

# **Public Assessment Report**

## **Decentralised Procedure**

**RHINOLAST S 0.15% NASAL SPRAY**

**ASTEPRO 0.15% NASAL SPRAY**

**(azelastine hydrochloride)**

**Procedure No: UK/H/0256/004/DC & UK/H/4757/001/DC**

**UK Licence No: PL 15142/0235-6**

**Meda Pharmaceuticals Limited**

## LAY SUMMARY

### Rhinolast S 0.15% Nasal Spray and Astepro 0.15% Nasal Spray (azelastine hydrochloride, nasal spray, 0.15 % solution)

This is a summary of the public assessment report (PAR) for Rhinolast S 0.15% Nasal Spray and Astepro 0.15% Nasal Spray. It explains how Rhinolast S and Astepro 0.15% Nasal Sprays were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Rhinolast S and Astepro 0.15% Nasal Sprays.

For practical information about using Rhinolast S and Astepro 0.15% Nasal Sprays, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What is Rhinolast S/Astepro 0.15% Nasal Spray and what is it used for?**

Rhinolast S and Astepro 0.15% Nasal Sprays contain the active ingredient azelastine hydrochloride, which belongs to a group of medicines called antihistamines. Rhinolast S and Astepro 0.15% Nasal Sprays are used to treat allergic rhinitis in adults, adolescents and children aged 6 years and older.

#### **How is Rhinolast S/Astepro 0.15% Nasal Spray used?**

The medicines can only be obtained with a prescription.

#### **How does Rhinolast S/Astepro 0.15% Nasal Spray work?**

Rhinolast S and Astepro 0.15% Nasal Sprays work by preventing the effects of histamine that the body produces as part of an allergic reaction. Allergic rhinitis is an allergic reaction to substances such as pollen, house dust mites or animal hair. Its symptoms can include a runny nose, sneezing, itching or a blocked nose. Rhinolast S and Astepro 0.15% Nasal Sprays should help control these symptoms.

#### **How has Rhinolast S/Astepro 0.15% Nasal Spray been studied?**

A lower strength of the nasal spray (0.1%) has already been approved for use and the active ingredient azelastine hydrochloride has been used in medicinal products for a long time. Additional studies were needed to look at the effects of these higher strength products.

Rhinolast S and Astepro 0.15% Nasal Sprays were first tested in experimental models before being studied in humans. Eight main clinical studies involving over 3000 patients with allergic rhinitis were conducted. All studies except one involved adolescents and adults aged 12 years and older, while one study was conducted in children aged 6 to 11 years. These studies lasted between 2 and 4 weeks. The main measure of effectiveness was the improvement in symptoms during the study in patients using Rhinolast S and Astepro 0.15% Nasal Sprays, compared to those using dummy (placebo) sprays that did not contain the active ingredient.

In addition, a long-term study which studied the use of Rhinolast S and Astepro 0.15% Nasal Sprays for a period of 1 year was conducted in adolescents and adults aged 12 years and older.

#### **What benefit has Rhinolast S/Astepro 0.15% Nasal Spray shown during studies?**

Rhinolast S/Astepro 0.15% Nasal Sprays were more effective than placebo sprays at improving the symptoms of allergic rhinitis, with significant changes in Total Nasal Symptom Score (TNSS) and

Secondary Symptom Complex Score (SSCS) in patients with Seasonal Allergic Rhinitis (SAR) and Perennial Allergic Rhinitis (PAR).

### **What is the risk associated with Rhinolast S/Astepro 0.15% Nasal Spray?**

The main side effects that were reported were an unpleasant taste in the mouth (common - may affect up to 1 in 10 people) and slight irritation of the inside of the nose, sneezing and nose bleed (uncommon - may affect up to 1 in 100 people). For a full list of all side effects reported with Rhinolast S and Astepro 0.15% Nasal Sprays, please see the package leaflet.

Rhinolast S/Astepro 0.15% Nasal Sprays should not be used in people who are hypersensitive (allergic) to azelastine hydrochloride or any of the other ingredients. These products have a minor influence on the ability to drive and use machines (dizziness and fatigue is experienced rarely due to the allergic rhinitis or when using the products). Alcohol may enhance these effects. These products contain the preservative benzalkonium chloride, which is an irritant and may cause skin reactions.

### **Why is Rhinolast S/Astepro 0.15% Nasal Spray approved?**

It was noted that the effect of Rhinolast S/Astepro 0.15% Nasal Spray to treat the symptoms of allergic rhinitis in adults, adolescents and children aged 6 years and older was significantly better than treatment with placebo.

It was considered that the benefits of Rhinolast S and Astepro 0.15% Nasal Sprays outweigh their risks and the grant of marketing authorisations was recommended.

### **What measures are being taken to ensure the safe and effective use of Rhinolast S/Astepro 0.15% Nasal Spray?**

Safety information has been included in the summary of product characteristics and the package leaflet for Rhinolast S/Astepro 0.15% Nasal Sprays, including the appropriate precautions to be followed by healthcare professionals and patients.

As the study in children aged 6 to 11 years lasted only 4 weeks, use longer than 4 weeks is not currently recommended in this age group.

### **Other information about Rhinolast S/Astepro 0.15% Nasal Spray**

Austria, Germany, Denmark, Spain, Finland, Ireland, Italy, the Netherlands, Portugal, Sweden and the UK agreed to grant Marketing Authorisations for Rhinolast S 0.15% Nasal Spray and Astepro 0.15% Nasal Spray on 08 August 2013. Marketing Authorisations were granted in the UK on 03 September 2013.

For more information about treatment with Rhinolast S/Astepro 0.15% Nasal Spray, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in 11-2013.

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## Module 1

### Information about initial procedure

|                                      |   |
|--------------------------------------|---|
| <b>Product Name</b>                  | Rhinolast S 0.15% Nasal Spray<br>Astepro 0.15% Nasal Spray  |
| <b>Type of Application</b>           | Article 8.3, Known active   |
| <b>Active Substances</b>             | Azelastine hydrochloride  |
| <b>Form</b>                          | Nasal spray   |
| <b>Strength</b>                      | 1.5 mg/ml   |
| <b>MA Holder</b>                     | Meda Pharmaceuticals Limited<br>Skyway House<br>Parsonage Road<br>Takeley<br>Bishop Stortford<br>CM22 6PU, UK |
| <b>Reference Member State (RMS)</b>  | UK  |
| <b>Concerned Member States (CMS)</b> | Austria, Germany, Denmark, Spain, Finland, Ireland, Italy,<br>the Netherlands, Portugal, Sweden               |
| <b>Procedure Number</b>              | UK/H/0256/004/DC<br>UK/H/4757/001/DC  |
| <b>Timetable</b>                     | Day 210 – 08 August 2013  |

