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Committee for Medicinal Products for Human Use (CHMP)

Avamys

(fluticasone furoate)

Procedure No. EMEA/H/C/000770/A46/0023

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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Rapporteur's Updated Final Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Avamys (fluticasone furoate)

EMEA/H/C/00770 (EU/1/07/434/001-003)

Marketing Authorisation Holder: GlaxoSmithKline Research & Development Limited

Rapporteur:	Poland
Start of the procedure:	16.01.2012
Date of this report:	15.03.2012
Preliminary Assessment Report:	14.02.2012
Deadline for CPMP's comments:	29.02.2012
Final Assessment Report	05.03.2012
CHMP Adoption	15.03.2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Avamys
INN (or common name) of the active substance(s):	Fluticasone furoate
MAH:	GlaxoSmithKline Group
Currently approved Indication(s)	Avamys is indicated for the treatment of the symptoms of allergic rhinitis in adults and adolescents (12 years and over) and children (6-11 years).
Pharmaco-therapeutic group (ATC Code):	R01AD12
Pharmaceutical form(s) and strength(s):	Nasal spray suspension; 27.5 mcg/spray

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION[1]

The efficacy data from two presented studies in AR support the current indication. It must be acknowledged that safety data from paediatric population are not complete because study nr 113342 does not state how many children were included in the study, and there is no summary of adverse events in paediatric population (n=43) in study nr 113203. Summary of safety from other two studies do not reveal any special risk in this population. The rapporteurs conclude that no changes in the product information are required.

III. INTRODUCTION

On 29 November 2011, the MAH submitted a completed paediatric studies for Avamys, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided, dated 04 November 2011, written by safety development leader Simon Ashworth.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Avamys, nasal spray and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

Avamys, fluticasone furoate, nasal spray, suspension 27.5 mcg/spray.

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final reports for:

- **FFR113342**; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Efficacy and Safety of Fluticasone Furoate Nasal Spray for 2 Weeks in Chinese Adult and Adolescent subjects with Allergic Rhinitis;
- **FFU111439**; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Once-Daily Intranasal Administration of Fluticasone Furoate Nasal Spray 110mcg in Adult and Adolescent Subjects 12 years of Age and Older with Periannial Allergic Rhinitis;

[1] *The recommendation from section V can be copied in this section*

- **FFR111158**; A Pilot, Randomised, Double-blind, Placebo-controlled, Parallel group, Multi-centre Study to Evaluate the Efficacy and Safety of Once-daily Intranasal Administration of Fluticasone Furoate Nasal Spray 110 mcg for 4 Weeks in Adults and Adolescents with Irritant (Non-Allergic) Rhinitis;
- **FFS113203**; A randomized, double-blind, placebo controlled, parallel group, multi-centre, 2-week treatment study to evaluate the safety and efficacy of fluticasone furoate nasal spray (FFNS) 110 mcg, administered either once daily or twice daily, compared with placebo, as effective monotherapy in the treatment of uncomplicated acute rhinosinusitis (ARS) in adult and adolescent subjects 12 years of age and older.

2. Clinical studies

STUDY - FFR113342; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Efficacy and Safety of Fluticasone Furoate Nasal Spray for 2 Weeks in Chinese Adult and Adolescent subjects with Allergic Rhinitis.

Methods

This study is to demonstrate the efficacy and safety of Avamys in treatment of Allergic Rhinitis (currently approved indication) in Chinese adult and adolescent subjects.

• Objective: The primary objective of this study was to compare the efficacy and safety of Fluticasone furoate, nasal spray 110µg once daily with vehicle placebo nasal spray for 2 weeks in Chinese adult and adolescent subjects with Allergic Rhinitis

• Study design: This randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase III study evaluated the efficacy and safety of Fluticasone Furoate Nasal Spray once-daily, 110µg once daily administered for 2 weeks in Chinese adult and adolescent subjects.

• Study population /Sample size: 365 Subjects from 7 sites in China

• Treatments: Fluticasone Furoate Nasal Spray 110 µg once daily or placebo nasal spray for two weeks.

• Outcomes/endpoints: The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective, total nasal symptom scores (rTNSS). The mean change from baseline to the end of study in nasal finding score by rhinoscopy was the secondary efficacy endpoint.

