promote the use of generic drugs over the more expensive branded medications. The strict pricing of drugs through negotiations and external and internal reference pricing is a major challenge for the launch of innovative molecules (GlobalData, 2013d). Another attempt by the Italian government to reduce healthcare costs is a pay-to-perform measure on new drugs, which was implemented in 2007. Under this program, the government may cut drug prices by up to 40% after launch. After a two-year review of performance to assess whether the drug provides a health benefit based on its efficacy, the price may be increased or lowered. This plan may hinder the market entry and penetration of all drugs in development for AR (Tonareili, 2011).

10.3.3.15 Barrier: Government Drug Pricing Restrictions in Spain May Limit the Uptake of New Branded Agents

The Spanish government has adopted two pricing strategies, both of which ultimately present a barrier to the pharmaceutical market (GlobalData, 2013e). The first is the generic reference pricing strategy, which is comparable to that in the other EU markets. Under this strategy, drug prices are based on the price of the least expensive comparable drug available. The second methodology entails the application of a 7.5% discount on branded drugs that are financed by the Spanish National Health System. As a result of these strategies, pharmaceutical companies take a loss when generics are allowed to enter the market. Thus, the government's control of drug pricing will stifle the growth of the AR market in Spain.

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10.3.3.16 Barrier: Reforms Promoting the Use of Generics Will Slightly Stifle the Growth of the Spanish AR Market

In 2011, the Spanish government introduced reforms to promote the use of generics. Doctors were mandated to state the active ingredient on the prescription instead of a brand name, and pharmacists were strictly required to dispense the cheapest medicine available containing the active ingredient (GlobalData, 2013e). These measures have led to an increase in the sale of generics. The share of generics in the SNS' total pharmaceutical bill increased from 20.9% in 2007 to 38.9% in 2011 in terms of volume, and from 9.2% in 2007 to 14.4% in 2011 in terms of value. This has reduced pharmaceutical companies' revenue. As a result of these reforms, the AR space in Spain could see an increase in use of generic versions of Pulmicort, Advair, and Symbicort.

10.3.3.17 Barrier: Uncertainty Regarding How the Proposed VBP System Will Impact Market Access for Novel AR Therapies in the UK

The NICE is often cited as being ineffective as a result of its tendency to focus almost exclusively on the cost-effectiveness of various treatment options, rather than on their clinical benefit. This system means that the best, most effective drugs do not always become available in the UK. The proposed introduction of a VBP system by the UK government has been met with uncertainty by drug manufacturers, with questions as to how the system would appraise drugs; weight them by innovation, unmet need, and the severity of disease; and determine prices for them (GlobalData, 2013f). This system may benefit the patient in that there may be greater access to novel therapies. However, this system is sure to affect the sales of branded drugs in the UK, as these drugs may not get approved for pricing and reimbursement in a timely fashion, which will result in the delayed uptake of novel AR therapies.

10.3.3.18 Barrier: Drug Price Cuts Will Stifle the Growth of the AR Market in the UK

Price cuts have led to a decline in the value of the pharmaceutical market in the UK. It fell to $24.1 billion in 2012 from $27.1 billion in 2008, due to price cuts on branded medicines of 3.9% in 2009 and 1.9% in 2010, in order to reduce NHS expenditures (GlobalData, 2013f). In June 2013, the Department of Health announced plans to cut prices by 10–20% on branded medicines that are not covered in the voluntary Pharmaceutical Price Regulation Scheme. These price cuts will adversely affect the revenues of manufacturers of branded medicines in the UK, and therefore, the growth of the AR market in the UK will be stifled.

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10.3.3.19 Barrier: The Decline in FDI in the UK Will Stifle Innovation in the AR Space

Capital investment in the UK declined by 0.8% between 2010 and 2012 to 14.3% of GDP, which is less than in other EU countries, such as France and Germany, where it was 19.9% and 17.2% of GDP, respectively (GlobalData, 2013f). The global economic slowdown, the Eurozone crisis, and the UK government's deficit reduction program have all hindered the economic recovery, resulting in a decline in FDI. This will be reflected negatively in the R&D investment that is needed for the development of novel AR therapies.

10.4 Japan

10.4.1 Forecast

Sales of AR products in Japan were $1.89 billion in 2014. GlobalData forecasts this figure to grow by 0.4% per year through 2024 (not accounting for inflation) to $1.96 billion. As in the global markets, the growth in the Japanese AR market will be fueled mainly by the uptake of the new AITs, and will be offset by the patent expiry of the best-selling AHs in 2013, and Merck's INCS, Nasonex, in 2017. In 2013, the Japanese cedar pollen count was considerably higher compared to 2012, resulting in a peak in the sales of anti-allergy medications. The forecast for Japan is based on consistent pollen levels; however, they are highly variable from one year to the next, which will ultimately have an effect on the OTC and prescription AR market in this country.

Japan had the largest oral AH market globally in 2014, with sales of $458m. The current version of the Japanese guidelines for the treatment of AR recommends monotherapy with AHs or LRAs as a first-line therapy, while the combination of two products, an AH and an INCS, or three products, with the addition of an LRA, can be prescribed, depending on the type of illness and severity. Prior to 2013, Allegra was the best-selling AH in Japan, followed by Allelock with Xyzal, and Alesion and Talion competing for the third most commonly used AH. However, several of the most popular AHs in Japan are due to lose patent protection during the forecast period. Allegra lost patent protection in February 2013, and Allelock lost its protection in December 2012. It is expected that the introduction of generics will decrease the daily cost of therapy of this drug class, but is not expected to alter the patient share, as there were numerous AHs available in Japan, both generic and OTC, prior to the start of the forecast period. The AH market size in Japan is due to decline to $433.3m in 2024.

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The INCS market in Japan is set to decline by 1%, from $931m in sales in 2014 to $843m in 2024. The most significant factor contributing to the decline of this market during the forecast period is the patent expiry of the leading branded INCS, Nasonex, in 2017, which will experience a decline in annual sales from $183m in 2014 to around $6m in 2024, following the launch of generic versions of the drug.

The blockbuster LRA, Singulair, has experienced significant generic erosion in the US and EU markets since its patent expiry. Singulair still has patent protection until 2016 in Japan. However, following the launch of generics, the LRA market in Japan is set to decline at a CAGR of negative 4%, from $300m in 2014 to $198m in 2024.

In 2014, the AIT drug treatment rate in Japan was very low, despite the large AR prevalent population. Allergen extracts have been available in Japan since 1963, and were prescribed more frequently in the past, albeit still modestly, when taking into account the size of overall AR population. The advent of symptomatic therapies that can provide an immediate reduction in nasal symptoms, such as the second-generation AHs, resulted in a significant decrease in the use of AIT in Japan. In addition to the standard barriers to immunotherapy (needle phobia, high cost, and inconvenience), the lack of allergen standardization, HDM-specific allergen extracts, and clinically demonstrable efficacy or long-term symptom relief have also contributed to the decline in SIT sales in Japan.

In 2013, there was only one allergen extract manufacturer in Japan, Torii, which had exclusivity on the SCIT market. The approval of Torii's Japanese cedar pollen immunotherapy, Cedartolen, an SLIT liquid, will represent an opportunity to fulfill a significant unmet need in the Japanese market. However, after initial talks with regulatory officials, Cedartolen failed to secure a place on the NHI reimbursement list. Cedartolen was placed on the reimbursement list, and subsequently launched on the Japanese market in October 8th 2014.

The launch of Cedartolen is expected to contribute to an increase in both the drug treatment rate and sales of Torii's SLIT portfolio in Japan. However, Torii's launch of a highly-anticipated AIT containing Japanese cedar pollen is expected to largely take the cedar pollen AR market share. As both products will be marketed by Torii, GlobalData expects the company to drive sales of the AIT formulation. AITs are expected to be more expensive, but are also easier to store and transport, than SLIT. Torii's SLIT portfolio is forecast to reach sales of $13.88m in 2018, at a CAGR of

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35.62%. This is a modest figure, as it is anticipated that allergists and patients alike will prefer the newer AIT formulations over inconvenient SCITs and SLITs.