## **Module 2**

### **Summary of Product Characteristics**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

## **Module 3**

### **Patient Information Leaflet**

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

## Module 4

### Labelling

The following text is the approved label text for Rhinolast S 0.15% Nasal Spray (PL 15142/0235). No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

|   |
|---|
| <b>PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING</b> |
|---|

|              |
|--------------|
| <b>Label</b> |
|--------------|

|   |
|---|
| <b>1. NAME OF THE MEDICINAL PRODUCT</b> |
|---|

Rhinolast S 0.15% Nasal Spray, Solution  
Azelastine hydrochloride

|  |
|--|
| <b>2. STATEMENT OF ACTIVE SUBSTANCE(S)</b> |
|--|

1 ml nasal spray contains 1.5 mg azelastine hydrochloride.  
One squirt (0.14 ml) contains 0.21 mg azelastine hydrochloride equivalent to 0.19 mg azelastine.

|                              |
|------------------------------|
| <b>3. LIST OF EXCIPIENTS</b> |
|------------------------------|

Excipients: Hypromellose, sucralose, sorbitol, liquid (crystallising), disodium edetate, sodium citrate, benzalkonium chloride, purified water.  
Read the package leaflet before use.

|  |
|--|
| <b>4. PHARMACEUTICAL FORM AND CONTENTS</b> |
|--|

4 ml nasal spray, solution  
30 ml nasal spray, solution  
30 ml nasal spray, solution x 10 (as hospital pack)

|   |
|---|
| <b>5. METHOD AND ROUTE(S) OF ADMINISTRATION</b> |
|---|

Read the package leaflet before use.  
Nasal use

|  |
|--|
| <b>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</b> |
|--|

Keep out of the sight and reach of children.

|  |
|--|
| <b>7. OTHER SPECIAL WARNING(S), IF NECESSARY</b> |
|--|

|                       |
|-----------------------|
| <b>8. EXPIRY DATE</b> |
|-----------------------|

EXP  
Do not use longer than 6 months after first use.



**9. SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Meda Pharmaceuticals Limited  
Skyway House,  
Parsonage Road,  
Takeley, Bishop's Stortford  
UK

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 15142/0235

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****Carton****1. NAME OF THE MEDICINAL PRODUCT**

Rhinolast S 0.15% Nasal Spray, Solution  
Azelastine hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 ml nasal spray contains 1.5 mg azelastine hydrochloride.  
One squirt (0.14 ml) contains 0.21 mg azelastine hydrochloride equivalent to 0.19 mg azelastine.

**3. LIST OF EXCIPIENTS**

Excipients: Hypromellose, sucralose, sorbitol, liquid (crystallising), disodium edetate, sodium citrate, benzalkonium chloride, purified water.  
Read the package leaflet before use.

**4. PHARMACEUTICAL FORM AND CONTENTS**

4 ml nasal spray, solution  
30 ml nasal spray, solution  
30 ml nasal spray, solution x 10 (as hospital pack)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Nasal use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

Do not use longer than 6 months after first use.

**9. SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Meda Pharmaceuticals Limited  
Skyway House,  
Parsonage Road,  
Takeley, Bishop's Stortford  
UK

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 15142/0235

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Rhinolast S 0.15% Nasal Spray

The following text is the approved label text for Astepro 0.15% Nasal Spray (PL 15142/0236). No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****Label****1. NAME OF THE MEDICINAL PRODUCT**

Astepro 0.15% Nasal Spray, Solution  
Azelastine hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 ml nasal spray contains 1.5 mg azelastine hydrochloride.  
One squirt (0.14 ml) contains 0.21 mg azelastine hydrochloride equivalent to 0.19 mg azelastine.

**3. LIST OF EXCIPIENTS**

Excipients: Hypromellose, sucralose, sorbitol, liquid (crystallising), disodium edetate, sodium citrate, benzalkonium chloride, purified water.  
Read the package leaflet before use.

**4. PHARMACEUTICAL FORM AND CONTENTS**

4 ml nasal spray, solution  
30 ml nasal spray, solution  
30 ml nasal spray, solution x 10 (as hospital pack)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Nasal use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP  
Do not use longer than 6 months after first use.

**9. SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Meda Pharmaceuticals Limited  
Skyway House,  
Parsonage Road,  
Takeley, Bishop's Stortford  
UK

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 15142/0236

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Astepro 0.15% Nasal Spray, Solution  
Azelastine hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 ml nasal spray contains 1.5 mg azelastine hydrochloride.  
One squirt (0.14 ml) contains 0.21 mg azelastine hydrochloride equivalent to 0.19 mg azelastine.

**3. LIST OF EXCIPIENTS**

Excipients: Hypromellose, sucralose, sorbitol, liquid (crystallising), disodium edetate, sodium citrate, benzalkonium chloride, purified water.  
Read the package leaflet before use.

**4. PHARMACEUTICAL FORM AND CONTENTS**

4 ml nasal spray, solution  
30 ml nasal spray, solution  
30 ml nasal spray, solution x 10 (as hospital pack)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Nasal use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

Do not use longer than 6 months after first use.

**9. SPECIAL STORAGE CONDITIONS**

Do not refrigerate or freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Meda Pharmaceuticals Limited  
Skyway House,  
Parsonage Road,  
Takeley, Bishop's Stortford  
UK

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 15142/0236

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Astepro 0.15% Nasal Spray

## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Rhinolast S 0.15% Nasal Spray (PL 15142/0235; UK/H/0256/004/DC) and Astepro 0.15% Nasal Spray (PL 15142/0236; UK/H/4757/001/DC) could be approved. These applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Germany, Denmark, Spain, Finland, Ireland, Italy, the Netherlands, Portugal and Sweden as Concerned Member States (CMS).

These products are prescription-only medicines (legal classification POM).

These are full-dossier applications for a known active substance, submitted via the Decentralised Procedure (DCP), according to Article 8.3 of Directive 2001/83/EC, as amended. These identical applications for Azelastine S 0.15% solution, nasal spray (under the brand names Rhinolast S 0.15% Nasal Spray and Astepro 0.15% Nasal Spray) are line-extensions of Azelastine S 0.1% solution, nasal spray, which was granted a Marketing Authorisation in the UK on 18 May 2012 (Meda Pharma GmbH & Co. KG, PL 23023/0001-5; UK/H/0256/003/DC & UK/H/4236-9/001/DC).

These products are indicated for the symptomatic treatment of allergic rhinitis in adults, adolescents and children 6 years and older. They contain the active ingredient azelastine hydrochloride. Azelastine is a phthalazinone derivative and is a potent long-acting anti-allergic compound with selective H<sub>1</sub>-antagonist properties. Data from *in vivo* (pre-clinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators (e.g. leukotrienes, histamine, platelet activating factor [PAF] and serotonin) that are known to be involved in early and late stage allergic reactions.

No new non-clinical pharmacology and pharmacokinetic studies were conducted, which is acceptable given that the application is for a known active substance, for which a comprehensive non-clinical evaluation has already been conducted. The applicant has submitted four new repeat-dose toxicity studies to demonstrate that the local tolerance of this higher strength formulation is comparable to that of the currently marketed formulation, Azelastine S 0.1% nasal spray (PL 23023/0001-5; UK/H/0256/003/DC & UK/H/4236-9/001/DC).