• Statistical Methods: The statistical analysis and generation of tables, listings and figures were performed using the SAS software package version 9.1. Using a two-sided significance level of 0.05, the proposed sample size should provide 92% power to detect a difference of 0.9 between Fluticasone Furoate Nasal Spray and placebo.

Results

• Recruitment/ Number analysed: A total of 365 subjects were randomized: 181 in FFNS and 182 in placebo group.

• Baseline data: At baseline, the mean daily rTNSS was similar between the two treatment groups.

• Efficacy results: The primary efficacy endpoint for this study was the mean change from baseline over the entire 2 Weeks treatment period in daily rTNSS. For this endpoint, once daily Fluticasone Furoate Nasal Spray 110μg was significantly more efficacious in reducing the nasal symptoms of AR (rhinorrhea, congestion, itching, sneezing) versus vehicle Placebo nasal spray in Chinese adult and adolescent subjects[LS mean difference: -1.498, 95% CI (-1.897, -1.099), p<0.0001]. Fluticasone Furoate Nasal Spray 110μg was also significantly more efficacious than vehicle Placebo nasal spray in the evaluation of nasal finding by rhinoscopy (p<0.0001).

Table 11 Mean Change from Baseline over the Entire Treatment Period in Daily rTNSS - FAS

	FFNS (N=181)	Placebo (N=182)
Baseline (n)	181	181
Mean (SD)	8.217 (1.6331)	8.432 (1.6549)
Entire treatment period (n)	179	179
Mean (SD)	4.273 (2.1199)	5.893 (2.1206)
Change from baseline (n)	179	178
Mean Change (SD)	-3.960 (2.1189)	-2.586 (2.0045)
LS Mean Change (SE)[a]	-4.226 (0.1646)	-2.728 (0.1656)
LS Mean Difference[a]		-1.498
p-value[a]		<0.0001
95% CI[a]		-1.897, -1.099

Source Data: Table 6.1, Table 6.2

a. Based on ANCOVA adjusting for baseline daily rTNSS, center, classification of AR (IAR OR PER), age, gender, and treatment

SD=Stand deviation SE = Standard error; LS = Least square; CI = Confidence Interval

LS Mean Difference = LS Mean Change in FFNS – LS Mean Change in Placebo

Table 14 Mean Change from Baseline to the End of Study in Nasal Finding Score by Rhinoscopy - FAS

	FFNS (N=181)	Placebo (N=182)
Baseline (n)	181	182
Mean (SD)	9.1 (1.59)	9.0 (1.83)
Visit 4/ Early Withdrawal (n)	176	177
Mean (SD)	5.5 (2.92)	6.7 (2.89)
Change from baseline (n)	176	177
Mean Change (SD)	-3.6 (3.06)	-2.3 (2.75)
LS Mean Change (SE)[a]	-4.2 (0.22)	-2.9 (0.22)
LS Mean Difference[a]		-1.3
p-value[a]		<0.0001
95% CI[a]		-1.9, -0.8

Source Data: Table 6.7, Table 6.8

a. Based on ANCOVA adjusting for baseline nasal finding score by rhinoscopy, center, classification of AR (IAR OR PER), age, gender, and treatment

SD=Stand deviation SE = Standard error; LS = Least square; CI = Confidence Interval

LS Mean Difference = LS Mean Change in FFNS – LS Mean Change in Placebo

Table 20 Multiple Comparison

	Endpoints	P value
Primary efficacy analysis	The mean change from baseline over the entire treatment period in daily rTNSS	<0.0001
Secondary efficacy analysis	The mean change from baseline to the end of study (Visit 4/Early Withdrawal) in nasal finding score by rhinoscopy	<0.0001
	The mean change from baseline to the end of study (Visit 4/Early Withdrawal) in severity of overall interference in activities of daily living	<0.0001
Other efficacy analysis	The mean change from baseline over the entire treatment period in daily rTOSS in subgroup	0.0853

- Safety results: The incidence of adverse events (AEs) was low in the two treatment groups: 7.2% of subjects treated with Fluticasone Furoate Nasal Spray 110µg and 4.9% of subjects treated with vehicle Placebo. The most common AEs demonstrated in short term AR studies conducted in the USA and Europe were headache, epistaxis, and nasopharyngitis. However, the AE profile observed in this study was different. Rhinalgia and dizziness were reported as the most common drug-related AEs in Chinese subjects.