The introduction of two HDM AITs by Shionogi and Torii via partnerships with the European manufacturers, Stallergenes and ALK, respectively, will significantly bolster the failing Japanese AIT market and increase the drug treatment rate. Currently, Japanese patients with HDM-induced AR are treated with house dust extract, which contains a number of components in addition to HDMs at an unstandardized concentration. Therefore, an HDM allergen tablet that contains a regulated HDM extract, whose efficacy has been demonstrated in a randomized controlled clinical trial, represents a large shift in the treatment of this allergy. Torii's HDM tablet is expected to enter the market H1 2016, and is expected have a 4% patient share. It is expected to generate sales of $1.32m in 2016, and reach $20.7m by 2018.

The introduction of two HDM AITs by Shionogi and Torii via partnerships with the European manufacturers, Stallergenes and ALK, respectively, will significantly bolster the failing Japanese AIT market and increase the drug treatment rate.

Shionogi will be the new entrant in a market that has been dominated by one player, Torii, for decades. This represents a unique situation; in addition, the launch of the company's HDM tablet at the same time as Torii's HDM AIT in H1 2016 will dampen the sales of this drug. However, Shionogi's HDM tablet is still expected to generate sales of $1.98m in 2016, which will increased to $12.28m in 2018.

Austerity measures and other regulations implemented in Europe have led AIT manufacturers to target Japan. The high prevalence of AR in Japan represents a significant market opportunity for AITs. The advent of novel sublingual formulations and the entry of a new drug into the market, Cedartolen, are set to increase the drug-treated population. As a result, GlobalData projects that immunotherapy sales in Japan will reach $110m in 2024, at a CAGR of 39.4%.

In addition to the launch of new AITs, Japan is set to have two pipeline products enter the market within the forecast period: Shionogi's S-555739 and Hisamitsu Pharmaceutical's HP-3060. S-555739 is expected to be launched in 2017, and gain respectable sales of $114m in 2024 in a saturated generic market. The transdermal treatment, HP-3060, is also expected to be launched in 2017. Despite its unknown active ingredient, this product is expected to be used specifically in the elderly and younger pediatric population. Given that HP-3060 is likely to compete directly compete with generic oral and intranasal AHs (which are widely available in syrup formulations for patients with a distaste for tablets), this product is expected to have a relatively low daily cost of therapy. Nonetheless, due to the popularity of transdermal preparations in Japan, the drug will generate sales of approximately $96m in 2024.

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Table 71 presents the sales forecasts for AR products in Japan from 2014–2024.

Table 71: Sales Forecasts ($) for AR in Japan, 2014–2024

Year	2014	2015	[illegible]	[illegible]	[illegible]	2019	2020	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Oral H1AHs	458.3	456.3	454.8	452.5	449.8	446.9	444.1	441.3	438.4	435.4	433.6	-0.6%
Intranasal H1AHs	91.8	91.4	91.1	90.6	90.1	89.5	88.9	88.4	87.8	87.2	86.8	-0.6%
INCS	532.4	530.2	528.4	525.7	522.6	519.3	516.0	512.7	509.3	505.9	503.7	-0.6%
Erizas capsule	141.6	141.0	140.5	139.8	138.9	138.1	137.2	136.3	135.4	134.5	133.9	-0.6%
Nasonex	182.5	58.8	40.8	13.0	6.5	6.4	6.4	6.3	6.3	6.2	6.2	-28.7%
Nasonex, generic	0.0	113.4	123.3	122.7	121.9	131.3	130.4	129.6	128.7	127.9	127.3	
Allermist	75.5	75.2	74.9	74.5	74.1	73.6	73.1	72.7	72.2	71.7	71.4	-0.6%
Singulair	223.4	222.4	175.0	4.6	3.5	2.3	1.1	1.1	0.9	0.8	0.8	-43.2%
Montelukast sodium	0.0	0.0	28.5	113.6	118.6	123.4	122.6	121.9	121.1	125.7	125.2	
Generic pranlukast	76.7	76.4	76.1	75.7	75.3	74.8	74.3	73.8	73.4	72.9	72.6	-0.6%
Mast cell stabilizers	1.8	1.8	1.8	1.8	1.8	1.8	1.7	1.7	1.7	1.7	1.7	-0.6%
TXA2 receptor antagonists	83.0	82.7	82.4	82.0	74.1	66.3	65.8	58.2	57.8	57.4	57.1	-3.7%
T_H2 cytokine inhibitors	22.1	22.0	22.0	21.9	21.7	21.6	21.5	21.3	21.2	21.0	20.9	-0.6%
SI-555739	0.0	0.0	0.0	49.7	74.1	98.2	97.5	109.0	113.1	114.8	114.3	
HP-3060	0.0	0.0	0.0	74.7	74.3	73.8	97.8	97.2	96.5	95.9	95.5	
SITs	4.0	8.9	21.5	32.3	40.1	51.4	62.1	73.4	85.3	98.0	110.3	39.4%
Total	**1893.0**	**1880.4**	**1880.9**	**1875.2**	**1887.3**	**1918.6**	**1940.7**	**1944.9**	**1949.2**	**1956.8**	**1961.3**	**0.4%**

Source: GlobalData
CAGR = Compound Annual Growth Rate

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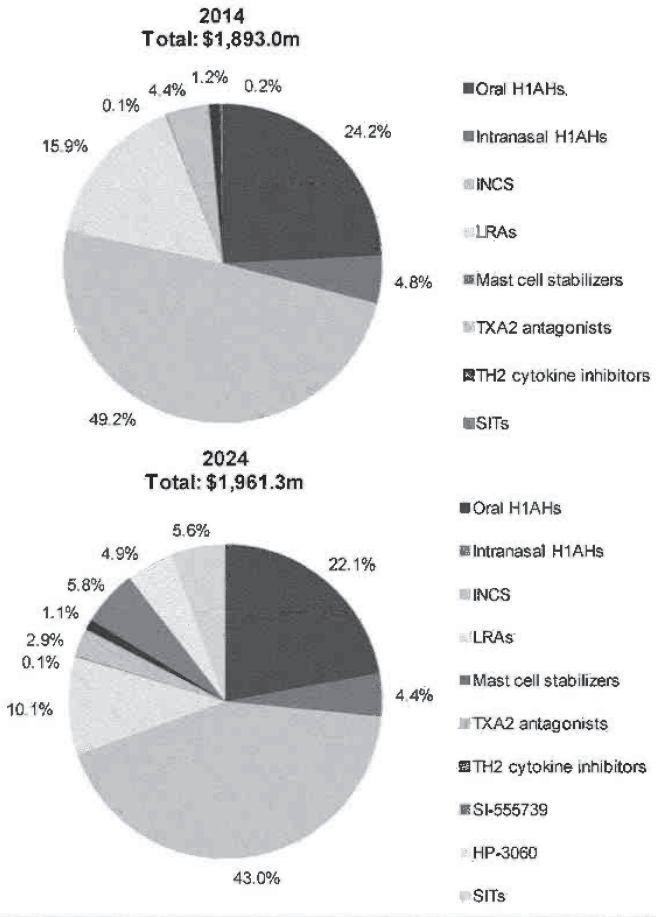
Figure 12 illustrates the sales for AR in Japan by drug class during the forecast period.

Figure 12: Sales for AR in Japan by Drug Class, 2014–2024



Source: GlobalData

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10.4.2 Key Events

Table 72 lists the key events impacting sales for AR in Japan during the forecast period.

Table 72: Key Events Impacting Sales for AR in Japan, 2014–2024

Year	Event	Level of Impact	Type of Impact
2015	Nasonex patent expiry	High	↓↓↓
2016	Singulair patent expiry	High	↓↓↓
2017	S-555739 launch	Medium	↑
2017	HP-3060 launch	Medium	↑
2014	Cedartolen added to the NHI reimbursement list	High	↑↑
2015	Torii HDM SCIT approval	Low	↑
2016	HDM AIT approval (Torii via a licensing agreement with ALK)	High	↑↑
2016	HDM AIT approval (Shionogi via a licensing agreement with Stallergenes)	High	↑
2017	Japanese cedar pollen AIT approval (Torii via a licensing agreement with ALK)	High	↑↑↑

Source: GlobalData

10.4.3 Drivers and Barriers

Table 73 presents the drivers and barriers of the AR market in Japan during the forecast period.

