Expert Opinion

Intranasal corticosteroids: the development of a drug delivery device for fluticasone furoate as a potential step toward improved compliance

William E Berger†, James W Godfrey & Anna L Slater
†*Allergy and Asthma Associates, 27800 Medical Center Road, Suite # 244, Mission Viejo, California 92691, USA*

Devices for the aqueous delivery of intranasal corticosteroids to patients with allergic rhinitis have been available since 1984, so there is a need for new devices to be developed to provide ease of use, efficacy and safety. A novel drug delivery system has been developed for fluticasone furoate (FF; GlaxoSmithKline): a new enhanced-affinity glucocorticoid with a scent-free formulation. The FF system was developed, giving attention to patients' unmet needs, in order to promote acceptance and compliance. It demonstrates a number of key features including its ergonomic design, side-actuation system and short delivery nozzle. Exploiting issues with present devices highlighted the need for the FF system. This review reports data from key studies and surveys conducted by GlaxoSmithKline during development, to determine ease of use and acceptance of the FF system. Findings suggest that the FF system should aid in improving attitudes to the use of intranasal corticosteroids amongst physicians and patients.

Keywords: allergic rhinitis, ergonomic design, fine mist, intranasal corticosteroids, nasal drug delivery, sensory attributes, short delivery nozzle, side-actuated mechanism

Expert Opin. Drug Deliv. (2007) 4(6):689-701

1. Introduction

1.1 Allergic rhinitis – a disorder with increasing socioeconomic burden

Allergic rhinitis (AR) is a chronic disorder of the upper respiratory airways initiated by an IgE-mediated inflammatory reaction following exposure of the nasal mucosal membranes to one or more allergens [1,2]. AR manifests through symptoms of nasal congestion, rhinorrhoea, nasal itching and sneezing [2]. These symptoms are often accompanied by ocular symptoms of itching, watering and red eyes [3].

Although not a fatal disorder, AR poses a significant burden on the affected individual's quality of life. AR can impair nocturnal sleep, resulting in daytime somnolence and reduced learning and productivity at school and at work [4]. Untreated, AR can trigger the development of other severe conditions, such as otitis media, sinusitis, nasal polyposis and asthma, further adding to the already considerable morbidity of this disorder [5]. In addition, healthcare costs for AR are often substantial; for example, costs for physician visits and AR treatment are estimated at $4.6 billion a year in the US [6]. Such costs are often exacerbated by treatment for associated morbidities. AR is a global health problem with prevalence increasing worldwide over the past 2 – 3 decades; it is estimated that 10 – 25% of the global population is affected [2]. In the US, AR affects ~ 10 – 30% of adults [7,8], compared with Europe where prevalence ranges from 17 to 29% [9].

10.1517/17425247.4.6.689 © 2007 Informa UK Ltd ISSN 1742-5247

AR, therefore, exacts a significant socioeconomic burden on both the affected individual and society. Consequently, the development of treatment strategies that will alleviate and prevent the symptoms of AR, and manage associated morbidities through continued patient compliance, is imperative for reducing this burden. This review discusses the benefits and inadequacies of such therapies, as viewed by both the prescribing physician and the patient, highlighting potential improvements. Such improvements have been taken into careful consideration during the development of fluticasone furoate (FF), a new enhanced-affinity glucocorticoid with a scent-free formulation and novel side-actuated nasal drug delivery system.

2. Overview of the drug delivery market for allergic rhinitis

Pharmacotherapy is the optimal strategy with which to treat individuals with AR. Although a number of pharmacological agents, each varying by mode of action and efficacy, are available for the treatment of AR, including antihistamines, decongestants, mast cell stabilisers, anti-cholinergics and anti-leukotrienes [10], intranasal corticosteroids (INSs) are recommended as first-line therapy in individuals with moderate-to-severe AR [8,11-13]. All of the major nasal symptoms associated with AR are relieved by INSs [14]. However, there is presently an unmet need for the effective treatment of the ocular symptoms of AR with INSs; although there is some evidence that INSs can relieve ocular symptoms [15], such data have proven inconsistent and non-reproducible in well-controlled, prospective clinical trials. An INS capable of consistently relieving both the nasal and ocular symptoms of AR might reduce the need for ancillary treatments. INSs are well tolerated with a good safety profile. Local adverse events, which may result from mechanical irritation [16], include anterior crusting and epistaxis (13 – 20%) [17,18,101]. Concerns regarding systemic side effects have been eased following the emergence of INSs with minimal bioavailability and extensive first-pass hepatic metabolism [19-22]. Furthermore, topical delivery of the drug directly to the site of action necessitates the application of only very low doses to achieve the desired therapeutic effect.

In view of their unsurpassed activity, proven overall symptom control and safety, the use of INSs in the treatment of AR has increased substantially [11,13,23]. Indeed, pharmacotherapy with INSs has become the cornerstone of treatment in AR [24]. Presently, several INSs are available for the treatment of seasonal and perennial allergic rhinitis (SAR and PAR, respectively), including beclomethasone dipropionate (BDP), budesonide, fluticasone propionate (FP), mometasone furoate (MF) and triamcinolone acetonide (TAA) [2,22]. However, although viewed as the most effective therapy available for AR treatment, several factors, mainly pertaining to existing nasal delivery devices and drug formulations, can limit the use of INSs.

3. How to improve existing nasal drug delivery devices

3.1 The challenge of nasal drug use – poor compliance as a disadvantage of presently available intranasal corticosteroids

Topical nasal corticosteroids account for > 50% of the nasal drug delivery market (US$8 – 10 billion) and this figure is growing annually at 10 – 15% [25-27]. Intranasal delivery offers several advantages over oral and injectable therapies, including pain-free administration, topical delivery direct to the site of action, rapid presentation to the site of action, and efficacy with a low drug dose [28]. However, product acceptance and compliance depends upon ease of use, sensory attributes, clinical efficacy and tolerability [29-34]. With AR, it is fundamental that patients maintain compliance to achieve and sustain long-term relief from their symptoms. Thus, an INS that positively influences patient acceptance should aid in promoting compliance with therapy.

Despite the increasing number of patients using self-administered nasal drug delivery devices, comparatively few studies have been conducted to investigate factors that influence patient compliance. However, available data show that patients' perceptions of INSs are influenced not only by effectiveness and safety, but also by ease of use, comfort during administration and sensory attributes [29-34]. Among the ideal requirements of a topical nasal delivery system (e.g., minimal delivery to the pharynx and consistency of drug delivery), Aggarwal *et al*. list user-friendliness as a factor that optimises patient compliance [35]. Existing devices for the treatment of AR use essentially the same technology – a mechanical pump mechanism – and offer several benefits (**Box 1**). However, device- and formulation-related drawbacks, which may vary significantly in presently available INSs depending on design (**Box 1**), could potentially discourage patients from maintaining compliance with their medication.