Table 22 Overall Summary of Adverse Event during Treatment Period - Safety Set

	FFNS (N=181)	Placebo (N=182)
Subjects with any adverse event	13 (7.2%)	9 (4.9%)
Subjects with any drug-related adverse event	6 (3.3%)	3 (1.6%)
Subjects with any serious adverse event	0	0
Subjects with any adverse event leading to discontinuation	0	1 (0.5%)
Death	0	0
Subjects with mild adverse event as the highest grade	8 (4.4%)	3 (1.6%)
Subjects with moderate adverse event as the highest grade	4 (2.2%)	6 (3.3%)
Subjects with severe adverse event as the highest grade	1 (0.6%)	0

Source Data: Table 7.2

STUDY- FFU111439; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Once-Daily Intranasal Administration of Fluticasone Furoate Nasal Spray 110mcg in Adult and Adolescent Subjects 12 years of Age and Older with Periannial Allergic Rhinitis.

- **Methods**

This study is for demonstrate the efficacy and safety of Avamys in treatment of Allergic Rhinitis (currently approved indication). This Periannial Allergic Rhinitis (PAR) study was conducted to determine the efficacy of fluticasone furoate nasal spray for the treatment of ocular symptoms associated with PAR.

• Objective: The primary objective of this study was to compare the efficacy and safety of 4 weeks of treatment with intranasal fluticasone furoate 110 mcg once daily and placebo nasal spray in subjects ≥12 years of age with perennial allergic rhinitis.

• Study design: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the efficacy and safety of FFNS.

• Study population /Sample size: 288 subjects from 30 - 40 investigative sites in North America, Europe, and the Russian Federation.

• Treatments: once-daily, intranasal administration of fluticasone furoate nasal spray 110 mcg or placebo administered for 4 weeks in adult and adolescent subjects (12 years of age and older) with PAR.

• Outcomes/endpoints: The primary efficacy measure for the study was the mean change from baseline over the entire treatment period in daily reflective total nasal symptom scores (rTNSS). Key secondary measures were the mean change from baseline over the entire treatment period in morning pre-dose instantaneous total nasal symptom scores (iTNSS) and the mean change from baseline over the entire treatment period in daily, reflective, total ocular symptom scores (rTOSS).

• Statistical Methods: The primary efficacy endpoint served as a gatekeeper for the interpretation of treatment comparisons for the key secondary efficacy and health outcomes endpoints. If H0 was rejected at the 0.05 level for the primary efficacy endpoint, the conclusion would be there was a difference between fluticasone furoate nasal spray 110 mcg once daily and placebo, and the p-values for the key secondary efficacy and health outcomes endpoints would be interpreted according to the rules for multiplicity adjustment.Using a two-sample t-test with a two-sided significance level of 0.05, the proposed sample size should provide 90% power to detect a difference of 1.0 between active treatment and placebo.

Results

• Recruitment/ Number analysed: A total of 509 subjects were screened for this study. The ITT population comprised 315 subjects who were randomized and received at least one dose of study medication (160 in FFNS group and 155 – placebo). Total number of participants in age between 12 to 18 yrs was 18 (9 in FFNS and 9 in placebo group). A total of 96% of subjects completed the study.

• Baseline data: The majority of subjects had reported having PAR for ≥10 years (61% - 68%).Mean scores over the four 24-hour periods prior to randomization for the total nasal, nasal congestion, and total ocular symptom scores were similar between the two treatment groups

• Efficacy results: In daily rTNSS the treatment difference between fluticasone furoate 110 mcg and placebo was significant for study weeks 2, 3, and 4, but not for Week 1. The LS mean differences ranged from -0.223 (Week 1; p=0.326) to -0.937 (Week 4; p=0.005). Over the entire treatment period in daily rTOSS the treatment difference between fluticasone furoate 110 mcg and placebo was not significant for any study week.