Table 73: AR Market – Drivers and Barriers in Japan, 2014–2024

Drivers	Barriers
Japanese pharmaceutical companies will have enhanced opportunities through increased partnerships with US and EU companies.	Japanese language requirements for regulatory submissions slow the approval process for non-Japanese pharmaceutical companies.
The decreased timeline for drug approval may allow faster access to novel AR therapies.	Pricing Reforms in Japan Will Increase the Use of Generics in the AR Space
Increased pollen counts and pollution will increase the intensity and duration of the allergy season in Japan. The rising prevalence AR in Japan will stimulate the growth of this market.	Physician preference for surgical interventions for patients with AR will negatively impact the drug treatment rate
The launch of novel AITs, in addition to two first-in-class AR pipeline drugs, during the forecast period will temper the effects of generic erosion.	Pricing Reforms in Japan Will Increase the Use of Generics in the AR Space

Source: GlobalData

Increased pollen counts and pollution will increase the intensity and duration of the allergy season in Japan. The rising prevalence AR in Japan will stimulate the growth of this market.

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10.4.3.1 Driver: Japanese Pharmaceutical Companies Will Have Enhanced Opportunities Through Increased Partnerships with US and EU Companies

Recent activity related to M&As has provided US and European pharmaceutical companies with enhanced opportunities to partner with Japanese companies. Japanese pharmaceutical companies can gain from the pipelines of the US and European companies, as well as compete globally, while the US and European companies can extend their business into the Japanese market. For example, Shionogi and Torii, through partnerships with European manufacturers, Stallergenes and ALK, are developing and launching novel AITs, which helps the drugs' success in this territory.

10.4.3.2 Driver: The Decreased Timeline for Drug Approval May Allow Faster Access to Novel AR Therapies

The Special Zone for Innovative Technology project was started in 2008 to overcome factors inhibiting the development of innovative technologies in Japan (GlobalData, 2013g). As a result, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) altered its longstanding policy of requiring separate and additional clinical trials in Japanese patients for drug approval. The new policy allows for global clinical data to be used in the Japanese approval process, as long as safety studies are conducted in Japanese patients. The PMDA has also increased its review staff and established a committee that reviews drugs approved elsewhere to make recommendations for fast-track approval in Japan. The hope is that such changes will decrease the regulatory timeframe for drug approval in the world's second-largest pharmaceutical market. This will be important for upcoming drugs in the AR development pipeline, as they will likely be able to hit the market earlier.

10.4.3.3 Driver: Increased Pollen Counts and Pollution Will Increase the Intensity and Duration of the Allergy Season in Japan

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

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global warming. Scientists have suggested that rising temperatures have helped plant growth in Japan.

10.4.3.4 Driver: The launch of novel AITs, in addition to two first-in-class AR pipeline drugs, during the forecast period will temper the effects of generic erosion.

The Japanese immunotherapy market is currently non-existent. Despite having a large population with AR, less than 6,000 patients were treated with SIT in 2013. Cedartolen, a sublingual liquid containing the standardized Japanese cedar pollen allergen, was evaluated in randomized controlled trials and subsequently approved in 2014. As a condition of approval, prescribing physicians must undergo an online training course. This will increase physician awareness of novel developments in allergen immunotherapies, an unmet need in the field of allergen immunotherapy. The approval of SITs with clinically proven efficacy will bolster the credibility of this therapy type in Japan, which has seen a rapid decline in previous decades, due to the advent of more convenient symptomatic therapies with a rapid onset of action. Within the five-year forecast period, three tablet formulations for Japanese cedar pollen and HDM will be launched in Japan. Torii has been the sole player in this market since SIT became available in Japan in the 1960s. However, Shionogi, in partnership with Stallergenes, is set to enter the SIT market in Japan. Their brand power and extensive marketing base in Japan will place them strongly in this field. Taken together, the extremely small SIT-treated population is set to increase ten-fold in the period between 2013 and 2018.

10.4.3.5 Barrier: Japanese Language Requirements for Regulatory Submissions Slow the Approval Process for Non-Japanese Pharmaceutical Companies

Japanese drug regulatory processes require that foreign drug applications be submitted in the Japanese language. This requirement poses a problem for foreign firms attempting to gain regulatory and intellectual property rights in Japan (GlobalData, 2013g). This policy not only slows the approval process for new drugs coming into the country, but also creates a barrier to patient access to novel therapies, thus making drug access in Japan a time-consuming process. This affects those companies requiring Japanese marketing partners more than those that have already established entry in Japan. This hurdle may be overcome by entering into an agreement with Japanese companies to co-develop and co-commercialize AR pharmaceuticals in Japan.

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10.4.3.6 Barrier: Reference Pricing and Comparator Pricing in Japan Could Present a Challenge for the Launch of New Drugs in the AR Space

The Japanese government strictly regulates drug prices through biennial pricing reviews, reference pricing, and comparator pricing in order to reduce healthcare expenditures (GlobalData, 2013g). The prices for new pharmaceuticals are determined by the MHLW, based on the comparator pricing system. Under this system, prices are set based on similarly-priced drugs already on the market that have the same or similar efficacy and side effect profiles. This could be a challenge for the launch of innovative molecules and stifle the growth of the Japanese AR market. Furthermore, the government can order repricing for classes of drugs if it determines that it is appropriate under the applicable rules.

10.4.3.7 Barrier: Pricing Reforms in Japan Will Increase the Use of Generics in the AR Space

Under the 2014 Japanese drug pricing reforms, a three-bracket price-grouping rule for listed generics was introduced. Under the new regulations, listed generics with the same APIs, formulations, and specifications were placed into three price brackets, based on their market prices. This resulted in products in the same bracket receiving a uniform NHI price, which was based on the weighted-average of their market prices. According to the plans for the 2016 pricing reform, the Central Social Insurance Medical Council is in talks to create a single NHI price for generics with the same APIs, formulations, and specifications. In 2013, the MHLW set a target that generics account for 60% of the market by the end of 2017. There is pressure for the government to set a higher goal as soon as possible. The Z2 rule introduced as part of the 2014 reform reduces the NHI prices of long-listed products, or off-patent brand-name drugs with slow generic penetration by up to 2%.

10.4.3.8 Barrier: Physician preference for surgical interventions for patients with AR will negatively impact the drug treatment rate

Surgical interventions, such as, laser turbinectomy resection, vidian neurotomy, and posterior nasal neurotomy are part of the treatment algorithm in Japan for AR, and are commonly used to treat patients with airborne allergies with nasal obstruction. An increase in physician preference for surgical interventions for patients with AR will decrease the drug treatment rate in the long term.

Appendix

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Appendix

11.2 Abbreviations

Table 74: Abbreviations	
7MM	seven major markets (US, France, Germany, Italy, Spain, and UK)
AAAI	American Academy of Allergy, Asthma, and Immunology
ACA	Affordable Care Act
ACOT	annual cost of therapy
AGR	Annual Growth Rate
AH	antihistamine
AIFA	Agenzia Italiana del Farmaco
AIT	allergen immunotherapy
ANCOVA	analysis of covariance
ANDA	Abbreviated New Drug Application
ANOVA	analysis of variance
ANS	aqueous nasal spray
ANSM	Agence Nationale de sécurité du Médicament et des produits de santé
APC	antigen-presenting cell
API	active pharmaceutical ingredient
AQ	aqueous
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ASK	Allergic Schoolchildren in Kyoto study
AUC	area under the curve
AZE	azelastine
BBB	blood-brain barrier
BDP	beclomethasone dipropionate
BKC	benzalkonium chloride
BLA	Biologics License Application
BSACI	British Society for Allergy & Clinical Immunology
CAGR	Compound Annual Growth Rate
CDC	Centers for Disease Control and Prevention
CEPS	Comité Economique des Produits de Santé
CFC	chlorofluorocarbon
CI	Confidence Interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disorder
COX	cyclooxygenase
$CysLTR_1$	cysteinyl leukotriene receptor 1
DP1	D prostanoid 1

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DP2	D prostanoid 2
DTC	direct-to-consumer
EAACI	European Academy of Allergy and Clinical Immunology
ECG	electrocardiogram
ECHRS	European Community Respiratory Health Survey
EEC	environmental exposure chamber
EFA	European Federation of Allergy and Airway Diseases
EMA	European Medicines Agency
ENT	ear, nose and throat specialist
ER	extended-release
EU	European Union
FCεRI	high-affinity IgE receptor
FDA	US Food and Drug Administration
FDC	fixed-dose combination
FDI	foreign direct investment
FP	fluticasone propionate
FY	fiscal year
GA2LEN	Global Allergy and Asthma European Network
GAP	Grazax Asthma Prevention
G-BA	Federal Joint Committee
GCSE	General Certificate of Secondary Education
GDP	Gross Domestic Product
GP	General Practitioner
GSK	GlaxoSmithKline
H1AH	H1 antihistamine
HAS	Haute Autorité de Santé
HDM	house dust mite
HFA	hydrofluoroalkane
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal axis
HRQoL	health-related quality of life
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
INAH	Intranasal antihistamine
INCS	intranasal corticosteroid
IFNγ	interferon-gamma
IPD®	suplatast tosilate