Studies have shown that sensory attributes, which vary greatly among INSs, are easily differentiated by patients and strongly influence their choice of, and adherence to, therapy. Indeed, a cross-sectional study conducted in AR patients in the US to investigate preferences for pairs of hypothetical INSs differing in their sensory attribute composition showed that preferences were inversely related to the increasing intensity of the sensory attributes. Aftertaste (taste remaining in the mouth following administration of the drug) was scored as the attribute most likely to influence preference for therapy, followed closely by taste and run-down in the throat, and then by run-out of the nose, smell and feel of spray [30].

Sensory attributes of INSs have also been assessed using preference evaluation questionnaires [31]. In a double-blind study in which patient preferences for FP, MF and TAA were compared, significantly better comfort, less irritation and odour, more moistness and milder taste were associated with TAA [36]. These findings were reconfirmed with data from two pooled double-blind studies in which TAA was associated with

Box 1. Advantages and disadvantages of nasal drug delivery devices presently available for the administration of intranasal corticosteroids in the treatment of allergic disease.

Advantages*	Disadvantages*
Device related	
Simple to use; no need for complicated instructions	Design and size can discourage patient use and compliance, particularly in young and elderly patient groups
Allow for generally pain-free administration	Priming procedures can complicate use and hinder continued compliance
Allow delivery direct to the site of action – the nasal mucosa	Can be difficult to trigger a dose, particularly for young and elderly patients
	Longer length delivery nozzles, particularly in young patient groups
	- Fit poorly into the nose
	- Can cause irritation and bleeding
	Inconsistent dosing/spraying can result from varied speed/pressure applied by the patient resulting in inconsistent dosing and reduced efficacy
Intranasal corticosteroids formulation related	
Moisturising effect of the liquid nasal spray can be comforting	Sensory attributes, such as odour and taste, can discourage patient use and compliance
Efficacy seen with continued use	Delivery of the nasal spray as a liquid (versus a fine mist) can cause drip out of the nose or run down back of throat
Tolerable and associated with minimal side effects	Lack of dose indicator or translucent bottle restricts patient's ability to view and accurately determine when refill is required, leading to wastage and reduced compliance
	Device- and formulation-related weaknesses can cause pain, nose bleeds and overall discomfort

*Not all advantages/disadvantages apply to all available intranasal corticosteroids.

less odour, taste, aftertaste and dryness of the nose/throat [32]. However, in a single-blind (patient) study investigating patient preferences for BDP, FP and MF, significantly more patients preferred MF to BDP and FP, owing to a liking of the odour, less irritation and aftertaste, and more moistness [29].

In summary, aftertaste, taste, run-down the back of the throat, run-out of the nose, and odour and feel of the nasal spray are attributes that could detrimentally affect a patient's willingness to adhere to therapy.

3.2 Factors responsible for poor compliance to intranasal corticosteroids – weaknesses of presently available intranasal corticosteroid preparations and their nasal drug delivery devices

Optimal efficacy of an INS is dependent not only on the pharmacological profile of the drug, but also on effective drug delivery, which is reliant upon both a formulation and a device that enables reproducible drug delivery to the nasal mucosa [33,37].

From a clinical perspective, several aspects can compromise a nasal drug delivery device; the main limitations are discussed here. Accurate and repeatable dosing is important with potent drugs and should be maintained throughout the lifetime of the device, even as the device begins to empty [25,38-40]. Furthermore, the dose needs to be delivered consistently to the site of action in the nasal mucosa to ensure that maximal and sustained efficacy against the symptoms of AR is achieved. With regards to patient use, it is important that the device delivers a consistent dose when pressure is applied to the actuation mechanism; conventional pump technology systems may allow the patient to receive a variable dose or spray depending on the speed and pressure applied by the patient. Therefore, a device that provides consistent dosing and is devoid of complicated priming procedures prior to first use or use after a period of several days of non-use is desirable [25]. In addition, the device should enable the user to easily determine the dose remaining and assess the need for re-supply to ensure continued compliance with the treatment regimen. Issues with inconsistent and inaccurate dosing, and difficulties with use resulting from poor device design are possible causative factors for reduced patient compliance.

INSs are available as liquid nasal drops, aqueous sprays/suspensions or dry powders [33]. The most commonly used are the aqueous nasal sprays. Their humidifying effect can be comforting [33], but conversely, effects of spraying a liquid into the nose are easily noticeable by the patient [41]. From the patient's perspective, among the drawbacks with which they associate aqueous nasal sprays is the risk of the liquid dripping out of their nostrils or running down the back of their throat. Swallowing the liquid can lead to an unpleasant aftertaste in the mouth. Some patients also experience stinging or burning in the nose; this is often due to the inclusion of an alcohol, which is present in some INS formulations.

The discussed drawbacks were confirmed by findings from a large US household questionnaire-based survey of ~ 7000 patients with moderate-to-severe AR, which revealed that commonly used INSs have several delivery device-related weaknesses (GSK data on file). Indeed, of the 1252 respondents queried with regards to key reasons for stopping the use of an INS, almost 20% indicated they would stop using the device owing to device issues alone (see **Table 1** for data on individual attributes). A further 45% reported that the sensory attributes of the INS formulation would deter them from continuing the use of such medication (**Table 1**). Although it seems reasonable for patients to stop their medication if they have not experienced recent symptoms of AR, this was not commonly provided as a reason, even in those participants who had no AR symptoms in the past 4 weeks.

Less than 50% of 1574 respondents who ranked features of prescription nasal spray medications considered that presently available INS devices were easy to use. Furthermore, < 25% of respondents thought that these devices delivered a soft, gentle spray (24.7%) or a consistent amount of medication (23.5%), allowed easy visualisation of the volume of medication remaining in the reservoir (21.0%; resulting in uncertainty regarding time to refill and frustration over the cost of unused medication), or fitted easily into the nostrils (16.2%).

In addition to the above, other major complaints included:

- Difficulties with handling/triggering the device, especially for the elderly and young children; patients felt these difficulties could result in ineffective spraying and/or incorrect dosage.
- The nozzle being too long and rigid, resulting in pain, nose bleeds and/or a feeling of general 'invasiveness'.
- The spray being administered as a squirt or jet, which can cause discomfort, nasal flooding and/or drip down the back of the throat.
- The need to prime the device on a regular basis, particularly with MF.
- The device being too bulky.