Table 9 Daily rTNSS (ITT Population)

	Placebo (N=155)	FF 110 mcg (N=160)
Baseline (n)	155	160
Mean (SE)	9.1 (0.13)	9.1 (0.14)
Weeks 1-4[a] (n)	155	160
Mean (SE)	6.9 (0.20)	6.1 (0.21)
Change from Baseline, mean (SE)		
Week 1	-1.5 (0.16)	-1.7 (0.15)
Week 2	-2.3 (0.20)	-2.9 (0.20)
Week 3	-2.6 (0.22)	-3.6 (0.23)
Week 4	-2.9 (0.24)	-4.0 (0.24)
Weeks 1-4[a]		
Mean Change (SE)	-2.2 (0.19)	-3.0 (0.19)
LS Mean Change (SE)[b]	-2.45 (0.24)	-3.19 (0.23)
LS Mean Difference[b]	-	-0.741
p-value[b]	-	0.004
95% CI[b]	-	-1.24, -0.24

Source: Table 7.1 and Table 7.2
a = entire treatment period; b = based on ANCOVA adjusting for baseline daily rTNSS, country, age, and gender
SE = Standard error; LS = Least square; CI = Confidence Interval;
LS mean difference = LS mean change in active – LS mean change in placebo

Table 11 Daily rTOSS (ITT Population)

	Placebo (N=155)	FF 110 mcg (N=160)
Baseline (n)	155	160
Mean (SE)	6.6 (0.11)	6.3 (0.12)
Weeks 1-4[a] (n)	155	160
Mean (SE)	4.7 (0.18)	4.2 (0.16)
Change from Baseline, mean (SE)		
Week 1	-1.3 (0.14)	-1.2 (0.11)
Week 2	-1.9 (0.17)	-2.0 (0.16)
Week 3	-2.1 (0.18)	-2.4 (0.18)
Week 4	-2.4 (0.20)	-2.8 (0.19)
Weeks 1-4[a]		
Mean Change (SE)	-1.9 (0.16)	-2.0 (0.15)
LS Mean Change (SE)[b]	-1.99 (0.20)	-2.23 (0.19)
LS Mean Difference[b]	-	-0.240
p-value[b]	-	0.243
95% CI[b]	-	-0.64, 0.16

Source: Table 7.5 and Table 7.6
a = entire treatment period; b = based on ANCOVA adjusting for baseline value, country, age, and gender
SE = Standard error; LS = Least square; CI = Confidence Interval;
LS mean difference = LS mean change in active – LS mean change in placebo

The mean change from baseline in daily rTNSS over the 4-week treatment period was greater for fluticasone furoate 110 mcg than for placebo in each age group: the 12 to <18 years group (-2.8 [fluticasone furoate 110 mcg], -1.7 [placebo]), the 18 to <65 years group (-3.0 [fluticasone furoate 110 mcg], -2.3 [placebo]), and the ≥65 years group (-3.9 [fluticasone furoate 110 mcg], -1.2 [placebo]). However, the sample sizes for the 12 to <18 years and ≥65 years groups were too small to make meaningful comparisons.

• Safety results: Sixty-seven subjects (42%) in the fluticasone furoate 110 mcg group and 52 subjects (34%) in the placebo group experienced at least one AE during the treatment period. The most common drug-related AE, epistaxis, was reported by 19 subjects (12%) in the fluticasone furoate 110 mcg group and 6 subjects (4%) in the placebo group. One subject (<1%) in fluticasone furoate 110 mcg group and two subjects (1%) in the placebo group reported drug-related events of nasal septum ulceration or nasal ulcer. No SAEs were reported during the study.

Table 27 AEs Occurring at Greater than or Equal to 1% Incidence and More Common than Placebo (ITT Population)

	Placebo (N=155) n (%)	FF 110 mcg (N=160) n (%)
Subjects with any AE	52 (34)	67 (42)
Epistaxis	13 (8)	24 (15)
Nasopharyngitis	2 (1)	8 (5)
Scab[a]	3 (2)	4 (3)
Arthralgia	1 (<1)	4 (3)
Cough	2 (1)	3 (2)
Pharyngolaryngeal pain	1 (<1)	3 (2)
Upper respiratory tract infection	1 (<1)	3 (2)
Bronchitis	1 (<1)	2 (1)
Nasal ulcer	1 (<1)	2 (1)
Nausea	1 (<1)	2 (1)
Respiratory tract infection viral	0	3 (2)
Viral infection	1 (<1)	2 (1)
Toothache	0	2 (1)