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ISAAC	International Study of Asthma and Allergies in Childhood
ISS	Istituto Superiore di Sanità
iTNSS	instantaneous total nasal symptom score
ITT	intent-to-treat
J&J	Johnson & Johnson
JPMA	Japan Pharmaceutical Manufacturers Association
JPY	Japanese yen
KOL	key opinion leader
LRA	leukotriene receptor antagonist
LTD-4	cysteinyl leukotriene D4
M&As	mergers and acquisitions
MA	marketing authorization
MAA	Marketing Authorization Application
MAST	multiple allergen simultaneous test
MDI	metered-dose inhaler
MHC	major histocompatibility complex
MHLW	Ministry of Health, Labour and Welfare
MRP	Mutual Recognition Procedure
NAR	non-allergic rhinitis
NHANES	National Health and Nutrition Examination Survey
NHI	National Health Insurance
NHIS	National Health Interview Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNSS	non-nasal symptoms score
NPP	named patient product
NSS	nasal symptoms score
OR	Odds Ratio
OTC	over-the-counter
P&G	Proctor & Gamble
PAR	perennial allergic rhinitis
PCP	primary care physician
PD	pharmacodynamic
PEI	Paul-Ehrlich-Institut
PGD2	prostaglandin D2
PgP	P glycoprotein
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PMPRB	Patented Medicines Prices Review Board

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POM	pharmacist-only medicine; proof of mechanism
PRR	Prevalence Rate Ratio
QoL	quality of life
R&D	research and development
RAST	radioallergosorbent test
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
rTNSS	reflective total nasal symptom score
Rx	prescription
SaKK	Sanofi-aventis KK
S&B	Section and Board (UEMS)
SAR	seasonal allergic rhinitis
SC	subcutaneous
SCIT	subcutaneous immunotherapy
SCUAD	severe chronic upper airway disease
SE	Standard Error
SEAIC	Spanish Society of Allergology and Clinical Immunology
SEK	Swedish Krona
SGA	second-generation antihistamine
SHI	Statutory Health Insurance
SIDRIA	Italian Studies of Respiratory Diseases in Childhood and the Environment
SIT	specific immunotherapy
SLIT	sublingual immunotherapy
sNDA	supplemental New Drug Application
SNS	Sistema Nacional de Salud
SWOT	strengths, weaknesses, opportunities, threats
TAV	Therapie-Allergene-Verordnung
TCM	Traditional Chinese Medicine
TCR	T-cell receptor
TDDS	Transdermal Drug Delivery System technology
TGA	third-generation antihistamine
TGF-β	transforming growth factor-beta
T_H	T helper cell
T_H1	T helper 1 cell
T_H2	T helper 2 cell
TNF	tumor necrosis factor
TNSS	total nasal symptom score
TRAE	treatment-related adverse events
T_{reg}	regulatory T cells
TSS	Total Symptoms Score

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TXA2	thromboxane A2
UEMS	European Union of Medical Specialists
USCB	United States Census Bureau
USPTO	United States Patent and Trademark Office
VBP	value-based pricing
WAO	World Allergy Organization
WHO	World Health Organization

Source: GlobalData

Appendix

11.3 Methodology

GlobalData's dedicated research and analysis teams consist of experienced professionals with marketing, market research, and consulting backgrounds in the pharmaceutical industry, and advanced statistical expertise.

GlobalData adheres to the codes of practice of the European Pharmaceutical Marketing Research Association (EphMRA, ephmra.org).

All GlobalData databases are continuously updated and revised. The following research methodology is followed for all databases and reports.

11.4 Forecasting Methodology

GlobalData uses a patient-based forecast to determine the market size for therapeutic indications. Estimates for the 2014 market for AR in the 7MM (US, France, Germany, Italy, Spain, UK, and Japan) are based on a number of sources, including KOL interviews, prescriber surveys, company reports, press releases, published articles, proprietary databases and general news media.

For asthma, the total patient share exceeds 100% when patients are prescribed more than one drug. The estimated number of compliant days for each drug is determined from prescriber surveys, KOL interviews and internal estimated compliance rates based on the drug's profile.

GlobalData's proprietary forecast model does not account for inflation and is in 2014 dollars. The following paragraphs outline the underlying assumptions for the forecast.

11.4.1 Pediatric Allergic Rhinitis Population

GlobalData's forecast for the allergen-specific immunotherapy market includes both the pediatric and adult populations. The methodology used by GlobalData epidemiologists to estimate the size of the adult AR population in each of the countries under study is described in the Epidemiology section of this report. To estimate the size of the pediatric AR population, the following country-specific methodologies were used.

11.4.1.1 US

GlobalData epidemiologists obtained the age-specific total prevalence of AR in the US from a nationally-representative study that provided the total prevalence of AR in the US in 1993. The study was divided into two parts. In the first part, the study investigators sent a screening

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questionnaire to 15,000 randomly selected households across the US. The researchers screened the household members for the number of days in the past 12 months during which they experienced symptoms of sneezing, runny nose, stuffy nose, itchy eyes, or watery eyes (Nathan et al., 1997). The researchers also screened the household members for doctor-diagnosed hay fever, rhinitis, persistent stuffy nose or head, or allergies involving the eyes, nose, or throat in the past 12 months. Around 10,000 households responded to the first part of the study, representing 22,285 people from across the US. In the second part of the study, the investigators sent a follow-up questionnaire to a sample of 1,450 persons, who responded affirmatively to having symptoms for >7 days within the past year, either singly or consecutively. In the follow-up questionnaire, the participants were asked to select the term that best described their symptoms. If the participants replied affirmatively to the options "seasonal allergy" or "an allergy I have all the time," then they were termed as having AR (Nathan et al., 1997).

To construct the epidemiological forecast for the total prevalent cases of AR in the US, GlobalData epidemiologists used data on the total prevalence of AR from the 1993 study by Nathan and colleagues. Although the study provided the 12-month prevalence, and not the lifetime prevalence, GlobalData epidemiologists selected the study, as epidemiological studies report that both prevalence measures are comparable for AR in children (Austin et al., 1999; Kusunoki et al., 2009). However, the study researchers only provided the overall age-specific total prevalence of AR. Because the researchers reported that there is no difference in the sex-specific total prevalence of AR, GlobalData epidemiologists applied the overall (both sexes) age-specific total prevalence of AR to both sexes to obtain the age- and sex-specific total prevalence of AR in the US (Nathan et al., 1997). Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (1993) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in the US for each year to forecast the total prevalent cases of AR in the US from 2013–2023 (Nathan et al.,1997; USCB, 2012).

11.4.1.2 France

GlobalData epidemiologists obtained the total prevalence of AR among children ages 13–14 years in France from cross-sectional surveys conducted in 2002 in Languedoc Roussillon, France. These surveys used the ISAAC protocol to collect information from randomly selected schools. The first survey consisted of 3,383 participants, and the second survey consisted of 1,642 participants. The

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questionnaires were the French version of the ISAAC core questionnaire, and were completed by the children themselves (Annesi-Maesano et al., 2009).

To construct the epidemiological forecast for the total prevalent cases of AR in France, GlobalData epidemiologists used data on the total prevalence of AR from the study by Annesi-Maesano and colleagues. The study researchers provided the total prevalence of AR in children ages 13–14 years in France, which was applied to age group 10–14 years. Additionally, as there were no data on the prevalence of AR in other age groups (0–4 years, 5–9 years, and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age groups 0–4 years, 5–9 years, and 15–17 years was the same as the prevalence in the age group 13–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2002) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in France in each year to forecast the total prevalent cases of AR in France from 2013–2023 (Annesi-Maesano et al., 2009; USCB, 2012).

11.4.1.3 Germany

Due to the lack of total prevalence data for AR in children in Germany, GlobalData epidemiologists assumed that the total prevalence of AR in children in Germany was the same as that in France (Annesi-Maesano et al., 2009).