The application is supported by a total of 10 clinical studies, including one pharmacokinetic study, four studies evaluating the twice a day (BID) dose regimen, four studies evaluating the once daily (OD) dose regimen and one long-term safety study for the BID dose regimen for a treatment period of 1 year.

The clinical studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 08 August 2013. After a subsequent national phase, a licence was granted in the UK on 03 September 2013.



**II. ABOUT THE PRODUCT**

|   |   |
|---|---|
| Name of the product in the Reference Member State         | Rhinolast S 0.15% Nasal Spray<br>Astepro 0.15% Nasal Spray  |
| Name(s) of the active substance(s) (INN)                  | Azelastine hydrochloride  |
| Pharmacotherapeutic classification<br>(ATC code)          | Antiallergic agents, excluding<br>corticosteroids<br>(R01AC03)  |
| Pharmaceutical form and strength(s)                       | Nasal spray, 1.5 mg/ml  |
| Reference numbers for the Mutual Recognition<br>Procedure | UK/H/0256/004/DC<br>UK/H/4757/001/DC  |
| Reference Member State                                    | United Kingdom  |
| Member States concerned                                   | Austria, Germany, Denmark, Spain,<br>Finland, Ireland, Italy, the Netherlands,<br>Portugal, Sweden            |
| Marketing Authorisation Number(s)                         | PL 15142/0235<br>PL 15142/0236  |
| Name and address of the authorisation holder              | Meda Pharmaceuticals Limited<br>Skyway House<br>Parsonage Road<br>Takeley<br>Bishop Stortford<br>CM22 6PU, UK |

### III SCIENTIFIC OVERVIEW AND DISCUSSION

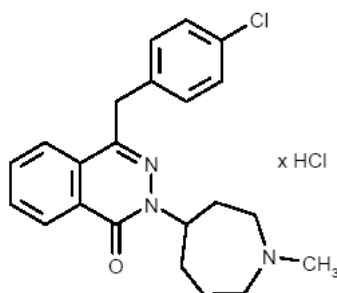
#### III.1 QUALITY ASPECTS

##### S. Active substance

rINN: Azelastine hydrochloride

Chemical name: D, L-4-(p-Chlorobenzyl)-2-(N-methyl-perhydro-azepin-4-yl)-1(2H)-phthalazinone hydrochloride  
4-(4-Chlorobenzyl)-2-[(4RS)-1-methylhexahydro-1H-azepin-4-yl] phthalazin-1(2H)-one hydrochloride  
(R,S)-4[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-phthalazin-1(2H)-one hydrochloride

Structure:



Molecular formula:  $C_{22}H_{24}ClN_3O \cdot HCl$

Molecular weight: 418.37

Appearance: White or almost white, crystalline powder

Solubility: Sparingly soluble in water and soluble in ethanol and in methylene chloride

Azelastine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance from its starting materials are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

##### P. Medicinal Product

###### Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely hypromellose, sucralose (E 955), liquid (crystallising) sorbitol, disodium edetate, sodium citrate, benzalkonium chloride and purified water.

All of the excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients contain material of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

###### Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious nasal spray formulation which minimises or masks the bitter taste of the active ingredient azelastine hydrochloride, but with a higher strength than the currently authorised Azelastine S 0.1% Nasal spray (PL 23023/0001-5; UK/H/0256/003/DC & UK/H/4236-9/001/DC), in order to offer more treatment options to the treating physician, to tailor to the needs of the individual patient.

A satisfactory account of the pharmaceutical development has been provided.

###### Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the finished product. The manufacturing process has been validated using three production-scale batches and has shown satisfactory results.

**Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is packaged in a white plastic high density polyethylene (HDPE) bottle fitted with a spray pump (the pump parts in contact with the solution consist of polypropylene, polyethylene, polyoxymethylene, elastomer and stainless steel). The product is presented in the following pack sizes:

- 4 ml fill volume in 15 ml bottles (as sales pack and as sample pack)
- 30 ml fill volume in 34.5 ml bottles
- 30 ml fill volume in 34.5 ml bottles x 10 (as hospital pack)

The marketing authorisation holder has stated that not all pack sizes are to be marketed, but has committed to submitting mock-up of any new pack sizes to the regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on three full-scale batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened bottle and an in-use shelf life (after first use) of 6 months, with the storage conditions "Do not refrigerate or freeze."

**Bioequivalence/bioavailability**

No bioequivalence studies were conducted and none are required for this type of application.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPCs, PIL and text versions of the labels are pharmaceutically acceptable.

A bridging report referring to the results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Optilast 0.5mg/ml Eye drops solution (PL 15142/0036) was provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

**Marketing Authorisation Application (MAA) forms**

The MAA forms are pharmaceutically satisfactory.

**Quality Overall Summary (Expert report)**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**

The grant of Marketing Authorisations is recommended.

## III.2 NON-CLINICAL ASPECTS

### Pharmacology

As the pharmacodynamic and pharmacokinetic properties of azelastine hydrochloride are well-known and as these applications concern a higher strength of a known product, for which a comprehensive non-clinical evaluation has already been conducted, the non-submission of additional pharmacology and pharmacokinetic studies is acceptable.

### Toxicology

The applicant has submitted four new repeat-dose toxicity studies in rats and dogs (Table 1) to demonstrate that the local tolerance of this higher strength formulation is comparable to that of the currently marketed formulation, Azelastine S 0.1% nasal spray (PL 23023/0001-5; UK/H/0256/003/DC & UK/H/4236-9/001/DC).

**Table 1. Overview of toxicology studies conducted with Azelastine S 0.15% nasal spray formulation**

| Study Type and Duration             | Route of Administration | Species and Strain No./Sex/Group | GLP | Treatments   |
|-------------------------------------|-------------------------|----------------------------------|-----|--|
| <b>Repeat-Dose Toxicity Studies</b> |                         |                                  |     |  |
| 14-day repeat-dose                  | Intranasal              | Sprague-Dawley rats<br>10        | Yes | 1. Vehicle (Azelastine S) <sup>1</sup><br>2. Vehicle without sucralose <sup>2</sup><br>3. Marketed azelastine 0.1% <sup>3</sup><br>4. Azelastine S 0.1% <sup>4</sup><br>5. Azelastine S 0.15% <sup>5</sup> |
| 14-day repeat-dose                  | Intranasal              | Sprague-Dawley rats<br>10        | Yes | 1. Vehicle (Azelastine S) <sup>1</sup><br>2. Azelastine S 0.15% <sup>5</sup>   |
| 6-month repeat-dose                 | Intranasal              | Sprague-Dawley rats<br>20        | Yes | 1. Vehicle (Azelastine S) <sup>1</sup><br>2. Marketed azelastine 0.1% <sup>3</sup><br>3. Azelastine S 0.1% <sup>4</sup><br>4. Azelastine S 0.15% <sup>5</sup>  |
| 14-day repeat-dose                  | Intranasal              | Beagle dogs<br>3                 | Yes | 1. Vehicle (Azelastine S) <sup>1</sup><br>2. Azelastine S 0.15% <sup>5</sup>   |

<sup>1</sup> 0.15% sucralose/4.51% sorbitol vehicle

<sup>2</sup> Contains all ingredients as Azelastine S vehicle except sucralose

<sup>3</sup> Marketed formulation in the US, identical to the first in Europe marketed azelastine nasal spray (containing BAC)

<sup>4</sup> Azelastine S 0.1% nasal spray formulation (0.15% sucralose/4.51% sorbitol vehicle)

<sup>5</sup> Azelastine S 0.15% nasal spray formulation (0.15% sucralose/4.48% sorbitol vehicle)

It is noted that one of the 14-day studies and the 6-month study in rats were also submitted and assessed in support of the Azelastine S 0.1% nasal spray applications (PL 23023/0001-5; UK/H/0256/003/DC & UK/H/4236-9/001/DC). As such, only the conclusions from these studies in relation to the higher strength will be discussed.