Source: Table 8.6 and Table 8.7

a. System Organ Class = Skin and subcutaneous tissue disorders

Summary of AEs in age group 12 -<18 years.:

Protocol: FFU111439 P
Population: ITT/Age 12 - <18 years

Table 8.18
Summary of All Adverse Events During the Treatment Period

System Organ Class Preferred Term	Placebo (N=9)	FF 110mcg QD (N=9)
ANY EVENT	0	2 (22%)
Infections and infestations		
Any event	0	1 (11%)
Bronchitis	0	1 (11%)
Respiratory, thoracic and mediastinal disorders		
Any event	0	1 (11%)
Epistaxis	0	1 (11%)

STUDY - FFR111158; A Pilot, Randomised, Double-blind, Placebo-controlled, Parallel group, Multi-centre Study to Evaluate the Efficacy and Safety of Once-daily Intranasal Administration of Fluticasone Furoate Nasal Spray 110 mcg for 4 Weeks in Adults and Adolescents with Irritant (Non-Allergic) Rhinitis.

Description: This study is a pilot trial in new indication for the product Avamys: treatment of Irritant (Non-Allergic) Rhinitis (IR). Non-allergic rhinitis is characterized by sporadic or persistent perennial symptoms that do not result from events mediated by immunoglobulin E (IgE). Additionally, non-allergic rhinitis can be sub-classified into infectious rhinitis, vasomotor rhinitis (VMR), occupational/irritant rhinitis, hormonal rhinitis, drug-induced rhinitis, gustatory rhinitis, and non-allergic rhinitis with eosinophilia syndrome (NARES). The sub-class of irritant rhinitis can be caused by a variety of irritant triggers which include environmental factors, such as physical and/or chemical compounds in the air.

Methods

- Objective: The objective of this study was to compare the efficacy and safety of fluticasone furoate nasal spray 110 mcg once daily with placebo nasal spray in subjects with irritant (nonallergic) rhinitis triggered predominantly by air pollution.

- Study design: This was a 4-week, Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in Thailand.

- Study population /Sample size: Approximately 100 subjects (50 per arm) were planned to be randomized in each of the two treatment groups (fluticasone furoate nasal spray 110 mcg once daily and placebo nasal spray).

The sample size was based on the estimation that the distance from the mean to the limit (½ width) of the 95 % confidence interval for the treatment effect was no larger than 0.666, assuming a standard deviation of 1.7 based on previous VMR studies with fluticasone furoate where the same assessment ratings were used.

- Treatments: FFNS 110mcg QD or placebo for 4 weeks.

- Outcomes/endpoints: The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily rTNSS (reflective total nasal symptoms score) as evaluated on a 4-point categorical scale. A key secondary efficacy endpoint was the mean change from baseline over the entire treatment period in AM pre-dose iTNSS (instantantaneous TNSS).

- Statistical Methods: No formal statistical hypotheses were tested. The analysis method used for comparison of the two treatment groups was ANCOVA.

Results

- Recruitment/ Number analysed: One hundred two (102) subjects were randomized into the study, including only three adolescent patients.

- Baseline data: At baseline, the mean daily rTNSS were similar for both treatment groups.

- Efficacy results:

For primary endpoint, a statistically significant difference between the two treatment groups was not demonstrated (LS mean difference was -0.0655; p=0.845). For the key secondary endpoint, mean change from baseline in the morning (pre-dose) instantaneous total nasal symptom score (AM pre-dose iTNSS), a statistically significant difference was also not seen between the two groups (LS mean difference was -0.075; p=0.827).