Due to the scarcity of total prevalence data for AR in children in Germany, GlobalData epidemiologists assumed that the age- and sex-specific total prevalence of AR in Germany were the same as that in France. GlobalData epidemiologists kept the age- and sex-specific prevalence proportions of AR constant throughout the forecast period due to the lack of historical data necessary to forecast future trends. GlobalData epidemiologists then applied the age- and sex-specific total prevalence proportions of AR to the respective age- and sex-specific population estimates in each year to forecast the total prevalent cases of AR in Germany from 2013–2023 (Annesi-Maesano et al., 2009; USCB, 2013).

11.4.1.4 Italy

GlobalData epidemiologists obtained the age-specific total prevalence of AR in Italy from a study by Galassi and colleagues. This study was a part of the ISAAC study, and was designed

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specifically to study the prevalence of AR and other allergic conditions in children ages 6–7 years and 13–14 years under a project called the Italian Studies of Respiratory Diseases in Childhood and the Environment (SIDRIA). Phase I of SIDRIA was conducted between October 1994 and May 1995, and Phase II of SIDRIA was conducted between January and May 2002, in Turin, Milan, Trent, Emilia-Romagna, Florence, Empoli, Siena, and Rome. During Phase I of the study, 16,115 questionnaires were filled out by the parents of the children ages 6–7 years, and 19,723 questionnaires were filled out by adolescents ages 13–14 years. Similarly, during the Phase II of the study, 11,287 questionnaires were filled out by the parents of the children ages 6–7 years, and 10,267 questionnaires were filled out by adolescents ages 13–14 years. The questionnaires consisted of ISAAC core questions on AR (Galassi et al., 2006).

To construct the epidemiological forecast for the total prevalent cases of AR in Italy, GlobalData epidemiologists used data on the self-reported total prevalence of AR from the study by Galassi and colleagues. Although the study provided the 12-month prevalence, and not the lifetime prevalence, GlobalData epidemiologists selected the study, as other epidemiological studies report that both prevalence measures are comparable for AR in children (Austin et al., 1999; Kusunoki et al., 2009). The study researchers provided the self-reported total prevalence of AR in children ages 6–7 years and 13–14 years in Italy, which was applied to the age groups 5–9 years and 10–14 years, respectively. Additionally, as there were no data on the prevalence of AR in the other age groups (0–4 years and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age group 0–4 years was the same as the prevalence in the age group 5–9 years, and that the prevalence in the age group 15–17 years was the same as the prevalence in the age group 10–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2002) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Italy in each year to forecast the total prevalent cases of AR in Italy from 2013–2023 (Galassi et al., 2006; USCB, 2012).

11.4.1.5 Spain

GlobalData epidemiologists estimated the total prevalence of AR among children ages 10–11 years in Spain from a cross-sectional study, which was carried out as part of ISAAC Phase II in 2001. The study included 1,143 children in 29 schools in Almeria, Spain, whose parents were

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administered questionnaires prepared on the basis of the ISAAC protocol. Additionally, the skin prick test was also conducted to test for a positive reaction to allergens. The current and past prevalence of AR was estimated by a positive response to the question, "Has your son/daughter sneezed or ever sneezed, or has he/she had a runny or blocked nose without having a cold or influenza during the last 12 months?" (Batlles-Garrido et al., 2010).

To construct the epidemiological forecast for the total prevalent cases of AR in Spain, GlobalData epidemiologists used data on the self-reported total prevalence of AR from the study by Battles-Garrido and colleagues. Although the study provided the 12-month prevalence, and not the lifetime prevalence, GlobalData epidemiologists selected the study, as other epidemiological studies report that both prevalence measures are comparable for AR in children (Austin et al., 1999; Kusunoki et al., 2009). The study researchers provided the self-reported total prevalence of AR in children ages 10–11 years in Spain, which was applied to the age group 10–14 years. Additionally, as there were no data on the prevalence of AR in the other age groups (0–4 years, 5–9 years, and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age groups 0–4 years, 5–9 years, and 15–17 years was the same as the prevalence in the age group 13–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2001) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Spain in each year to forecast the total prevalent cases of AR in Spain from 2013–2023 (Battles-Garrido et al., 2010; USCB, 2012).

11.4.1.6 UK

GlobalData epidemiologists obtained the total prevalence of AR among children ages 12–14 years in the UK from a survey that was carried out as part of the ISAAC study conducted by Anderson and colleagues during the years 1995 and 2002. The researchers conducted the study in England, Scotland, Wales, and the offshore islands of Guernsey, Isle of Man, and Jersey in the UK. The researchers administered 15,083 questionnaires during 1995, and 15,755 questionnaires during 2002, among secondary school children ages 12–14 years. The questionnaire was adopted from the ISAAC protocol, and all the questionnaires were filled out by the children themselves (Anderson et al., 2004).

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To construct the epidemiological forecast for the total prevalent cases of AR in the UK, GlobalData epidemiologists used data on the total prevalence of AR from the study by Anderson and colleagues. The study researchers provided the total prevalence of AR in children ages 12–14 years in the UK, which was applied to the age group 10–14 years. Additionally, as there were no data on the prevalence of AR in the other age groups (0–4 years, 5–9 years, and 15–17 years), GlobalData epidemiologists assumed that the prevalence in the age groups 0–4 years, 5–9, years, and 15–17 years was the same as the prevalence in the age group 13–14 years. Also, the study did not provide any sex-specific prevalence, so GlobalData epidemiologists applied the age-specific total prevalence of AR to both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2002) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in the UK in each year to forecast the total prevalent cases of AR in the UK from 2013–2023 (Anderson et al., 2004; USCB, 2012).

11.4.1.7 Japan

GlobalData epidemiologists obtained data on the prevalence of AR in Japan from a population-based survey called the Allergic Schoolchildren in Kyoto (ASK) study conducted in Kyoto, Japan during 2006. The study enrolled 13,215 schoolchildren ages 7–15 years from 30 schools, whose parents were administered questionnaires prepared on the basis of the ISAAC questionnaire, which was validated by the Study Group of Epidemiology of Allergic Diseases established by the Japanese MHLW (Kusunoki et al., 2009).

To construct the epidemiological forecast for the total prevalent cases of AR in Japan, GlobalData epidemiologists used data on the total prevalence of AR from the study by Kusunoki and colleagues. The study researchers provided the sex-specific total prevalence of AR in children ages 7–15 years in Japan, which was applied to the age groups 5–9 years, 10–14 years, and 15–17 years. Additionally, as there were no data on the prevalence of AR for the age group 0–4 years, GlobalData epidemiologists assumed that the prevalence in the age group 0–4 years was the same as the prevalence in the age group 5–9 years in both sexes. Due to the lack of historical data needed to develop future trends, GlobalData epidemiologists chose to keep the age- and sex-specific total prevalence of AR for the most recently reported year (2006) constant throughout the forecast years. GlobalData epidemiologists then applied the age- and sex-specific total prevalence of AR to the respective age- and sex-specific population estimates in Japan in each year to

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forecast the total prevalent cases of AR in Japan from 2013–2023 (Kusunoki et al., 2009; USCB, 2012).

11.4.2 Diagnosed AR Patients

The total AR population includes both undiagnosed and diagnosed patients. GlobalData multiplied the total AR population by a diagnosis rate obtained from our prescriber surveys to determine the diagnosed patient population. The diagnosis rate was modified in order to account for the fact that the AR prevalence numbers represent the lifetime AR prevalence.

11.4.3 Percentage of Drug-Treated Patients

The drug treatment rates for AR were obtained from GlobalData's survey of high-prescribing physicians and KOL interviews. This number will remain constant during the forecast period in the 7MM (US, France, Germany, Italy, Spain, UK, and Japan).

11.4.4 Drugs Included in Each Therapeutic Class

Due to the large number of drugs in each therapeutic class, the lists below are not exhaustive, but rather, a representation of the drugs considered.

Antihistamines

AHs include, but are not limited to:

US: Generic versions of brompheniramine, cetirizine hydrochloride, fexofenadine hydrochloride, levocetirizine, loratadine, acrivastine, and desloratadine

Europe: Illaxten (bilastine), Mizollen (mizolastine), Rupafin (rupatadine fumarate), and generic versions of fexofenadine, levocetirizine, loratadine, cetirizine hydrochloride, acrivastine, and desloratadine

Japan: Generic versions of epinastine hydrochloride, cetirizine hydrochloride, bepotastine besilate, fexofenadine hydrochloride, olopatadine hydrochloride, loratadine, and levocetirizine

Intranasal Antihistamines

The INAHs include, but are not limited to, Livostin and generic versions of azelastine and olopatadine.