The dosing regimens of 0.4 mL/day (0.1 mL/nostril, BID) for rats and 0.548 mL/day (using a clinical spray applicator dispensing 0.137 mL (1 spray) per nostril, BID) for dogs were selected for the toxicology studies because they were considered the maximum feasible dose and closely mimicked the regimen intended for use in the clinic [i.e., 1 or 2 sprays of 0.137 mL/spray, twice daily (total BID volume would be 0.548 mL – 1.096 mL/day)]. Thus, it is anticipated that the concentrations of 0.15% azelastine in the Azelastine S formulation in the smaller nasal passages of rats will be considerably higher than those of humans, thus providing an additional safety factor.

#### ***14-day repeat-dose toxicity study in rats following intranasal administration***

In a GLP-compliant study, Sprague-Dawley rats (10 groups of 5M or 5F/group) were administered either i) vehicle alone (US marketed formulation); ii) vehicle + 0.15% sucralose; iii) 0.1% azelastine

(US marketed formulation); iv) 0.1 % azelastine + 0.15% sucralose or v) 0.15% azelastine + 0.15% sucralose by intranasally, twice daily for 14 days.

No treatment-related mortalities, clinical signs of toxicity or overall effects on body weight, body weight gain or gross necropsy findings were observed that were considered related to the nasal application of the test formulations. Similar histomorphological lesions were noted in the nasal turbinates of both male and female rats treated with of 0.1 % azelastine, 0.1 % azelastine plus 0.15% sucralose, or 0.15% azelastine plus 0.15% sucralose.

#### ***14-day repeat-dose toxicity study in rats following intranasal administration***

A GLP repeat-dose study was conducted in Sprague-Dawley rats to investigate the potential for local nasal irritation following intranasal administration of 0.15% azelastine in sucralose/sorbitol formulation or vehicle twice daily for 14 consecutive days.

There were no mortalities, test article-related clinical signs of toxicity, changes in body weight, or changes in food consumption. Additionally, no gross findings were reported at necropsy. Female animals administered 0.15% azelastine had significantly decreased mean pancreas (approximately -30%) and tracheobronchial lymph node weights (approximately -50%) (absolute and relative-to-body and-brain weight) compared to the vehicle animals. There were no corresponding changes in gross necropsy or histopathology that correlated with these decreases in organ weights. These effects were not observed in male animals, and no other significant changes in body weight were observed. Microscopic changes of minimal to mild severity were observed in the nasal cavity and turbinates. Focal to multifocal squamous metaplasia was observed in both vehicle control (5/20) and 0.15% azelastine-treated (10/20) animals (minimal to mild, maxilloturbinates respiratory mucosa and middle meatus lateral wall). The study pathologist suggested that the variability of the section obtained during preparation of the tissue may have influenced the presence of the squamous epithelia. Minimal degenerative or metaplastic changes (focal to multifocal) were observed for the olfactory epithelium (dorsal portions of levels 2 or 3) in vehicle control (5/20) and 0.15% azelastine-treated (3/20) animals. This finding is likely an adaptive response to experimental manipulation during the dosing procedure. Minimal to mild inflammation (mixed) was observed in the nasal mucosa of vehicle control (14/20) and 0.15% azelastine-treated (19/20) animals. These findings were attributed to normal variation, with the changes likely representing an adaptive response. Thus, no treatment-related microscopic findings were identified in any tissue examined in this study.

#### ***6-month repeat-dose toxicity study in rats following intranasal administration***

The potential local toxicity of twice daily intranasal administration of two concentrations of azelastine (0.1% and 0.15%) formulated with sucralose (0.15%) was compared with that of 0.1% azelastine (US marketed formulation) or 0.15% sucralose (placebo) alone in Sprague-Dawley rats (4 groups of 20M +20F) over 6 months.

No test article-related mortalities or definitive test article-related clinical signs of toxicity were noted. In conclusion, no additional local toxicity was observed following intranasal administration of 0.1 or 0.15% azelastine with 0.15% sucralose, twice daily, for six months in rats compared to treatment with placebo or the azelastine marketed formulation. The only changes noted were sporadic, transient changes in body weight or food consumption that did not occur across both sexes.

#### ***14-day repeat-dose toxicity study in dogs following intranasal administration***

A GLP repeat-dose study was conducted in Beagle dogs to investigate the potential for nasal irritation following intranasal administration of 0.15% azelastine in the sucralose/sorbitol formulation twice daily for 14 consecutive days. There were no mortalities during this study, no test article-related clinical signs of toxicity, and no changes in body weight or food consumption, or organ weights (absolute and organ-to-body weight or organ-to-brain weight ratios). Additionally, there were no gross findings at necropsy.

All of the histological findings observed in this study were present in vehicle control- and 0.15% azelastine-treated animals. Thus, the observed changes were considered non-test article related, with incidental findings related to the route of administration, background findings for this species, and associated with restraint procedures used for dosing administration.

The most common microscopic finding was inflammation of minimal to mild severity in the anterior levels of the nasal cavity, along with infrequent epithelial degeneration, of all dogs (vehicle control- and 0.15% azelastine-treated). Other findings for the nasal cavity/turbinates included epithelial degeneration (minimal) and goblet cell hyperplasia (minimal to mild). Epithelial degeneration was characterized by intraepithelial cysts, cellular vacuolation, de-ciliation, and epithelial thinning. Goblet cell hyperplasia, characterised by an increase in the number of goblet cells, was observed in all animals. Inflammation of the nasopharynx (minimal to mild), lung (minimal), and trachea (minimal), as well as some of the bronchial lymph node findings of minimal to mild severity (sinusoidal erythrophagocytosis, neutrophil infiltration, follicular hyperplasia), are common in Beagle dogs and were considered to be incidental findings. Despite the presence of active inflammation (mixed to lymphoplasmacytic) in the laryngeal epithelium or mucosa, fibrosis in the submucosa and surrounding laryngeal muscle indicate a chronic process. As findings were also observed in tissues not directly exposed to the test article (e.g., peri-laryngeal tissue), the totality of these lesions is likely secondary to restraint of animals during the dosing procedure. Mild to moderate lymphoid necrosis of the bronchial lymph nodes was observed in 3/6 0.15% azelastine-treated animals. These findings were considered sporadic in nature and consistent with the frequency of spontaneous findings for Beagle dogs for test articles administered intranasally. Overall, the administration of 0.15% azelastine in Azelastine S formulation did not augment the findings observed for vehicle control-treated animals.