Table 7 Mean Change from Baseline in Daily rTNSS (ITT Population – FFR111158)

	Placebo (N=49)	FFNS 110mcg (N=53)
Baseline (n)		
Mean (SE)	6.4 (0.17)	6.7 (0.17)
Weeks 1-4[a] (n)	49	53
Mean (SE)	4.4 (0.24)	4.4 (0.25)
Change from Baseline		
Week 1		
Mean Change (SE)	-1.3 (0.19)	-1.6 (0.22)
Week 2 (n)	49	53
Mean Change (SE)	-1.8 (0.28)	-2.1 (0.26)
Week 3	47	51
Mean Change (SE)	-2.4 (0.28)	-2.5 (0.29)
Week 4 (n)	46	49
Mean Change (SE)	-2.8 (0.29)	-2.9 (0.30)
Weeks 1-4[a]		
Mean Change (SE)	-2.0 (0.24)	-2.2 (0.24)
LS Mean Change (SE)[b]	-2.10 (0.25)	-2.17 (0.23)
LS Mean Difference[b]		-0.065
p-value		0.845
95% CI	---	-0.72, 0.59

Source Data: Table 7.1, Table 7.2

a. Entire treatment period;

b. Based on ANCOVA and adjusted for baseline value, baseline eosinophils, age and gender

SE = Standard error; LS = Least square; CI = Confidence Interval;

LS mean Difference = LS mean Change in FFNS – LS mean Change in placebo

• Safety results: The safety findings of this study showed fluticasone furoate 110mcg once daily to be well tolerated. Cough, migraine, nasal ulcer, and epistaxis were the most common AEs that occurred during the treatment period (≥3% incidence and more common than placebo) however these numbers were low, comparatively, due to the small population (N=102).

Table 24 Adverse Events Occurring at Greater than or Equal to 3% Incidence and More Common than Placebo (ITT Population – FFR1111158)

Adverse Event	Placebo N=49	FFNS 110mcg N=53
Subjects with any Adverse Event, n (%)	18 (37)	21 (40)
Cough	1 (2)	3 (6)
Migraine	1 (2)	2 (4)
Nasal Ulcer	1 (2)	2 (4)
Epistaxis	0	2 (4)

Source Data: Table 8.6

STUDY - FFS113203; A randomized, double-blind, placebo controlled, parallel group, multi-centre, 2-week treatment study to evaluate the safety and efficacy of fluticasone furoate nasal spray (FFNS) 110 mcg, administered either once daily or twice daily, compared with placebo, as effective monotherapy in the treatment of uncomplicated acute rhinosinusitis (ARS) in adult and adolescent subjects 12 years of age and older.

➢ **Description**

This study is a trial in a new indication for the product Avamys: uncomplicated acute rhinosinusitis (ARS). ARS was definied as a clinically-diagnosed inflammatory condition of the upper respiratory tract lasting less than 4 weeks. Uncomplicated RS may be further classified by a critical assessment of the duration and pattern (e.g., improving, persistent, worsening) of symptoms including nasal congestion, nasal discharge (anterior/posterior nasal drip), and facial pain/pressure. Patients with ARS generally have one of the following two clinical presentations (persistent or worsening) consistent with uncomplicated ARS: symptoms or signs of acute RS persist ≥10 days beyond onset or symptoms or signs of acute RS worsen within 5-10 days after an initial improvement. ARS patients with fever >38°C and severe pain were classified as having fulminant bacterial rhinosinusitis (FBRS) were excluded from the study. Subjects who developed FBRS during the study were withdrawn and were treated with an antibiotic.

➢ **Methods**

- Objective: The objective of this study was to evaluate the safety and efficacy of two doses of FFNS (110 mcg once daily and 110 mcg twice daily) compared with placebo as monotherapy in the treatment of adult and adolescent subjects 12 years of age and older with uncomplicated ARS.

- Study design: This was a Phase IIb, randomized in 3 groups, double-blind, placebo-controlled, parallel-group, multicenter study.

- Study population /Sample size: A total of 1023 subjects were screened for this study.
- Treatment: Treatment in 3 Groups for 2-week treatment period:

- FFNS 110mcg QD (morning) and placebo (evening);
- FFNS 110mcg BID (morning and evening);
- Placebo (morning and evening).

- Outcomes/endpoints: The primary efficacy endpoint was mean change from baseline in daily Major Symptoms Score (MSS: nasal congestion/stuffiness, sinus headache/pressure or facial pain/pressure, and postnasal drip) over the entire treatment period (Weeks 1-2). First time to symptom improvement was the key secondary efficacy endpoint.