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Intranasal Corticosteroids

Veramsyt/Avamys (fluticasone furoate), Omnaris (ciclesonide), Zetonna (ciclesonide) Qnasl (beclomethasone dipropionate) Erizas (dexamethasone cipecilate), and generic versions of beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, triamcinolone acetonide, and flunisolide

Intranasal Corticosteroid/Antihistamine

Dymista

Leukotriene Receptor Antagonists

Singulair and generic versions of montelukast sodium

Anticholinergics

Generic versions of ipratropium bromide

Decongestants

Generic versions of pseudoephedrine, phenylephrine, and oxymetazoline

Mast cell stabilizers

Sodium cromoglycate

Thromboxane A2 receptor antagonist

Baynas (ramatroban)

TH2 cytokine inhibitor

Suplatast tosilate (IPD®)

Subcutaneous immunotherapy

Includes extracts manufactured by:

US: ALK-Abello A/S, Allergy Laboratories, Greer Laboratories and Jubilant Hollister-Steir Laboratories LLC

EU: ALK-Abello A/S, Stallergenes, Allergy Therapuetics, HAL Allergy, Merck KGaA, Leti, and other smaller companies

Japan: Torii Pharmaceuticals

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Sublingual immunotherapy

Includes extracts manufactured by:

US: Greer

EU: ALK-Abello A/S, Stallergenes, Allergy Therapuetics, HAL Allergy, Merck KgaA, Leti, and other smaller companies

Japan: Torii

Allergen immunotherapy tablets

Includes extracts manufactured by:

US: Merck (including Grastek, Ragwitek, and Mitizax) and Greer (Oralair)

EU: ALK-Abello A/S, Stallergenes, Allergy Therapuetics, HAL Allergy, Leti, and other smaller companies

Japan: Torii and Shionogi

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11.4.5 Launch and Patent Expiry Dates

Table 75 lists the key launch dates of the currently available AR therapies.

Table 75: Key Launch Dates of the Currently Available AR Therapies

Product	US	5EU	Japan
Allegra (fexofenadine)	1996	1997	2000
Allelock (olopatadine)	N/A	N/A	2001
Astelin (azelastine)	1996	2000	-
Astepro (azelastine hydrochloride)	2009	2013	N/A
Baynas (ramatroban)	N/A	N/A	2000
Beconase (beclomethasone)	1976	1975	-
Benadryl (diphenhydramine)	1946	-	1998
Clarinex (desloratadine)	2002	2001	Phase III
Claritin (loratadine)	1993	1988	2002
Dymista (azelastine/fluticasone propionate)	2012	2013	N/A
Flonase (fluticasone propionate)	1995	-	-
Ilaxten (bilastine)	N/A	2011	Phase II
Nasacort (triamcinolone acetonide)	1991	1997	2013
Nasalcrom (sodium cromoglycate)	1997	-	-
Nasonex (mometasone furoate)	1997	1997	N/A
Omnaris (ciclesonide)	2008	N/A	N/A
Patanase (olopatadine hydrochloride)	2008	N/A	N/A
Qnasl (beclomethasone diproprionate)	2012	N/A	2002
Rhinocort (budesonide)	1994	-	1986
Singulair (montelukast sodium)	1998	2001	2008
Suplatast tosilate (IPD®)	N/A	N/A	1995
Talion (bepotastine)	N/A	N/A	2000
Veramyst (fluticasone furoate)	2007	2008	2009
Xyzal (levocetirizine dihydrochloride)	2007	2001	N/A
Zetonna (ciclesonide)	2008	N/A	N/A
Zyrtec (cetirizine hydrochloride)	1996	1989	1998
Zyrtec-D (cetirizine hydrochloride and pseudoephedrine hydrochloride)	2001	-	-
S-555739	2018	N/A	2017
HP-3060	N/A	N/A	2017

Source: GlobalData

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Table 76 lists the key loss of exclusivity dates of the currently available AR therapies.

Table 76: Key Loss of Exclusivity Dates of the Currently Available AR Therapies

Product	US	5EU	Japan
Astepro (azelastine)	2028	-	2025
Baynas (ramatroban)	N/A	N/A	2016
Dymista (azelastine/fluticasone propionate)	2026	2023	
Flonase (fluticasone propionate)	2004	2005	-
Ilaxten (bilastine)	2017	2022	2017
Nasonex (mometasone furoate)	2018	2014	2016
Patanase (olopatadine hydrochloride)	2011	N/A	N/A
Qnasl (beclomethasone diproprionate)	2017	N/A	N/A
Singulair (montelukast sodium)	2012	2013	2016
Veramyst (fluticasone furoate)	2021	2023	2025
Zetonna (ciclesonide)	2017	2016	2016
Omnaris (ciclesonide)	2017	2016	2016

Source: GlobalData

11.4.6 1General Pricing Assumptions

GlobalData uses national formularies to gather pricing information and recognizes that the prices presented in formularies can differ, representing prices at different stages in the supply chain. As such, when ex-factory wholesale prices are not available, GlobalData uses conversion formulas, which remove taxes, and/or pharmacy and wholesale margins, in order to obtain estimated ex-factory wholesale prices for each country.

Currency conversion to US dollars utilized the 2014 yearly average from OANDA (www.oanda.com).

The following references were used as price sources, backing-out formulas, and discount rates for each market covered in this report to estimate ex-factory wholesale pricing:

- US: prices were obtained from Thomson Reuter's Red Book.
- France: prices were obtained from Ministry of Social Affairs and Health (Ministère des Affaires Sociales et de la Santé)
- Germany: prices were obtained from the Rote List, and conversion formulas were determined based on information from the Patented Medicine Prices Review Board (PMPRB) (2013).

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- Italy: prices were obtained from the Italian Medicines Agency (Agenzia Italiana del Farmaco, l'Informatore Farmaceutico), and conversion formulas were determined based on information from the PMPRB (2013).
- Spain: prices were obtained from the Spanish Agency for Medicines and Products (Agencia Española de Medicamentos y Productos, Organización Farmacéutica Colegial).
- UK: prices were obtained from the British National Formulary (BNF) and conversion formulas were determined based on information from the European Parliament (2011) and National Institute for Health and Care Excellence (NICE) (2014).
- Japan: prices were obtained from SSRI's NHI drug price database (April 2012). Conversion formulas were determined based on information from the Japan Pharmaceutical Manufacturers Association (JPMA) (2012) and *The Wall Street Journal* (Mochizuki, 2014).

11.4.7 Individual Drug Assumptions

Oral antihistamine assumptions:

- Clinical Positioning: GlobalData expects that AHs will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 140 in the US and 200 in the 5EU and Japan.
- ACOT: Treatment with oral AHs costs: US ($92.40); France ($38.00); Germany ($66.00); Italy ($37.00); Spain ($63.00); UK ($14.00); Japan ($139.00).
- Compliance: Oral AHs' average compliance rate, according to GlobalData's primary research, is estimated to be: US (63%); EU (73%); Japan (64%).

Intranasal antihistamine assumptions:

- Clinical Positioning: GlobalData expects that intranasal antihistamines will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 240 in the US and 200 in the 5EU and Japan.
- ACOT: Treatment with intranasal antihistamines costs: US ($269.00); France ($32.00); Germany ($48.00); Italy ($32.00); Spain ($48.00); UK ($80.00); Japan ($144.00). The ACOT

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for the US will decrease upon the patent expiry of two key drugs, Astepro and Patanase, to ($224.00).

- Compliance: INAHs' average compliance rate, according to GlobalData's primary research, is estimated to be: US (44%); EU (48%); Japan (33%).

Intranasal corticosteroid assumptions:

- Clinical Positioning: GlobalData expects that INCS will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment with INCS costs: US ($304.00); France ($39.00); Germany ($66.00); Italy ($125.00); Spain ($57.00); UK ($35.00); Japan ($224.00).
- Compliance: INCS' average compliance rate, according to GlobalData's primary research, is estimated to be: US (60%); EU (59%); Japan (67%).