3.3 The physician's and patient's perspective

The studies discussed above demonstrate that the ideal therapy should be pleasing to the patient in terms of sensory properties. These findings were verified in a US-based, focus group, market research study conducted to gain feedback regarding the advantages and disadvantages of INS use. Participants consisted of four focus groups of physicians (primary care physicians [n = 7], paediatricians [n = 7], allergists [n = 8] and ear, nose and throat specialists [n = 7]) and four focus groups of patients, some of whom had never used an INS (n = 15) and others who had discontinued use (n = 22). Participants were asked to discuss their perceptions during one of eight 1-h facilitated interviews that were audiotaped (GSK data on file).

Patients reported that they became frustrated with using their prescribed INS before any benefit was even gained. The reason for this included a 'nasty' taste and drip down the back of the throat. Physicians reinforced these findings, indicating that they were reluctant to prescribe INSs as patients commonly complained about their unpleasant taste and/or smell. Physicians and patients were asked to offer suggestions for potential improvements to INSs with focus on aspects that may help overcome avoidance of their use. The main feedback suggested that treatment would be more appealing if the nasal tip of the drug delivery device did not feel so 'invasive', and if the spray was delivered as a fine mist that was free of scent, taste and drying of nasal membranes (GSK data on file).

4. Development of a patient-driven drug delivery system for intranasal corticosteroids

The findings discussed above provide strong evidence that improvements in both the INS drug delivery devices, in terms of ease and reliability of use, and the INS formulation, in terms of sensory attributes, are required and are likely to improve patient compliance. In view of this, a novel system that specifically takes into account patient concerns has been developed for the new enhanced-affinity glucocorticoid, FF.

FF is characterised by its potent and selective glucocorticoid activity, rapid uptake, sustained pharmacological action, and enhanced binding affinity for the glucocorticoid receptor [42]. Clinical studies have demonstrated that FF nasal spray, administered once daily using a novel side-actuated delivery system, has low systemic bioavailability [43,44] and is well tolerated, with epistaxis (broadly defined as any observation of blood irrespective of size or location) being the most common drug-related adverse event [17] and consistent with that reported for other INSs. FF has proven 24-h efficacy in treating the nasal and ocular symptoms of SAR and PAR in adults and adolescents [45]. FF has demonstrated safety and efficacy in children as young as 2 years of age.

4.1 The development of the novel fluticasone furoate drug delivery system

The drug delivery system for FF was developed from concept to clinical trial device over 2 years. Five experimental devices (single-sided actuation with a removable lid; single-sided actuation with hinged lid; single-sided actuation

Table 1. The most likely reasons for stopping intranasal corticosteroids medication use among US residents, stratified by experience of allergic rhinitis symptoms in the past 4 weeks*.

	AR symptoms* in past 4 weeks n (%)‡	No AR symptoms in past 4 weeks n (%)‡	Overall n (%)‡
Device related			
Do not know if receiving right amount of medication in each spray	78 (6.6)	2 (2.9)	80 (6.4)
Do not know when refill is needed	55 (4.7)	4 (5.7)	59 (4.7)
Awkward to use/administer	54 (4.6)	4 (5.7)	58 (4.6)
Difficult to administer to children	24 (2.0)	4 (5.7)	28 (2.2)
Nozzle tip is too long	11 (0.9)	2 (2.9)	13 (1.0)
Formulation related			
Medication runs down throat/out of nose	309 (26.1)	19 (27.1)	328 (26.2)
Bitter taste	173 (14.6)	12 (17.1)	185 (14.8)
Dislike smell/odour	75 (6.4)	4 (5.7)	79 (6.3)
Efficacy related			
Does not provide 24-h symptom relief	139 (11.8)	5 (7.1)	144 (11.5)
Does not relieve symptoms quickly enough	125 (10.6)	11 (15.7)	136 (10.9)
Other	124 (10.5)	2 (2.9)	126 (10.1)
Total	1182 (100.0)	70 (100.0)	1252 (100.0)

Based on GSK data on file.
*Allergic rhinitis symptoms included: watery eyes, itchy eyes, runny nose/sniffling, sneezing, itchy nose, congested/blocked nose and post-nasal drainage.
‡Number and proportion of patients who ranked symptoms as the most likely reason to stop use of nasal spray.
AR: Allergic rhinitis.

with rotating lid; single-sided actuation pen-shaped device with removable lid; double-sided actuation) were tested among physicians and patients in the US to determine which system to develop further. Participants were recruited voluntarily via newspaper advertisements. Patients were those who reported suffering from nasal or airborne allergies and were a mix of prescription nasal spray or antihistamines-only users; physicians included those who were ear, nose and throat specialists, paediatricians, allergists or primary care physicians. A series of 77 one-to-one interviews were conducted, with 36 sessions being held with physicians and 41 with patients. When asked to rank devices on a scale of 1 to 4 (1 = most preferred and 4 = least preferred), physicians and patients consistently preferred one particular system for its ergonomic design (which makes the system easier to hold and operate) and its fine consistent mist (which enables comfortable and optimal dispersion of the drug within the nasal cavity).

5. How the technology works

5.1 Key design points of the novel fluticasone furoate drug delivery system

The novel FF drug delivery system, termed the 'container closure system' has been designed and developed for use in AR patients aged ≥ 2 years (**Figure 1**). The container closure system consists of a bottle fitted with a metering pump, which is inserted into the outer device. The key features of this innovative new system are highlighted in **Box 2** and detailed below.

The outer device is designed with a contoured thumb and index finger grip, which promotes easy gripping for effective delivery of the drug using a side-actuation mechanism (**Figure 2**) [102]. The side-actuation trigger allows the patient's fingers to be located away from the nozzle while actuating the delivery system. This design eliminates the need to place fingers on the nozzle base, thereby allowing for a shorter delivery nozzle (**Figure 3**) and ensuring that the delivery nozzle remains stationary in the nostril during use. This makes the system user-friendly, in terms of both comfort (it is less invasive and may reduce the pain some patients report when using INS drug delivery devices [GSK data on file]) and control, to a wider population of individuals, including young children and the elderly. Furthermore, it allows for easier and more stable third-party administration, which is of benefit in young children. Ease of use of the FF system is also aided by the flexible seal (the stopper) that eliminates the need for the user to prime the system prior to each dose or after a period of several days of non-use.