### ***Conclusions on toxicology***

A comprehensive nonclinical safety evaluation of azelastine hydrochloride including individual toxicology reports was submitted for the previous azelastine applications. Data from these studies adequately support this application. Sufficient safety margins exist based on exposures associated with adverse effects in animals and those anticipated clinically on increase of azelastine nasal spray concentration to 0.15%.

The current toxicology data to support a higher strength (0.15%) was limited to 4 new GLP repeated-dose toxicity studies in rats and dogs, to demonstrate that no additional local toxicity is associated with the introduction of this higher strength in comparison to currently marketed nasal spray formulations of azelastine. Overall, similar findings were observed across all studies which were predominantly attributed to injury or insult (i.e., can be referred to as degenerative lesions which also includes inflammatory, reparative, adaptive, or proliferative lesions), rather than a direct treatment-related effect.

### **Non-Clinical Expert Report**

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

### **Environmental Risk Assessment**

The applicant has provided an acceptable Environmental Risk Assessment.

### **Conclusion**

There are no objections to the approval of these products from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

#### Clinical Pharmacology

No new pharmacokinetic or pharmacodynamic data were submitted with these applications. This is acceptable as these applications concern a higher strength of a known product, for which a comprehensive evaluation of the clinical pharmacology has already been conducted.

The following pharmacokinetic study was previously assessed for the currently marketed formulation, Azelastine S 0.1% nasal spray (PL 23023/0001-5; UK/H/0256/003/DC & UK/H/4236-9/001/DC), but also relates to the 0.15% strength solution, so will be discussed below:

A Phase 1, randomised, parallel-group study to compare the pharmacokinetic characteristics of the following treatments, in healthy male subjects:

Treatment A (MP03-33): Azelastine S 0.1% nasal spray (137 mcg per spray x 4 sprays = 548 mcg)

Treatment B (MP03-36- Test formulation): Azelastine S 0.15% nasal spray (i.e. Rhinolast/Astepro 0.15% Nasal Spray; 205.5 mcg per spray x 4 sprays = 822 mcg)

Treatment C: Astelin 0.1% azelastine (commercial formulation without sucralose; 137 mcg per spray x 4 sprays = 548 mcg)

All treatments were administered as two sprays per nostril, as a single treatment. Volunteers fasted for 4 hours prior to dosing until 4 hours post dosing. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 120 hours post dose. Samples were analysed for azelastine hydrochloride and its metabolite, desmethyazelastine.

The main pharmacokinetic results are presented in the tables below.

Table 1. Primary pharmacokinetic parameters and AUC<sub>(0-∞)</sub>

| Analyte                    | PK parameters                | Treatment A<br>MP03-33 | Treatment B<br>MP03-36 | Treatment C<br>Astelin <sub>original</sub> | Treatment C<br>Astelin <sub>re-analysed</sub> |
|----------------------------|------------------------------|------------------------|------------------------|--|---|
| Azelastine                 | C <sub>max</sub> (pg/ml)     | 200 ± 67               | 409 ± 160              | 235 ± 88                                   | 233 ± 91                                      |
|                            | AUC <sub>0-t</sub> (h*pg/ml) | 4917 ± 1394            | 8941 ± 3749            | 5903 ± 2264                                | 5806 ± 2294                                   |
|                            | AUC <sub>0-∞</sub> (h*pg/ml) | 5122 ± 1546            | 9312 ± 3950            | 6122 ± 2373                                | 6025 ± 2409                                   |
| N-Desmethyl-<br>azelastine | C <sub>max</sub> (pg/ml)     | 23 ± 11                | 38 ± 15                | 24 ± 8                                     | n. calc.                                      |
|                            | AUC <sub>0-t</sub> (h*pg/ml) | 1634 ± 603             | 2780 ± 857             | 1873 ± 553                                 | n. calc.                                      |
|                            | AUC <sub>0-∞</sub> (h*pg/ml) | 2131 ± 609             | 3824 ± 1184            | 2615 ± 779                                 | n. calc.                                      |

Table 2. Estimates for ratios of pharmacokinetic parameters for azelastine

| Variable             | Comparison                               | Estimate | 90% CI |       |
|----------------------|--|----------|--------|-------|
|                      |  | [%]      | Lower  | Upper |
| AUC <sub>(0-t)</sub> | MP03-36 / Astelin <sub>re-analysed</sub> | 153.4    | 120.1  | 195.9 |
|                      | MP03-36 / MP03-33                        | 173.8    | 136.6  | 221.2 |
| AUC <sub>(0-∞)</sub> | MP03-36 / Astelin <sub>re-analysed</sub> | 154.1    | 120.7  | 196.7 |
|                      | MP03-36 / MP03-33                        | 174.1    | 136.9  | 221.4 |
| C <sub>max</sub>     | MP03-36 / Astelin <sub>re-analysed</sub> | 172.9    | 136.0  | 219.8 |
|                      | MP03-36 / MP03-33                        | 197.5    | 155.9  | 250.2 |

A higher exposure was expected from Azelastine S 0.15% (MP03-36) as compared to the other commercial formulation of 0.1% azelastine (without sucralose) and the Azelastine S 0.1%, based on the 50% increase in the administered dose. However, the measured systemic exposure appeared to be more than 50% higher. Therefore, dose adjusted analyses were performed and are presented in the tables below:

Table 3. Dose adjusted pharmacokinetic parameters:

| Treatment | n  | AUC <sub>(0-∞)</sub><br>[pg*h/ml] |      | AUC <sub>(0-t)</sub><br>[pg*h/ml] |      | C <sub>max</sub><br>[pg/ml] |     |
|-----------|----|-----------------------------------|------|-----------------------------------|------|-----------------------------|-----|
|           |    | Mean (SD)                         | GM   | Mean (SD)                         | GM   | Mean (SD)                   | GM  |
| MP03-36   | 18 | 6208 (2633)                       | 5652 | 5961 (2500)                       | 5429 | 273 (110)                   | 248 |
| Astelin   | 17 | 6025 (2409)                       | 5502 | 5806 (2294)                       | 5309 | 233 (91)                    | 215 |
| MP03-33   | 18 | 5122 (1546)                       | 4870 | 4917 (1394)                       | 4685 | 200 (67)                    | 189 |

SD = standard deviation

GM = geometric mean

Table 4. Point estimates and confidence intervals for dose-adjusted pharmacokinetic parameter ratios

| Variable             | Comparison        | Estimate [%] | 90% CI |       |
|----------------------|-------------------|--------------|--------|-------|
|                      |                   |              | Lower  | Upper |
| AUC <sub>(0-∞)</sub> | MP03-36 / Astelin | 102.7        | 80.5   | 131.1 |
|                      | MP03-36 / MP03-33 | 116.1        | 91.2   | 147.6 |
| AUC <sub>(0-t)</sub> | MP03-36 / Astelin | 102.3        | 80.1   | 130.6 |
|                      | MP03-36 / MP03-33 | 115.9        | 91.1   | 147.5 |
| C <sub>max</sub>     | MP03-36 / Astelin | 115.3        | 90.7   | 146.5 |
|                      | MP03-36 / MP03-33 | 131.7        | 104.0  | 166.8 |

After dose adjustment, the point estimates of the treatment ratio of Azelastine S 0.15% to the older formulations were higher, but the actual differences were small and can probably be explained by variability due to the parallel-group design and low sample size, rather than an actual difference in exposure. Therefore, there is not a clinically significant increase in exposure with the new formulation.