Nasonex assumptions:

- Clinical Positioning: GlobalData expects that Nasonex will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment with Nasonex costs: US ($152.00); France ($24.00); Germany ($48.00); Italy ($68.00); Spain ($32.00); UK ($32.00);
- Compliance: Nasonex's average compliance rate, according to GlobalData's primary research, is estimated to be: US (60%); EU (59%)

Qnasl assumptions:

- Clinical Positioning: GlobalData expects that Qnasl will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200 in the US .
- ACOT: Treatment with Qnasl costs: US ($912.00);
- Compliance: Qnasl's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

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Zetonna assumptions:

- Clinical Positioning: GlobalData expects that Zetonna will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200 in the US .
- ACOT: Treatment with Zetonna costs: US ($1,176.00);
- Compliance: Zetonna's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Omnaris assumptions:

- Clinical Positioning: GlobalData expects that Omnaris will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200 in the US .
- ACOT: Treatment with Omnaris costs: US ($1,176.00)
- Compliance: Omnaris' average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Veramyst assumptions:

- Clinical Positioning: GlobalData expects that Veramyst will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment with Veramyst costs: US ($992.00); France ($56.00); Germany ($56.00); Italy ($144.00); Spain ($96.00); UK ($56.00); Japan ($304.00)
- Compliance: Veramyst's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Dymista assumptions:

- Clinical Positioning: GlobalData expects that Dymista will be used for all AR severities as a medication to provide quick relief of AR symptoms.

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- Treatment days: The number of treatment days per year for all AR patients is 260 in the US and 200 in the 5EU .
- ACOT: Treatment with Dymista costs: US ($146.00); France ($144.00); Germany ($176.00); Italy ($208.00); Spain ($144.00); UK ($176.00)
- Compliance: Dymista's average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Leukotriene receptor antagonist assumptions:

- Clinical Positioning: GlobalData expects that LRAs will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 260 in the US and 200 in the 5EU .
- ACOT: Treatment with LRAs costs: US ($304.00); France ($124.00); Germany ($124.00); Italy ($60.00); Spain ($134.00); UK ($36.00); Japan (Singulair: $466.00)
- Compliance: LRAs' average compliance rate, according to GlobalData's primary research, is estimated to be: US (60%); EU (54%); Japan (32%).

Decongestant assumptions:

- Clinical Positioning: GlobalData expects that decongestants will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 27.
- ACOT: Treatment for 365 days with decongestants costs: US ($16.20).
- Compliance: Decongestants' average compliance rate, according to GlobalData's primary research, is estimated to be: 47%

Mast cell stabilizers assumptions:

- Clinical Positioning: GlobalData expects that mast cell stabilizers will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with mast cell stabilizers costs: Japan ($32.00).

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- Compliance: Mast cell stabilizers' average compliance rate, according to GlobalData's primary research, is estimated to be: 60%

Thromboxane A2 receptor antagonist (Baynas) assumptions:

- Clinical Positioning: GlobalData expects that Baynas will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with Baynas costs: Japan ($532.00).
- Compliance: Baynas' average compliance rate, according to GlobalData's primary research, is estimated to be 70%.

TH2 cytokine inhibitors (suplatast tosilate, IPD®) assumptions:

- Clinical Positioning: GlobalData expects that suplatast tosilate, IPD®, will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with suplatast tosilate, IPD®, costs: Japan ($234.00).
- Compliance: Suplatast tosilate, IPD®'s average compliance rate, according to GlobalData's primary research, is estimated to be 60%.

S-555739 assumptions:

- Clinical Positioning: GlobalData expects that S-555739 will be used for all AR severities as a medication to provide quick relief of AR symptoms.
- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with S-555739 costs: US ($1,056.00); Japan ($532.00).
- Compliance: S-555739 average compliance rate, according to GlobalData's primary research, is estimated to be 60%.

HP-3060 assumptions:

- Clinical Positioning: GlobalData expects that HP-3060 will be used for all AR severities as a medication to provide quick relief of AR symptoms.

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- Treatment days: The number of treatment days per year for all AR patients is 200.
- ACOT: Treatment for 200 days with HP-3060 costs: Japan ($400.00).
- Compliance: HP-3060's average compliance rate, according to GlobalData's primary research, is estimated to be 80%. Subcutaneous Immunotherapy:

US

- Clinical positioning: GlobalData estimated that 100% of patients treated with SIT will receive SCIT in 2018. This is because, despite the approval of AITs, it is thought that they will be prescribed as second-line treatments to SCIT, or to those who have refused SCIT, owing to the lack of financial incentives for US allergists, and their single-allergen composition.
- Average ACOT: Based on KOL guidance, prices obtained directly from several manufacturers, and a 2014 research paper by Dranitsaris and Ellis that analyzed the direct and indirect costs of SIT, suggesting that the average cost of an allergen extract administered as a SCIT is $200 per year, based on an estimated three-year treatment course and a high dropout rate of over 50% in Year 1. (Dranitsaris and Ellis, 2014)
- Compliance: We assumed a compliance rate of 40%, based KOL insight, due to the undesirable nature of injections and the frequent clinic visits required.

5EU

- Clinical positioning: GlobalData estimates that the use of SCIT will decline within the forecast period.
- ACOT: Based on KOL guidance suggesting that the average cost of an allergen extract administered as a SCIT is $1,050 per year.
- Compliance: We assumed a compliance rate of 51%, based on KOL insight and a survey of patients receiving SCIT in Germany from 2005–2007, published in Current Medical Research Opinion (Sieber et al., 2011).

Japan

- Clinical positioning: KOL insight suggested that in 2014, approximately 10% of prescription drug-treated Japanese AR patients received SCIT, most commonly for HDM allergy. GlobalData estimated that only 1% of patients receiving SIT will receive SCIT in 2018. The

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launch of two AITs containing the standardized HDM extract will largely take the patient share of HDM-allergic AR patients, due to their increased convenience, as they can be administered at home and are preferable to injections for most patients, especially children.

- ACOT: Based on KOL guidance and secondary research suggesting that the average cost of an allergen extract administered as an SCIT is $1,224 per year.
- Compliance: We assumed a compliance rate of 40%, based KOL insight, due to the undesirable nature of injections and the frequent hospital visits required for each treatment.

Sublingual Immunotherapy Drops:

US

- Clinical positioning: GlobalData estimated that 0.9% of SIT-treated AR patients will be treated with Greer's SAIL short ragweed sublingual liquid in 2018, following its estimated launch in 2016. This slow uptake will be tempered by the launch of Ragwitek in 2014, a tablet containing the short ragweed allergen, marketed by Merck in collaboration with ALK-Abello.
- Treatment days: SAIL is a once-daily sublingual drop therapy used for 8–16 weeks pre-seasonally and during the entire ragweed pollen season.
- ACOT: Based on the ex-manufacturer price of sublingual therapies in the 5EU, SAIL was assigned a price of $513.20 per year.
- Compliance: We assumed a compliance rate of 70%, based on KOL insight and a survey of patients receiving SLIT in Germany from 2005–2007 published in Current Medical Research Opinion (Sieber et al., 2011).

5EU

- Clinical positioning: GlobalData estimated that the SLIT market will decline slightly over the forecast period, as physicians would prescribe a tablet over a liquid drop in patients prescribed allergen immunotherapy sublingually.
- ACOT: Based on KOL guidance suggesting that the average cost of an allergen extract administered as a SLIT is $513.20 per year.

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- Compliance: We assumed a compliance rate of 70%, based on KOL insight and a survey of patients receiving SLIT in Germany from 2005–2007 published in Current Medical Research Opinion (Sieber et al., 2011).

Japan

- Clinical positioning: KOL insight suggested that in 2014, approximately 90% of SIT-treated Japanese patients received SLIT; most patients receive SLIT for seasonal allergies, predominantly Japanese cedar pollen. GlobalData estimated that this patient share will decrease to 40% by 2018, primarily due to the launch of a sublingual AIT containing the cedar pollen allergen.
- ACOT: Based on KOL guidance and secondary research, GlobalData assumed that the average cost of an allergen extract administered as an SLIT is $1,224 per year.
- Compliance: We assumed a compliance rate of 50%, based KOL insight, due to the inconvenience of this treatment option and its delayed onset of action compared with the symptomatic therapies.