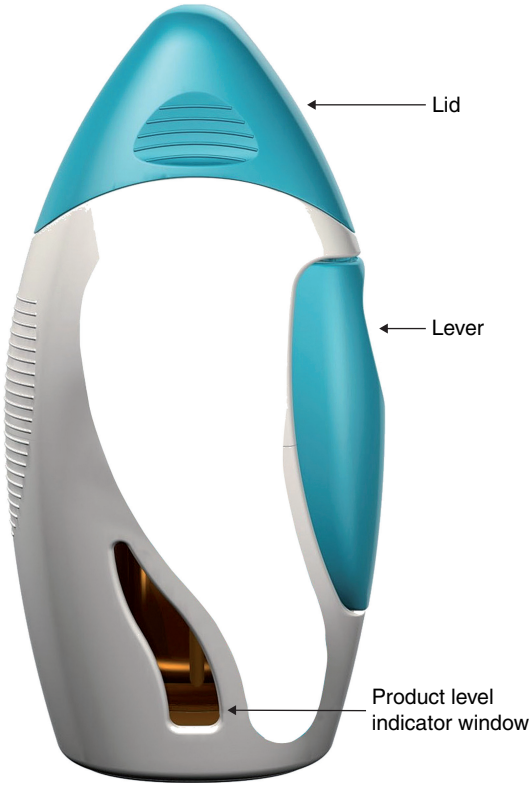

Figure 1. The fluticasone furoate nasal drug delivery system – the 'container closure system'.

Once the minimum pressure is applied to the device trigger, the FF system allows consistent dose delivery with each spraying. Dosing accuracy is of critical importance in the delivery of corticosteroid drugs in order to minimise the potential for side effects, while assuring effective relief from the nasal symptoms of AR [102]. The FF system delivers a nominal metered volume of 50 µl per spray (i.e., 100 µl per nostril when using the recommended two sprays per nostril once daily; this volume is ideal when taking into consideration findings that show lower volumes help to limit discomfort and leakage from the nasal cavity [102]). In addition, a smaller volume of drug is less likely to run down the back of the throat or leave an aftertaste in the mouth. Theoretically, a small dose volume may increase the potential for local adverse events, such as epistaxis, because of the higher drug concentration delivered to the non-ciliated anterior nasal segment [16,46]; however, there is no clinical evidence for FF nasal spray to show that this is the case. Clinical trials consistently demonstrate that FF nasal spray is effective in reducing the nasal and ocular symptoms of AR, and epistaxis rates in both short- and long-term trials fall within the range reported for other INSs [17,47,48].

Given nasal anatomy and physiology, with the the non-ciliated and ciliated regions located in the anterior and posterior part of the nasal cavity, respectively, the site of deposition is of importance for microciliary clearance and retaining the formulation in the nose [33]. Deposition in the anterior nasal cavity further reduces the potential for run-off, and the absence of beating movements of the cilia reduces clearance, thereby permitting increased contact time within the nasal mucosa [46]. Relative anterior deposition is of importance for INSs as this is the site where inhaled allergenic particles might deposit and, thus, is an important site of action [46]. Development studies using a glass nose (designed based on published anatomical measurements [49]) and high-speed video to visualise deposition patterns indicated the FF delivery system reduces the potential for a portion of the formulation to immediately run down the back of the throat. This potential, together with dripping from the nostril, is further reduced by the low dose volume (50 µl) and that the fine mist distributes the dose evenly and effectively over a wide area, with minimal material penetrating the pharyngeal region, thereby reducing the risk of very small droplets being available for inhalation [50]. The FF system was designed to deliver the drug as a fine, consistent mist with ~ 50% of the dose volume delivered as droplets of 10 – 60 µm to assure both safety and efficacy. Both the pump and the nozzle of the FF system help to minimise the risk of creating droplets < 10 µm in size, which reduces the theoretical risk of drug delivery into the lung with very small droplets [46], which is of concern to regulators [51-53], although lung deposition has been shown to be low with nasal sprays in some studies [26,46].

Overall, the improved appearance and size of the FF system means individuals should feel more comfortable using it, thus facilitating acceptance and long-term compliance.

6. Findings with the registered fluticasone furoate drug delivery system

6.1 Does the novel fluticasone furoate drug delivery system meet the needs of patients and physicians?

Findings from recently completed assessments of the new FF drug delivery system (device plus formulation) suggest that it is well received by both patients and physicians in the US. Much of the data provided in this section has not previously been presented in the peer-reviewed literature.

6.1.1 Qualitative assessment among patients and physicians

The FF drug delivery system was compared with INS drug delivery devices presently on the market. The system was tested among volunteers in the US who were recruited using the same criteria and methods as described in the study above. A series of 24 physician and 25 patient one-to-one interviews was undertaken. Features of the system identified as 'key strengths' included the attractive appearance; the design, which makes it easier to hold and operate; the side actuation, which allows for better control during administration; its fine, consistent mist; and its delivery nozzle, which feels more comfortable in the nose (GSK, data on file). Overall,

Box 2. Key design points of the novel fluticasone furoate nasal drug delivery system and the resulting benefits for individuals with allergic rhinitis.

Features	Potential benefit to the patient
Ergonomic design	
Visually more appealing	Patients feel more comfortable using it
Less bulky – fits into the hand easier	Easily portable and allows for discreet use
	Overall, should facilitate acceptance and long-term compliance
Trigger mechanism and pump design	
Delivers the same dose (50 µl) following minimum patient actuation force	Accurate and consistent delivery to the nasal mucosal membranes with each spray
	Patients should receive prescribed dose each time
	Should allow for consistent efficacy
	Smaller volumes reduce the potential of post-nasal drip
Flexible stopper seal	
Occludes the orifice of nozzle when lid is attached	Maintenance of prime for up to 30 days eliminates need to prime the system before each use or after long periods of non-use
	Ensures the delivery system remains charged and ready to use
	Speeds up and eases use
	Reduces product wastage
Contoured grip	Maximises patient's natural grip to ease actuation
	Eliminates need to place fingers on the nozzle base, thereby allowing for a shorter delivery nozzle
Side-actuated system	
Makes triggering and administration easier	Enables use in a wide patient population, including the elderly and young
	Allows for easier third-party administration
	Ensures the delivery nozzle remains stationary in the nostril during use
Comfortable short delivery nozzle	
Removes feeling of 'invasiveness'	Provides comfort during use
	Reduces potential of pain and nasal bleeding
	Should facilitate acceptance and long-term compliance
Dose-indicator window	
See-through to allow user to visualise amount of medication remaining	Should help patient in determining when refill is required
	Prevents wastage of unused medication, thereby reducing costs
Well-dispersed fine mist	Smaller droplets, 20 – 50 µm in diameter, aid in even nasal distribution
Formulation	
No addition of alcohol	Prevents burning and/or stinging in the nasal cavity
Thickened with microcrystalline cellulose and	Eliminates aftertaste in the mouth
	Sustains the drug in the nasal mucosa for maximum efficacy