## Efficacy

### Introduction

Nine clinical studies that evaluated the efficacy and safety of Azelastine S 0.15% nasal spray have been submitted. Of these, four studies evaluated the BID regimen and four studies evaluated the OD regimen. In addition a long-term safety study evaluating the BID dose regimen for a period of 1 year has been submitted. This study also provides data on the long-term maintenance of efficacy.

A brief overview of these studies is presented in the tables below:



Table 1

**Listing of placebo-controlled studies and BID regimen**

| Study design      | Groups, doses   | Indication, target population  | N   | Duration |
|-------------------|---|--|-----|----------|
| R, DB, PC, AC, PG | 2 sprays per nostril:<br>1) MP03-36 OD (AM) + placebo OD (PM)<br>2) MP03-36 BID (AM and PM)<br>3) Astelin BID (AM and PM)<br>4) Placebo BID (AM and PM) | SAR<br>Both sex, $\geq 12$ years, minimum 2-year history of SAR          | 617 | 2 weeks  |
| R, DB, PC, AC, PG | 2 sprays per nostril:<br>1) MP03-36 (AM and PM)<br>2) MP03-33 (AM and PM)<br>3) Placebo (AM and PM)   | PAR<br>Both sex, $\geq 12$ years, minimum 2-year history of PAR          | 581 | 4 weeks  |
| R, DB, PC, AC, PG | 2 sprays per nostril:<br>1) MP03-36 (AM and PM)<br>2) MP03-33 (AM and PM)<br>3) Placebo (AM and PM)   | SAR<br>Both sex, $\geq 12$ years, minimum 2-year history of SAR          | 526 | 2 weeks  |
| R, DB, PC, AC, PG | 1 spray per nostril:<br>1) MP03-36 (AM and PM)<br>2) MP03-33 (AM and PM)<br>3) Placebo (AM and PM)  | PAR<br>Both sex, $\geq 6$ to $< 12$ years, minimum 1-year history of PAR | 489 | 4 weeks  |

AC: Active controlled, AM: In the morning (*ante meridiem*) DB: Double-blind, PAR: Perennial allergic rhinitis, PC: Placebo-controlled, PG: Parallel group, PM: in the evening (*post meridiem*), R: Randomised, SAR: Seasonal allergic rhinitis.

MP03-33: Azelastine S 0.1% nasal spray (vehicle with sucralose and sorbitol)

MP03-36: Azelastine S 0.15% nasal spray (vehicle with sucralose and sorbitol)

Placebo: Nasal spray without active ingredient (vehicle with sucralose and sorbitol)

Astelin: Commercial formulation in the US, identical to the first in Europe marketed azelastine nasal spray (containing BAC)

Table 1b Long term safety study of BID regimen

|               |  |  |     |        |
|---------------|--|--|-----|--------|
| R, OL, AC, PG | 2 treatments, 2 sprays per nostril<br>1) MP03-36 BID (AM and PM)<br>2) Nasonex OD (AM) | Both sex, $\geq 12$ years, minimum 1-year history of PAR | 703 | 1 year |
|---------------|--|--|-----|--------|

AC: Active controlled, AM: In the morning (*ante meridiem*), OL: open-label, PAR: Perennial allergic rhinitis, PG: Parallel group, PM: in the evening (*post meridiem*), R: Randomised,

MP03-33: Azelastine S 0.1% nasal spray (vehicle with sucralose and sorbitol)

MP03-36: Azelastine S 0.15% nasal spray (vehicle with sucralose and sorbitol)

Astelin: Commercial formulation in the US, identical to the first in Europe marketed azelastine nasal spray (containing BAC)

Nasonex: Commercial mometasone nasal spray

Table 2

| Listing of placebo-controlled studies and OD regimen |   |   |     |          |
|--|---|---|-----|----------|
| Study design   | Groups, doses   | Indication, target population   | N   | Duration |
| R, DB, PC, PG  | 2 sprays per nostril:<br>1) MP03-36 (AM)<br>2) MP03-36 (PM)<br>3) Placebo (AM)<br>4) Placebo (PM) | PAR<br>Both sex, $\geq 12$ years,<br>minimum 2-year history<br>of PAR | 156 | 4 weeks  |
| R, DB, PC, PG  | 2 sprays per nostril:<br>1) MP03-36 (AM)<br>2) Placebo (AM)                                       | SAR<br>Both sex, $\geq 12$ years,<br>minimum 2-year history<br>of SAR | 481 | 2 weeks  |
| R, DB, PC, PG  | 2 sprays per nostril:<br>1) MP03-36 (AM)<br>2) Placebo (AM)                                       | SAR<br>Both sex, $\geq 12$ years,<br>minimum 2-year history<br>of SAR | 536 | 2 weeks  |
| R, DB, PC, PG  | 2 sprays per nostril:<br>1) MP03-36 (AM)<br>2) Placebo (AM)                                       | SAR<br>Both sex, $\geq 12$ years,<br>minimum 2-year history<br>of SAR | 506 | 2 weeks  |

AM: In the morning (*ante meridiem*) DB: Double-blind, PAR: Perennial allergic rhinitis, PC: Placebo-controlled, PG: Parallel group, PM: in the evening (*post meridiem*), R: Randomised, SAR: Seasonal allergic rhinitis.  
MP03-33: Azelastine S 0.1% nasal spray (vehicle with sucralose and sorbitol)  
MP03-36: Azelastine S 0.15% nasal spray (vehicle with sucralose and sorbitol)  
Placebo: Nasal spray without active ingredient (vehicle with sucralose and sorbitol)

### Main clinical studies

All the eight main clinical studies that evaluated the efficacy of BID and OD regimens were randomised, double-blind, placebo-controlled, parallel-group studies. Altogether 3892 patients were randomised (and also safety evaluable) in the eight efficacy studies. According to the principles of intention to treat (ITT), 3874 patients (99.5%) were evaluable.

The applicant asserts that the studies were designed to be consistent with recommendations for allergic rhinitis clinical development programs provided in the US Guidance for Industry. The applicant further asserts that the study designs were also consistent with recommendations of respective European guidelines and those of the ICH.

Four studies evaluated the BID dose regimen. Two studies were in Seasonal allergic Rhinitis (SAR) and two studies were in Perennial Allergic Rhinitis (PAR). Of these studies, three evaluated the two sprays per nostril dose, while only one study evaluated the one spray per nostril dose. Three studies compared the proposed higher strength (0.15%) to the already approved (0.1%) strength.