Allergen Immunotherapy Tablets:

US

- Clinical positioning: GlobalData estimates that 6.1% of the SIT drug-treated population will be treated with an AIT by 2018.
- Treatment days: Oralair, a once-daily tablet, was used as a benchmark. Treatment should start four months before grass pollen is expected to appear, and be continued until the end of the pollen season (usually 2–6 months). On average, we assumed that Oralair would be taken for eight months a year. Grazax (Grastek), a once-daily tablet, should be initiated at least four months before the start of the pollen season, and be continued year-round for up to three years. The grass pollen season, on average, begins around April in the US. On average, we assumed that Grazax would be taken for 12 months a year. Based on these two products, we determined that tablet formulations would be used for 10 months each year.
- Average cost of therapy: Based on the ex-manufacturer price of Grazax and Oralair in the 5EU, allergen immunotherapy tablets were assigned an average annual cost of ($2685.00), (ex-factory wholesale price).

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- Compliance: We assumed a compliance rate of 70%, based on the convenience of Grazax and Oralair compared with other SIT formulations and its once-daily dosing.

5EU

- Clinical positioning: GlobalData estimates that 10% of the SIT drug-treated population will be treated with either a tablet by 2018.
- Treatment days: Oralair, a once-daily tablet, was used as a benchmark. Treatment should start four months before grass pollen is expected to appear and be continued until the end of the pollen season (usually 2–6 months). On average, we assumed that Oralair would be taken for eight months a year. Grazax (Grastek), a once-daily tablet, should be initiated at least four months before the start of the pollen season and be continued year round for up to three years. The grass pollen season on average begins in April in the 5EU. On average, we assumed that Grazax would be taken for 12 months a year. Based on these two products we averaged that tablet formulations would be used for 10 months each year.
- Average ACOT: Based on the ex-manufacturer price of Grazax and Oralair in the 5EU, AIT tablets were assigned an average annual cost of ($1,206.50), (ex-factory wholesale price).
- Compliance: We assumed a compliance rate of 70%, based on the convenience of Grazax and Oralair compared with other SIT formulations, and its once-daily dosing.

Japan

- Clinical positioning: GlobalData estimates that 59% of the SIT drug-treated population will be treated with either a Torii or a Shionogi tablet by 2018.
- Average ACOT: Using the average annual cost of Grazax and Oralair in the 5EU ($1,206.50), a ratio was applied to the ACOT for SCITs in Japan and the 5EU. The price for an AIT in Japan was extrapolated, generating an ACOT of $1,407, which was applied to both Torii and Shionogi's pipeline tablets.
- Compliance: We assumed a compliance rate of 70%, based on convenience of AIT compared with other SIT formulations, and its potential once-daily dosing.

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11.4.8 Generic Erosion

The prices of drugs with expiring patents are decreased during our forecast to account for generic competition. The percentage of branded prescriptions shifting to generics is adjusted to reflect the overall strength of the generic drug market in each country.

11.4.9 Pricing of Pipeline Agents

- S-555739 is priced similarly to the branded TXA2 receptor antagonist, Baynas, as it will be used for the third-line treatment of patients with chronic refractory AR, targeting a related pathway with specific biological and clinical features.
- HP-3060 is priced at a 40% premium over the class of INCS therapies, including multiple generic products, due to its more convenient transdermal administration. This will be a first-in-class product on the Japanese market, where there is a preference for patch formulations, particularly among elderly and pediatric patients.

Appendix

11.5 Physicians and Specialists Included in This Study

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Appendix

High-Prescribing Physician Survey

In addition to the KOLs cited above, high-prescribing physicians (non-KOLs), including allergists and PCPs, represented the seven markets covered in this report. All of the non-KOL responses were obtained through an electronic survey created by the report authors in collaboration with the GlobalData primary research team. The survey was launched in October 2014, and was completed in November 2014.

Table 77 provides a summary of the high prescribers surveyed for this report, by country.

Table 77: High-Prescribing Physicians (non-KOLs) Surveyed, by Country

Country	Total Number of Physicians Surveyed
US	20
France	15
Germany	10
Italy	16
Spain	16
UK	9
Japan	10

Source: GlobalData

Appendix

11.6 About the Authors

11.6.1 Analyst

Claire Gibson, PhD, Managing Analyst, Oncology

Claire Gibson, PhD, is an Oncology Healthcare Managing Analyst at GlobalData in London. Claire's previous academic research experience in the biomedical field included the formulation of extended-release drug formulations containing small molecules. Prior to working at GlobalData, she was an analyst at Q Chip, a Cardiff-based biotechnology company, evaluating metabolic disorders. Claire received a BBSRC CASE award to complete an industrially-led PhD in stem cell and regenerative medicine at Cardiff University, sponsored by Q Chip. Here, she developed a novel microfluidics-generated microcarrier technology to isolate, rapidly expand, and differentiate mesenchymal stem cells. Prior to this, she completed a BSc in Biochemistry from the School of Biomedical Sciences, Cardiff University. In addition to her academic career, Claire also worked within the NHS in prescription services, and also ran several healthcare screening programs.

11.6.2 Therapy Area Director

Valentina Gburcik, PhD, Director, Cardiovascular and Metabolic Disorders

Valentina Gburcik, PhD, is the Director of Cardiovascular and Metabolic Disorders at GlobalData in London. Valentina has previously produced reports and forecasting models for the type 2 diabetes, microvascular complications of diabetes, and gout markets. Valentina's previous academic research experience in the biomedical field included the molecular and systems biology approach to diabetes and obesity. She also participated in the development of a novel nanoparticle-based system for the delivery of nucleic acids and drugs into cells, which led her to co-author a patent application, and co-found Tecrea Ltd., a spinoff company based in London's Bioscience Innovation Centre. Previously, in parallel with her academic research, she worked part-time as a Business Development/Project Manager for the biotech company, Imuthes Ltd., in London. Valentina received her PhD in Biological Sciences from the Department of Cell Biology, University of Geneva, where she worked on the mechanisms of drug resistance in breast cancer. During that time, she also obtained a Certificate in Entrepreneurship from CTI – Venture Challenge Program, Switzerland. Previously, she obtained her BSc degree in Biochemistry from the Faculty of Chemistry, University of Belgrade.

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11.6.3 Epidemiologist

Lizzy Sunny, PhD, Project Manager, Epidemiology

Lizzy Sunny, PhD, currently serves as Project Manager of the Epidemiology Division at GlobalData in Hyderabad, India. Dr. Sunny has worked with various national-level cancer registries, academic institutions, and pharmaceutical consulting companies around the globe. She is experienced in the design and execution of many large-scale population-based epidemiological studies, including breast cancer screening studies, and in analyzing epidemiology research data. During her career, she has published several research articles in various international peer-reviewed journals, and has written several reports and monographs related to cancer epidemiology. Additionally, she has worked for top pharmaceutical companies in the US and Europe on epidemiology consulting projects. She has received large project grants from national and international organizations, and has headed various national-level epidemiology projects in India. Dr. Sunny holds a Master's degree in Science from MG University, India; a Doctoral Programs in Public Health (DPPH) degree from Tampere School of Public Health at Tampere University, Finland; and a PhD in Epidemiology from Tampere University, Finland. She completed her post-doctoral research in clinical cancer epidemiology at Gothenburg University in Sweden.

11.6.4 Global Head of Healthcare

Jim Coutcher, MS, Global Head of Healthcare

Jim Coutcher, MS, is Global Head of Healthcare for GlobalData in Boston, managing the Medical and Pharmaceutical arms of the business. Jim has more than 20 years' experience in the pharmaceutical industry, in which time he has focused on both the preclinical and clinical aspects of drug development. He began his career in the laboratories of Pfizer, where he was involved in preclinical research for diabetes, diabetic complications and obesity. After more than 10 years in research, he transitioned into positions in sales and marketing for ALPCO Diagnostics; consulting for CNS, CVMD, immunology and oncology projects for Citeline, and business development for KCAS. Jim received his B.A. in Chemistry from Boston University and an MS in Neuropharmacology from the University of South Florida.

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11.7 About GlobalData

GlobalData is a leading global provider of business intelligence in the healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports, and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

GlobalData has offices in New York, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

11.8 Disclaimer

The facts of this report are believed to be correct at the time of publication, but cannot be guaranteed. Please note that the findings, conclusions and recommendations that GlobalData delivers will be based on information gathered in good faith from both primary and secondary sources, whose accuracy we are not always in a position to guarantee. As such, GlobalData can accept no liability whatsoever for actions taken based on any information that may subsequently prove to be incorrect.

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