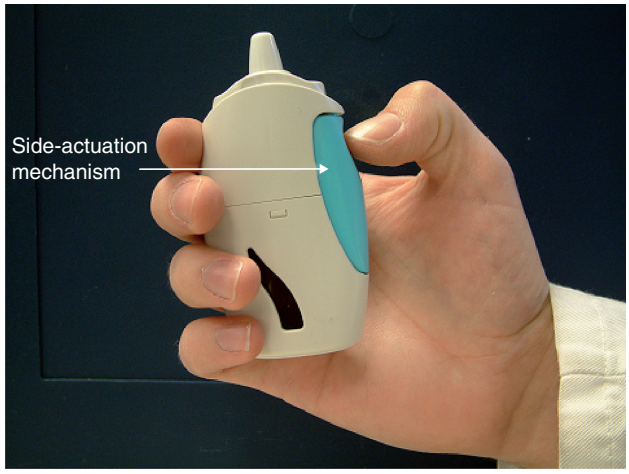

Figure 2. The side-actuation mechanism of the fluticasone furoate nasal drug delivery system.

physicians indicated that they would feel positive with regard to prescribing the new FF system. A point of caution is that, owing to limitations in sample size, the presented data have been used only qualitatively to learn about physician and patient perspectives, and are not statistically applicable to the entire population.

6.1.2 *Human factor studies*

Human factor studies were conducted in association with an external ergonomic agency to evaluate users' perceptions of the FF delivery system. In one study, ease of self-administration using the new device was assessed in 23 individuals aged 6 – 69 years with a history of AR and familiarity with using nasal sprays. The population comprised 5 children, aged 6 – 10 years; 10 adults, aged 22 – 55 years; and 8 elderly adults, aged 61 – 69 years. Of these, seven individuals suffered from a condition that affected their hand grip, including arthritis (n = 3) [54]. All patients were interviewed for 45 – 60 min by the same ergonomist.

The participants were asked to rate the extent to which they agreed or disagreed that their own nasal device (the reference device) possessed 12 attributes, such as ease of use and comfort in the nose, using a 7-point scale ranging from strongly agree (+3) to strongly disagree (-3). Towards the end of the interview, participants were asked to rate the study device using the same 7-point scale. The combined results for the 12 attributes indicated that participants perceived a 17% improvement in the present device over existing devices. The three attributes rated most important for participants were:

- Ease of operation: 76% of participants found the system easy to operate, an increase of 23% over existing devices (GSK data on file).
- Comfort: 86% of participants agreed that the delivery nozzle felt comfortable in the nose (an increase of 33% over existing devices).
- Reliability: 63% of participants rated the device as positive for the attribute of reliability (an improvement of 28%).

6.1.3 *Qualitative assessment among clinical trial patients*

The results from the ergonomic analyses were further supported by data from a Phase III clinical trial in 302 patients (aged ≥ 12 years) with PAR to US mountain cedar pollen. Patients completed a product questionnaire at the final safety evaluation; they were asked to answer six questions pertaining to their experience with the FF system (**Box 3**). The majority of patients reported that the delivery system was easy to carry (95%), easy to operate (84%) and comfortable to use (97%) [54]. Furthermore, most patients found the nasal spray nose tip to be comfortable (97%), the spray to be gentle (91%), a weak or lack of aftertaste (90%), and little or no leakage of medication out the nose or down the throat (94%) (GSK data on file).

Patient perception of the novel FF drug delivery system was also assessed in those patients (n = 54) who had recently completed Phase II clinical trials. Patients comprised a mix of allergy sufferers, who were either present/past users of nasal sprays or nasal spray-naive. Approximately two-thirds of participants reported the system as a 'superior delivery system' when compared with other nasal spray devices. This finding was driven by the ergonomic appearance, nozzle size, ease of use of the delivery system, and small volume and fine mist of the nasal spray. During a discussion on how present or past over-the-counter therapy users felt about INS therapy, many patients remarked on an unaided basis that the FF system offers a superior system to presently available nasal sprays. These findings suggest this novel system may help build patient acceptance of, and compliance to, long-term INS therapy (GSK data on file).

7. Alternative novel technologies

A novel breath-actuated, bidirectional, prototype device has recently been developed [26]. In an initial study in nine healthy volunteers, this device provided a significantly larger ($p < 0.004$) initial and cumulative deposition in the upper posterior segment of the nasal passage and significantly lower ($p < 0.004$) deposition in the anterior segment of the nose than traditional spray pump delivery systems [26]. This may provide an opportunity for improved therapy for chronic rhinosinusitis and polyposis and extended use for nose–brain delivery [26]. However, as yet there are no clinical data for the efficacy of this device. Furthermore, the bidirectional administration is not appropriate in patients with AR because local deposition and, thus, effect at sites important for therapeutic efficacy in AR would be low. Furthermore, the device is non-intuitive, cannot be used discretely, and is not easily adaptable for use in children.

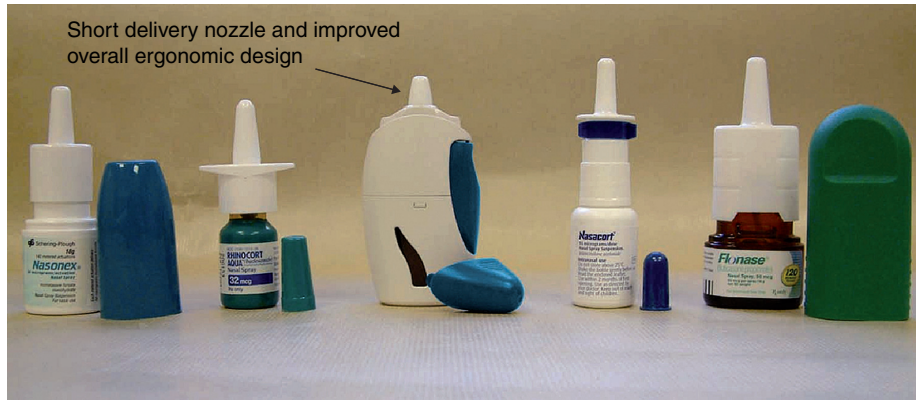

Figure 3. Nasal drug delivery devices for the most frequently prescribed intranasal corticosteroids, compared with the new delivery system for fluticasone furoate.
From left to right: mometasone furoate, budesonide, fluticasone furoate, triamcinolone acetonide, fluticasone propionate.