- Statistical Methods: Analysis performed using ANCOVA with baseline value, country, AR status, age, and gender as covariates. Age and AR status were based on subject demographics and baseline characteristics captured on the eCRF.

➢ **Results**

- Recruitment/ Number analysed: The ITT Population included 737 subjects: 245 in the placebo group, 240 in the FFNS 110 mcg QD group, and 252 in the FFNS 110 mcg BID group. Children aged from 12 to 18 yr. compromised 43 subjects (6%): 14; 14 and 15 according the treatment group. The majority of subjects in each treatment group (≥93%) completed the 2-week study.

- Baseline data

- Efficacy results: Based on the primary efficacy endpoint, the mean change from baseline over the entire treatment period in daily MSS, the study demonstrated a statistically significant treatment benefit of FFNS compared with placebo in reducing the overall symptoms of uncomplicated ARS for both BID and QD dosing regimens (LS mean differences vs. placebo of -0.357 [p=0.014] and -0.386 [p=0.008] for BID and QD, respectively). Between the two FFNS doses investigated, a dose response was not observed.

  The key secondary endpoint, first time to symptom improvement, did not provide supporting evidence for the efficacy of FFNS in subjects with uncomplicated ARS. The difference in the median time to symptom improvement between each regimen of FFNS and placebo was 1 day (8 days for the placebo group and 7 days for each FFNS group) and it was not statistically significant.

Table 7 Analysis of Mean Change from Baseline in Daily MSS (Study FFS113203, ITT Population)

Daily MSS[1]	Placebo N=245	FFNS 110 QD N=240	FFNS 110 BID N=252
Baseline, n	244	238	249
Mean (SE)	7.1 (0.06)	7.0 (0.07)	7.0 (0.06)
Change from Baseline			
Week 1, n	242	237	244
Mean change (SE)	-2.1 (0.10)	-2.3 (0.11)	-2.4 (0.11)
Week 2, n	232	234	238
Mean change (SE)	-4.1 (0.14)	-4.5 (0.15)	-4.4 (0.13)
Weeks 1-2, n	242	237	245
Mean change (SE)	-3.0 (0.11)	-3.4 (0.12)	-3.3 (0.11)
Analysis[2]:			
LS Mean change (SE)	-2.97 (0.12)	-3.36 (0.13)	-3.33 (0.13)
LS Mean Diff vs. Placebo [95% CI]	---	-0.386 [-0.67, -0.10]	-0.357 [-0.64, -0.07]
p-value	---	0.008	0.014

Source: Table 6.1 and Table 6.2

1. MSS = sum of the three individual symptom scores for nasal congestion/stuffiness, sinus headache/pressure or facial pain/pressure, and postnasal drip. Score scale for individual symptoms 0-3: 0 = none, 1 = mild, 2 = moderate, 3 = severe
2. Analysis performed using ANCOVA with baseline value, country, AR status, age, and gender as covariates. Age and AR status were based on subject demographics and baseline characteristics captured on the eCRF.

Table 8 Mean Change from Baseline in Daily MSS for Age and Allergic Rhinitis Subgroups (Study FFS113203, ITT Population)

	Age 12 to <18 Years						Age >=18 Years					
Timepoint	Placebo N=14		FFNS QD N=14		FFNS BID N=15		Placebo N=230		FFNS QD N=224		FFNS BID N=234	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Baseline	14	7.1	14	7.2	15	6.7	230	7.1	224	7.0	234	7.0
Weeks 1-2	14	-3.7	14	-3.8	15	-2.9	228	-3.0	223	-3.3	230	-3.4
	Allergic Rhinitis						No Allergic Rhinitis					
Timepoint	Placebo N=44		FFNS QD N=34		FFNS BID N=38		Placebo N=200		FFNS QD N=204		FFNS BID N=211	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Baseline	44	6.9	34	6.9	38	6.8	200	7.1	204	7.1	211	7.0
Weeks 1-2	44	-3.0	34	-3.1	38	-2.8	198	-3.1	203	-3.4	207	-3.4

Source: Table 6.33, Table 6.34, Table 6.35, and Table 6.36

Table 10 First Time to Symptom Improvement (Study FFS113203, ITT Population)