Four studies evaluated the two sprays in each nostril OD dosing regimen. Three studies were in SAR and one study was in PAR. The study in PAR was a pilot study to help determine the sample size for the OD dosing regimen. The other three studies were pivotal studies to establish efficacy of the OD dosing regimen.

All studies except one were conducted in adolescents and adults 12 years of age and older, while one study was conducted in children of 6 to 11 years. Only one study investigated the one spray per nostril, in this case BID, while all other studies investigated two sprays per nostril, either OD or BID.

Seven of these efficacy studies were confirmatory in a statistical sense and tested primarily a hypothesis against placebo; one further study was prospectively classified as a pilot study, as the sample size was insufficient for reasonable hypothesis testing. The results of this study were used for calculation of sample size for three later OD studies.

As all studies had a similar design, the study methodology aspects are discussed for all studies and only study results are discussed for individual studies.

## **Methods**

All the eight main clinical studies were randomised, double-blind, placebo-controlled, parallel-group studies.

All of the efficacy studies began with a screening visit at which subjects were required to meet the inclusion/exclusion criteria and a minimum 12-hour reflective Total Nasal Symptom Score (TNSS) requirement consistent with moderate-to-severe symptoms. The TNSS (nasal congestion, rhinorrhea, nasal itching, and sneezing) was scored on a 4-point scale with 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. Subjects who met the minimum symptom score requirement (8 of 12 for SAR and 6 of 12 for PAR) then underwent a 1-week, placebo nasal spray lead-in period. Prior to the lead-in period, minimum medication washout periods were observed for all medications that could potentially interfere with or confound study results. All SAR studies had treatment duration of 2 weeks and all PAR studies were of 4 weeks treatment duration.

## **Study Participants**

All studies enrolled male or female subjects 12 years or above, except one study which enrolled male or female subjects aged 6 to 11 years. The concomitant use of other treatments for allergic rhinitis was prohibited before and during the trials. Patients receiving immunotherapy injections (antigen desensitization) had to be on a stable maintenance regimen for at least 30 days before the first study visit.

### Studies in SAR:

Five randomised, double-blind studies of 2 weeks duration were conducted in subjects with SAR. One study was conducted in the autumn 2006 allergy season, two of the studies were conducted in the autumn 2007 allergy season, and two studies were conducted in the winter Texas mountain cedar seasons 2007/2008 and 2008/2009.

The main selection criterion in the SAR studies was a 12-hour reflective TNSS (AM or PM) of at least 8 on three separate symptom assessments towards the end of the Lead-in Period (one of which was within 2 days before randomisation); in addition, an AM or PM 12-hour reflective nasal congestion score of 2 or 3 had to be recorded on three separate symptom assessments. Subjects must have at least a 2-year history of SAR with the presence of IgE mediated hypersensitivity to a local prevalent seasonal allergen confirmed by a positive response to skin prick.

### Studies in PAR:

Three randomized, double-blind studies of 4 weeks duration were conducted in subjects with moderate-to-severe PAR in 2007, and in 2009 to 2011.

The main selection criterion in the PAR studies was a 12-hour reflective TNSS (AM or PM) of at least 6 on three separate symptom assessments towards the end of the Lead-in Period; in addition, an AM or PM 12-hour reflective nasal congestion score of 2 or 3 had to be recorded on three separate symptom assessments. Subjects must have a minimum history of PAR and a positive skin test to dust mite, cockroach, mould, or cat or dog dander.

## Treatments

All the eight studies compared MP03-36 (Azelastin S 0.15%) nasal spray against placebo. Moreover the studies evaluating the BID dosing regimen also had MP03-33 (Azelastin S 0.1%) as a comparator and one of the BID studies had in addition a treatment arm of conventional Azelastin 0.1% (without sucralose).

As previously stated, three studies evaluated Azelastin S 0.15% two sprays in each nostril BID and one study evaluated Azelastin S 0.15% one spray in each nostril BID. The four studies evaluating the once daily dosing regimen evaluated Azelastin S 0.15% two sprays in each nostril.

## Outcomes/endpoints

In all eight efficacy studies, efficacy was assessed by the same primary endpoint:

- Change from baseline in AM and PM combined 12-hour reflective Total Nasal Symptom Score (TNSS, consisting of runny nose, itchy nose, nasal itching, nasal congestion) for the entire 14-day (SAR) or 28-day (PAR) study period compared to placebo.

In OD studies a key secondary endpoint was used:

- Change from baseline in instantaneous TNSS (end of 24-hour dosing interval) for the entire 14-day (SAR) or 28-day (PAR) study period compared to placebo

Secondary endpoints also included:

- Change from baseline in AM and PM combined instantaneous TNSS for the entire 14-day (SAR) or 28-day (PAR) study period compared to placebo.
- Change from baseline in 12-hour reflective and instantaneous individual symptom scores for the entire 14-day (SAR) or 28-day (PAR) study period compared to placebo.
- Onset of action - change from baseline in instantaneous TNSS compared to placebo over the 4-hour period following initial administration of study drugs
- Daily scores – Daily change from baseline in 12-hour reflective and instantaneous TNSS compared to placebo for the 14-day (SAR) or 28-day (PAR) study period.
- Change from baseline in 12-hour reflective Secondary Symptom Complex Score (SSCS consisting of postnasal drip, itchy eyes, cough, and headache) for the entire 14-day (SAR) or 28-day (PAR) study period compared to placebo
- Change from baseline to Day 14 (SAR) or Day 28 (PAR) in the rhinoconjunctivitis quality of life questionnaire (RQLQ) compared to placebo in subjects 18 years of age and older

## Results

### Studies with twice daily (BID) regimen

Each of the placebo-controlled efficacy studies of the BID regimen showed a homogenous distribution of the randomisation groups with respect to demographic and baseline characteristics. No obvious difference in the overall drop-out rates was found (pooling data of four BID studies showing 40 and 46 drop-outs in the MP03-36 and placebo group, respectively). Drop-outs due to treatment failure tended to occur more frequently in the placebo groups (overall: two drop-outs in the MP03-36 group compared to five after placebo, Table 3).