8. Conclusions

There is clear evidence that AR is increasing in prevalence worldwide and impacts heavily on both the individual and society. Despite the large body of evidence highlighting the symptomatic burden of AR, this chronic disorder is often trivialised and remains under-treated, leading to reduced quality of life. There is also dissatisfaction with presently available therapies. Although INSs are the most effective medication available for treatment of the symptoms of AR and intranasal drug delivery offers an attractive route of administration, patients may be reluctant to use these drugs for a variety of reasons. Foremost among these are negative sensory perceptions in terms of odour, aftertaste, drip out of the nose resulting from high delivery volumes, drip down the throat and/or dryness of nose/throat; and inconvenience or difficulty of use.

Problems associated with sensory perceptions have been addressed to some extent by patient education and improved formulations. Improvements in design have also been applied in the development of some prototype devices [26], although little effort has been made to address the difficulties associated with presently marketed nasal drug delivery devices. The need for sophisticated, carefully designed, drug delivery devices for successful application of INSs is now being recognised. Extensive market research and tests conducted among physicians and patients during the development of a novel nasal drug delivery system resulted in the development of the FF system, which demonstrates several advantages. The system was designed with the patient in mind: its ergonomic design allows for improved handling and comfort during use, and the system demonstrates consistent dose delivery characteristics across a wide patient population. The FF nasal spray itself has a favourable profile in terms of its sensory attributes, including its reduced taste and scent, reduced dosing volume and fine consistent mist.

It is anticipated that the FF system will aid in improving the attitudes of both patients and physicians towards the use of INSs and serve to improve compliance with medication in individuals affected by AR. Improvements in compliance should aid in the long-term management of the symptoms of AR.

9. Expert opinion

Nasal drug delivery represents the ideal way to treat nasal allergies. However, the development of new technologies or devices has been limited for > 30 years; original devices were based on the simple theory that they needed to be placed into the nose. Also, little was known at that time about the physiology of the nose and nasal cavity, and the ergonomics of the hand. Young and elderly patient groups were particularly at a disadvantage, as original devices proved difficult, even for third-party caregivers, to use. Previously, companies concentrated on the chemistry of the INS, viewing efficacy as the key critical factor for patient acceptance and use. However, evaluation and re-design of existing nasal drug delivery devices is imperative if compliance and disease management are to be achieved and sustained.

Development of the new FF nasal spray drug delivery system has aided in overcoming many of the challenges posed by existing nasal delivery devices, including:

- Easing patient use through the side-actuated mechanism and removing the need for repeated priming of the device.
- Consistent dosing as a result of the trigger mechanism.
- Reducing both the size of the delivery nozzle and the delivered dose volume, to reduce pain and discomfort.
- Improving the nasal spray formulation to aid in both simplifying the treatment regimen with once-daily dosing and providing comfort upon application.

Box 3. Product characteristic questionnaire used in Phase III clinical trial.

Question	Choice of responses (only one selected)
Overall, how easy is it to carry the nasal spray you are using for your allergies?	Extremely difficult; somewhat difficult; somewhat easy; extremely easy
Overall, how comfortable is the nose tip of the nasal spray you are using for your allergies?	Extremely uncomfortable; uncomfortable; comfortable; extremely comfortable
Overall, how easy is it to operate the nasal spray you are using for your allergies?	Extremely difficult; somewhat difficult; somewhat easy; extremely easy
Overall, how strong an aftertaste does the nasal spray you are using for your allergies have?	An extremely strong aftertaste; a moderately strong aftertaste; a weak aftertaste; no aftertaste
Overall, how much of the medication that is released from the nasal spray you are using for your allergies leaks out of your nose or down your throat?	None of the medication; some of the medication; a lot of the medication; all of the medication
Overall, how gentle is the mist that is released from the nasal spray you are using for your allergies?	Not at all gentle; slightly gentle; moderately gentle; extremely gentle

Such improvements should ensure that the INS is delivered directly to the site of action and may lead to improved patient compliance, which is important for sustaining long-term efficacy.

Despite these significant advances, devices should continue to be improved to help further address more efficient use, reduce treatment costs and disease burden, and improve overall disease management. In the long term, further development of nasal spray systems could include adding novel features such as:

- A signal for the patient to ensure the delivery system is positioned correctly for accurate delivery of the spray to the nasal mucosa. Administration of the drug directly to the site of action will improve and sustain consistent efficacy. This type of tracking device would be of particular value in young patients who may be unsure how to use nasal spray devices.
- A dose counter (countdown feature) that accurately predicts the number of doses/sprays remaining in the delivery system as an aid to reducing medication wastage and maintaining treatment compliance.
- A signal to highlight to the patient when their next dose needs to be administered; this will further aid in improving compliance.
- A switch mechanism that will allow the patient to change between doses as needed.
- A link to a centrally-based computer or website where patients could receive feedback with regards to accurate administration and use of their medication. This may act as an incentive for patients to ensure they sustain dosing with their medication.

Importantly, further development of innovative nasal delivery devices and formulations should meet requirements of cost and of the patients themselves. Moreover, new technologies may become viable options for the administration of other drug classes, such as oral agents and vaccines.

Acknowledgements

This review was funded by GlaxoSmithKline R&D Limited. The authors would like to thank J Gladwin of User Centered Solutions for her assistance with the human factor studies, and wish to acknowledge the editorial contribution of V Bachoo, MSc and A Koundouris, PhD, employees of Innovex Medical Communications in the development and author review of this manuscript.

Declaration of interest

Two of the authors (J Godfrey and A Slater) are employees of GlaxoSmithKline. The first author, William Berger, has the following financial interests to disclose:

- **Consultant arrangements**: Alcon, Apieron, AstraZeneca, Dey, Genentech, GlaxoSmithKline, Medpointe, Merck, Novartis, Nycomed GmbH, Sanofi-Aventis, Schering-Plough, Teva and Verus.
- **Stock/other equity ownership**: none.
- **Patent licensing arrangements**: none.
- **Grants/research support**: Schering-Plough, Alcon, Apieron, Dey, Altana, Verus, Novartis, Genentech, GlaxoSmithKline, Medpointe, AstraZeneca, Sanofi-Aventis, Teva and Merck.
- **Employment**: none.
- **Speakers' bureau**: Schering-Plough, Alcon, Apieron, Dey, Altana, Verus, Novartis, Genentech, GlaxoSmithKline, Medpointe, AstraZeneca, Sanofi-Aventis, Teva and Merck.