	Placebo N=245	FFNS 110 QD N=240	FFNS 110 BID N=252
n	243	239	252
Uncensored subjects (events), n (%)	181 (74)	188 (79)	188 (76)
Censored subjects, n (%)	62 (26)	51 (21)	59 (24)
Median time to improvement (day)[1]	8	7	7
Cumulative proportion with event (%)	50.64	53.55	51.39
p-value vs. placebo[2]	---	0.174	0.328

Source: Table 6.3
1. Day on which at least 50% of subjects had event; Kaplan-Meier estimates based on LIFETEST table.
2. p-value based on log-rank test

- Safety results: The incidence of AEs during the treatment period was similar across the three treatment groups (17-18%) (Table 16). SOCs with the highest incidence of AEs (≥5% in at least one treatment group) included Infections and Infestations (5-6%), Nervous System Disorders (2-6%), and Respiratory, Thoracic and Mediastinal Disorders (4-5%). The incidence of nervous system disorders was slightly higher in the FFNS groups (4% QD, 6% BID) compared with the placebo group (2%).

Table 16 Most Common (>=1% Incidence in Any Treatment Group and More Common than Placebo) Adverse Events During Treatment (Study FFS113203, ITT Population)

	Number (%) of Subjects		
Adverse Event	Placebo N=245	FFNS 110 QD N=240	FFNS 110 BID N=252
Any AE	41 (17)	41 (17)	46 (18)
Headache	6 (2)	9 (4)	12 (5)
Sinusitis bacterial[1]	6 (2)	6 (3)	4 (2)
Epistaxis	5 (2)	6 (3)	3 (1)
Oropharyngeal pain	2 (<1)	2 (<1)	3 (1)
Dizziness	1 (<1)	0	4 (2)
Pharyngitis	0	1 (<1)	3 (1)

Source: Table 7.3, Table 7.4, and Table 7.5
1. One subject in the placebo group (Subject 224) was not diagnosed with FBRS and did not receive antibiotic.

Most of the AEs reported during this study occurred in subjects ≥18 years old: 17% placebo, 18% FFNS 110 mcg QD, and 19% FFNS 110 mcg BID and were similar to the ITT Population. Four subjects in the adolescent age group (n=43) reported AEs which included headache (1 subject in the placebo group and 2 subjects in the FFNS 110 mcg BID group) and gastritis (1 subject in the FFNS 110 mcg QD group).

3. Discussion on clinical aspects

STUDY- FFU111439 -
Results of this study showed once-daily fluticasone furoate 110 mcg aqueous nasal spray produced greater reductions from baseline in subjects' self-assessed, allergy nasal symptom scores as compared with placebo nasal spray. These reductions were inferentially significant for the primary endpoint (rTNSS) as well as for the key secondary nasal symptom endpoint (iTNSS).
A significant difference between the study treatments was not seen for the key secondary ocular symptom endpoint (rTOSS) or for other ocular symptom endpoints, including any of the three individual ocular symptoms (eyes itching/burning, eyes tearing/watering, and eye redness).
The summary of AE for age group 12 to <18 (n=9) was presented.

STUDY - FFR113342 –
The efficacy results in this study were similar to the studies conducted in USA, Europe, and Japan. There are not specified efficacy and safety data on participants by age group.

STUDY FFR111158 -
This pilot study demonstrated a lack of efficacy of FFNS in the treatment of IR developed by air pollution in Bangkok. The safety findings of this study showed fluticasone furoate 110mcg once daily to be well tolerated in population included to the study. Only three participants were adolescent (12-18 yrs).

STUDY FFS113203 –
Due to small number of participants aged 12-18 yrs (n=43) the results did not provide supporting evidence for the efficacy of the product in the treatment of uncomplicated ARS in this population. The safety data for this population collected in this study confirmed known safety profile of FFNS without any unexpected adverse event.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The efficacy data from two presented studies in AR support the current indication. It must be acknowledged that safety data from paediatric population are not complete because study nr 113342 does not state how many children were included in the study, and there is no summary of adverse events in paediatric population (n=43) in study nr 113203. Summary of safety from other two studies do not reveal any special risk in this population. The rapporteurs conclude that no changes in the product information are required.
No further action required

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

There are no additional requests.