Bibliography

Papers of special notes have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. CIPRANDI G, PASSALACQUA G: Emerging anti-inflammatory agents for allergic rhinitis. *Expert Opin. Emerging Drugs* (2005) **10**:689-705.
2. BOUSQUET J, VAN CAUWENBERGE P, KHALTAEV N: Allergic rhinitis and its impact on asthma. *J. Allergy Clin. Immunol.* (2001) **108**:S147-S334.
3. GANDHI RK, BLAISS MS: Current concepts and therapeutic strategies for allergic rhinitis. *Otorinolaringologia* (2005) **55**:187-201.
4. MELTZER EO: Quality of life in adults and children with allergic rhinitis. *J. Allergy Clin. Immunol.* (2001) **108**:S45-S53.
5. LEYNAERT B, NEUKIRCH F, DEMOLY P, BOUSQUET J: Epidemiologic evidence for asthma and rhinitis comorbidity. *J. Allergy Clin. Immunol.* (2000) **106**:S201-S205.
6. REED SD, LEE TA, MCCRORY DC: The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* (2004) **22**:345-361.
7. BAROODY FM: Allergic rhinitis: broader disease effects and implications for management. *Otolaryngol. Head Neck Surg.* (2003) **128**:616-631.
8. TASK FORCE ON ALLERGIC DISORDERS: The Allergy Report. Milwaukee, WI: American Academy of Allergy. Asthma Immunology (2000).
9. BAUCHAU V, DURHAM SR: Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur. Respir. J.* (2004) **24**:758-764.
10. VAN DRUNEN C, MELTZER EO, BACHERT C *et al.*: Nasal allergies and beyond: a clinical review of the pharmacology, efficacy, and safety of mometasone furoate. *Allergy* (2005) **60**(Suppl. 80):5-19.
11. DYKEWICZ MS, FINEMAN S, SKONER DP *et al.*: Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann. Allergy Asthma Immunol.* (1998) **81**:478-518.
12. INTERNATIONAL RHINITIS MANAGEMENT WORKING GROUP: International consensus report on the diagnosis and management of rhinitis. *Allergy* (1994) **49**:1-34.
13. VAN CAUWENBERGE P, BACHERT C, PASSALACQUA G *et al.*: Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy* (2000) **55**:116-134.
14. BERGER WE: Long-term combination therapy is often necessary – getting allergic rhinitis under control: Part II. *J. Respir. Dis.* (2005) **26**:188-194.
15. BERNSTEIN DI, LEVY AL, HAMPEL FC *et al.*: Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. *Clin. Exp. Allergy* (2004) **34**:952-957.
16. WADDELL AN, PATEL SK, TOMA AG, MAW AR: Intranasal steroid sprays in the treatment of rhinitis: is one better than another? *J. Laryngol. Otol.* (2003) **117**:843-845.
17. ROSENBLUT A, BARDIN PG, MULLER B *et al.*: Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy* (2007) **62**:1071-1077.

•• **A study assessing the long-term safety and tolerability of fluticasone furoate 110 µg once daily in adults and adolescents with PAR.**

18. KOEPKE JW, BEAUCHER WN, KOBAYASHI RH *et al.*: Long-term safety and efficacy of triamcinolone acetonide aqueous nasal spray for the treatment of perennial allergic rhinitis. *Allergy Asthma Proc.* (1997) **18**:33-37.
19. BACHERT C, LUKAT KF, LANGE B: Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic–pituitary–adrenal-axis activity in healthy volunteers. *Clin. Exp. Allergy* (2004) **34**:85-90.
20. BRANNAN MD, HERRON JM, AFFRIME MB: Safety and tolerability of once-daily mometasone furoate aqueous nasal spray in children. *Clin. Ther.* (1997) **19**:1330-1339.
21. GALANT SP, MELAMED IR, NAYAK AS *et al.*: Lack of effect of fluticasone propionate aqueous nasal spray on the hypothalamic–pituitary–adrenal axis in 2- and 3-year-old patients. *Pediatrics* (2003) **112**:96-100.
22. TRANGSRUD AJ, WHITAKER AL, SMALL RE: Intranasal corticosteroids for allergic rhinitis. *Pharmacotherapy* (2002) **22**:1458-1467.
23. WALLS RS, HEDDLE RJ, TANG ML *et al.*: Optimising the management of allergic rhinitis: an Australian perspective. *Med. J. Aust.* (2005) **182**:28-33.
24. BOUSQUET J, VAN CAUWENBERGE P, BACHERT C *et al.*: Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). *Allergy* (2003) **58**:192-197.
25. SOUTHALL J, ELLIS C: Developments in nasal drug delivery. *Innov. Pharmaceut. Technol.* (2000):110-115.
26. DJUPESLAND PG, SKRETTING A, WINDEREN M, HOLAND T: Breath actuated device improves delivery to target sites beyond the nasal valve. *Laryngoscope* (2006) **116**:466-472.
27. SHECKLER MT, THEODORAKIS A: Bespak nasal drug delivery devices. Milton Keynes, UK: Bespak nasal drug delivery focus group – Quarterly Newsletter (2002).
28. AGARWAL V, MISHRA B: Recent trends in drug delivery systems: intranasal drug delivery. *Indian J. Exp. Biol.* (1999) **37**:6-16.

•• **A pivotal review of intranasal drug delivery, providing insight into the nasal cavity, factors affecting drug absorption through the nasal route and strategies to improve this, and advantages and limitations of various delivery systems.**

29. KHANNA P, SHAH A: Assessment of sensory perceptions and patient preference for intranasal corticosteroid sprays in allergic rhinitis. *Am. J. Rhinol.* (2005) **19**:316-321.

• **A single-blind crossover study assessing patients' perceptions of the sensory attributes of three intranasal corticosteroids.**

30. MAHADEVIA PJ, SHAH S, LEIBMAN C *et al.*: Patient preferences for sensory attributes of intranasal corticosteroids and willingness to adhere to prescribed therapy for allergic rhinitis: a conjoint analysis.

Ann. Allergy Asthma Immunol. (2004) **93**:345-350.

• **A cross-sectional study in US allergy and immunology clinics to assess sensory attributes contributing to patients' adherence to therapy.**

31. MELTZER EO, BARDELAS J, GOLDSOBEL A, KAISER H: A preference evaluation study comparing the sensory attributes of mometasone furoate and fluticasone propionate nasal sprays by patients with allergic rhinitis. *Treat. Respir. Med.* (2005) **4**:289-296.
32. STOKES M, AMOROSI SL, THOMPSON D *et al.*: Evaluation of patients' preferences for triamcinolone acetonide aqueous, fluticasone propionate, and mometasone furoate nasal sprays in patients with allergic rhinitis. *Otolaryngol. Head Neck Surg.* (2004) **131**:225-231.

• **Data from two randomised trials of identical design comparing patients' preferences for the sensory attributes of three INSs, and their impact on adherence to treatment.**

33. KUBLIK H, VIDGREN MT: Nasal delivery systems and their effect on deposition and absorption. *Adv. Drug Deliv. Rev.* (1998) **29**:157-177.

•• **A key review exploring the effects of nasal anatomy and physiology on drug deposition and absorption, and considering the implications of these in the development and use of various nasal delivery systems.**

34. PATEL RS, MCGARRY GW: Most patients overdose on topical nasal corticosteroid drops: an accurate delivery device is required. *J. Laryngol. Otol.* (2001) **115**:633-635.
35. AGGARWAL R, CARDOZO A, HOMER JJ: The assessment of topical nasal drug distribution. *Clin. Otolaryngol. Allied Sci.* (2004) **29**:201-205.

•• **A recent review exploring the delivery and intranasal distribution of topical nasal drugs and the potential clinical importance of this for treatment of rhinoconjunctivitis. Future directions for research are highlighted.**

36. BACHERT C, EL AKKAD T: Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. *Ann. Allergy Asthma Immunol.* (2002) **89**:292-297.
37. MARTINI A, MUGGETTI L, WARCHOL MP: Nasal and pulmonary drug delivery systems. *Expert Opin. Ther. Patent* (2000) **10**:315-323.
38. ASTRAZENECA: Rhinocort product leaflet. Macclesfield, UK: AstraZeneca (2005).
39. GLAXOSMITHKLINE: Flonase product leaflet. Brentford, UK: GlaxoSmithKline (2005).
40. SCHERING-PLOUGH: Nasonex product leaflet. Kenilworth, NJ: Schering-Plough (2005).
41. BENNINGER MS, HADLEY JA, OSGUTHORPE JD *et al.*: Techniques of intranasal steroid use. *Otolaryngol. Head Neck Surg.* (2004) **130**:5-24.
42. SALTER M, BIGGADIKE K, MATTHEWS JL *et al.*: Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate *in vitro* and in an *in vivo* model of respiratory inflammatory disease. *Am. J. Physiol. Lung Cell Mol. Physiol.* (2007) **293**:L660-L667.

•• **A review of the preclinical data for fluticasone furoate, a novel glucocorticoid demonstrating a potent and selective pharmacological profile suggestive of an effective, safe, and sustained topical treatment for allergic rhinitis.**

43. ALLEN A, DOWN D, NEWLANDS A *et al.*: Tolerability, safety, pharmacokinetics and bioavailability of the new cortocosteroid aqueous nasal spray fluticasone furoate in healthy subjects. *Presented at the American College of Allergy, Asthma & Immunology Annual Meeting,* Philadelphia, PA, (9 – 15 November 2006).
44. ALLEN A, DOWN G, NEWLAND A *et al.*: Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin. Ther.* (2007) **29**:1415-1420.

• **A single-centre, randomised, open-label, crossover trial to estimate the absolute oral bioavailability of fluticasone furoate in healthy subjects.**

45. STUEBNER P: Effects of the novel intranasal glucocorticosteroid GW685698 (200 µg once-daily) on seasonal allergic rhinitis (SAR) symptoms induced in the Vienna Challenge Chamber model (VCC). *J. Allergy Clin. Immunol.* (2006) **117**(2 Suppl. S):S319.
46. NEWMAN SP, MOREN F, CLARKE SW: Deposition pattern of nasal sprays in man. *Rhinology* (1987) **26**:111-120.

• **A classic study in healthy volunteers to explore the deposition of nasal sprays.**

47. KAISER HB, NACLERIO R, GIVEN J *et al.*: Once-daily fluticasone furoate nasal spray (FFNS) is effective for the treatment of seasonal allergic rhinitis (SAR) caused by ragweed. *J. Allergy Clin. Immunol.* (2007) **119**(1 Suppl.):S232.
48. FOKKENS WJ, JOGI R, REINARTZ S *et al.*: Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. *Allergy* (2007) **62**:1078-1084.

• **A primary paper presenting results from a randomised, double-blind, placebo-controlled trial of fluticasone furoate, a novel INS, in patients with SAR.**

49. HALLWORTH GW, PADFIELD JM: A comparison of the regional deposition in a model nose of a drug discharged from metered aerosol and metered-pump nasal delivery systems. *J. Allergy Clin. Immunol.* (1986) **77**:348-353.
50. SLATER A, ELDER D, FISHER C *et al.*: A quality by design approach for the development of a next generation nasal spray delivery system. *XXVI Congress of the European Academy of Allergology and Clinical Immunology.* Göteborg, Sweden (9 – 13 June 2007).
51. EMEA: Guideline on the pharmaceutical quality of inhalation and nasal products. London, UK: European Medicines Agency (2006).
52. FDA: Guidance for industry: Nasal spray and inhalation solution, suspension, and spray drug products – chemistry, manufacturing, and controls documentation. Rockville, MD: US Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (2002).
53. HEALTH CANADA: Guidance for industry: pharmaceutical quality of inhalation and nasal products. Ottawa, ON: Health Canada (2006).
54. GODFREY JW, GRANT AC, SLATER AL: Fluticasone furoate (FF) nasal spray – ergonomic considerations for a next generation delivery system. *J. Allergy Clin. Immunol.* (2007) **119**:S230.

Websites

101. www.fda.gov/cder/foi/nda/index97.htm
Schering Data on File: Trial C94-052. Efficacy and safety of mometasone furoate nasal spray vs fluticasone propionate nasal spray and vs placebo in the treatment of perennial allergic rhinitis (PAR). From summary basis of approval (SBA) for Nasonex (2007). Accessed 21st June 2007.

102. http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=128
Devillers G: Exploring a pharmaceutical market niche & trends: nasal spray drug delivery (2003). Accessed 14th September 2007.

Affiliation

William E Berger[†1] MD,
James W Godfrey[2] M. Inst. Pkg (Dip) &
Anna L Slater[3] BSc
[†]Author for correspondence
[1]Clinical Professor,
Allergy and Asthma Associates,
27800 Medical Center Road, Suite # 244,
Mission Viejo, California 92691, USA
Tel: +1 949 364 2900; Fax: +1 949 365 0117;
E-mail: weberger@exchange.uci.edu
[2]Device Technology Group Manager,
GlaxoSmithKline, Ware, UK
[3]Director of Intranasal Product Development,
GlaxoSmithKline, Ware, UK