Table 3. Premature discontinuations in MP03-36 and placebo groups from BID studies

| MP03-36, N (%) |          |         |          |          | Placebo, N (%) |          |         |          |          |
|----------------|----------|---------|----------|----------|----------------|----------|---------|----------|----------|
| Rand.          | All      | TF      | AE       | Oth      | Rand.          | All      | TF      | AE       | Oth      |
| 153 (100)      | 9 (5.9)  | 0       | 5 (3.3)  | 4 (2.6)  | 153 (100)      | 6 (3.9)  | 2 (1.3) | 4 (2.6)  | 0        |
| 192 (100)      | 12 (6.3) | 1 (0.5) | 7 (3.6)  | 4 (2.1)  | 192 (100)      | 17 (8.9) | 1 (0.5) | 3 (1.6)  | 13 (6.8) |
| 178 (100)      | 6 (3.4)  | 0       | 4 (2.2)  | 2 (1.1)  | 178 (100)      | 7 (3.9)  | 0       | 5 (2.8)  | 2 (1.1)  |
| 161 (100)      | 13 (8.1) | 1 (0.6) | 2 (1.2)  | 10 (6.2) | 162 (100)      | 16 (9.9) | 2 (1.2) | 6 (3.7)  | 8 (4.9)  |
| 684 (100)      | 40 (5.8) | 2 (0.3) | 18 (2.6) | 20 (2.9) | 685 (100)      | 46 (6.7) | 5 (0.7) | 18 (2.6) | 23 (3.4) |

**Study 1 (SAR):**

The aim of this study was to evaluate the efficacy and safety of MP03-36 at dosages of two sprays per nostril once daily and two sprays per nostril twice daily in subjects with SAR. Of note, patients in the MP03-36 OD group also received placebo in the evening; hence, the data of this group should be considered as supportive only for the assessment of efficacy of the OD regimen.

A total of 617 subjects were randomised at 30 sites. After the one week placebo run-in period, subjects who were eligible were randomised in a 1:1:1:1 ratio to one of the following treatment arms:

- 1) M1: MP03-36, two sprays per nostril once daily (AM) plus placebo, two sprays per nostril once daily (PM)
- 2) M2: MP03-36, two spray per nostril twice daily (AM and PM)
- 3) A2: Astelin, two spray per nostril twice daily (AM and PM)
- 4) P2: Placebo, two sprays per nostril twice daily (AM and PM)

More than 95% of patients completed the trial. There was no obvious difference between the groups in the rates of premature discontinuations.

The statistical analysis plan stipulated a gate-keeping strategy (in order to control for multiplicity) for the confirmatory test, i.e. comparing M2 with P2 at first instance and then M1 with P2.

**Primary efficacy variable:**

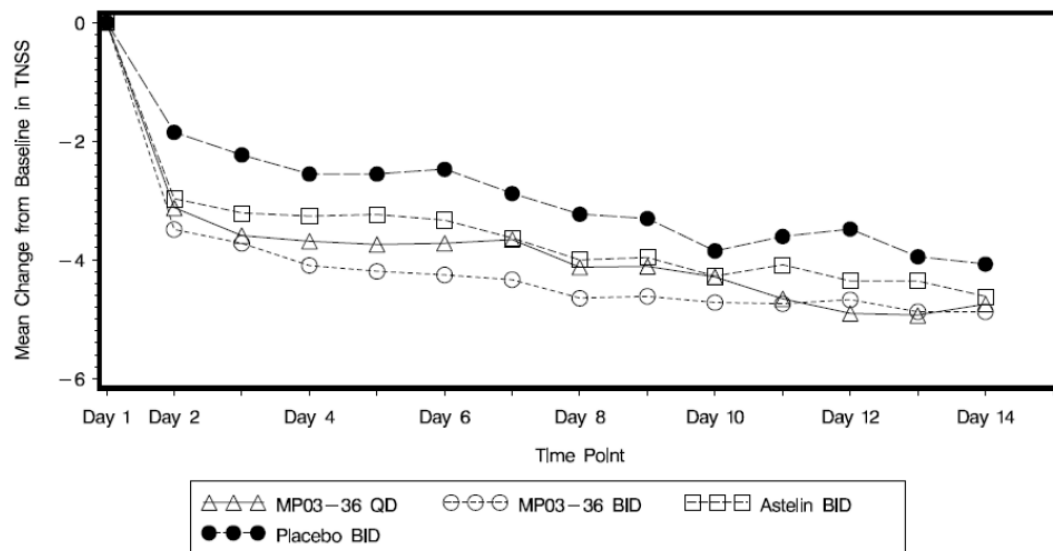
After 2 weeks of treatment, the LS mean improvements from baseline in the 12-hour reflective AM and PM combined TNSS were significantly greater for the MP03-36 BID group (M2,  $p=0.002$ ) and for the MP03-36 OD group (M1,  $p=0.022$ ) than for the placebo group (Table 4). In this study, Astelin BID (A2) only approached borderline statistical significance ( $p=0.055$ ) in the comparison to placebo. There were no statistically significant differences between any of the active treatment groups.

Table 4. Combined AM and PM 12-hour reflective TNSS, ITT

| Treatment groups <sup>a</sup> | Baseline, mean (SD) <sup>a</sup> | Change from baseline, LS mean (SE) <sup>b</sup> |                     |
|-------------------------------|----------------------------------|---|---------------------|
| M2 (n=150)                    | 18.28 (2.82)                     | -4.32 (0.294)                                   |                     |
| M1 (n=158)                    | 18.70 (2.99)                     | -3.97 (0.283)                                   |                     |
| A2 (n=152)                    | 18.00 (2.81)                     | -3.91 (0.347)                                   |                     |
| P2 (n=152)                    | 18.18 (3.01)                     | -3.02 (0.317)                                   |                     |
| Pairwise comparison           | Point estimates <sup>b</sup>     | P-value <sup>b,c</sup>                          | 95% CI <sup>b</sup> |
| M2 vs. P2                     | -1.29                            | 0.002   | -2.11, -0.48        |
| M1 vs. P2                     | -0.95                            | 0.022 <sup>d</sup>                              | -1.76, -0.14        |
| A2 vs. P2                     | -0.88                            | 0.055   | -1.78, 0.02         |
| M2 vs. M1                     | -0.35                            | 0.380   | -1.13, 0.43         |
| M2 vs. A2                     | -0.41                            | 0.352   | -1.28, 0.46         |
| M1 vs. A2                     | -0.06                            | 0.883   | -0.92, 0.79         |

The time course of AM and PM combined reflective TNSS is shown in Figure 1. The difference between MP03-36 BID and placebo was significant at each treatment day until Day 9. Treatment differences between MP03-36 OD and Astelin were significant on single days only.

Figure 1. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT

Secondary efficacy variables:

**Instantaneous TNSS:** The LS mean changes from baseline in AM and PM combined instantaneous TNSS demonstrated similar response profiles as the 12-hour reflective scores, although none of the active dosage groups (M1, M2 or A2) demonstrated statistical significance compared to placebo over the entire 14-days study period.

**RQLQ: Overall score:** This was statistically significant only in the MP03-36 and Astelin BID arms as compared to placebo and did not meet significance in the MP03-36 AM+Placebo PM arm as compared to placebo though the results were numerically superior.

Study 2 (PAR):

The objective of this study was to evaluate the efficacy and safety of MP03-36 and MP03-33 compared to placebo at a dosage of two sprays per nostril twice daily in subjects with PAR. The efficacy and safety of MP03-36 was also compared to MP03-33.

The study was conducted during the winter to avoid the possibility of symptoms due to seasonal pollens. After the 1-week placebo run-in period, eligible subjects were randomized in a 1:1:1 ratio to one of the following treatment arms:

- 1) MP03-36, two sprays per nostril twice daily (AM and PM)
- 2) MP03-33, two sprays per nostril twice daily (AM and PM)
- 3) Placebo, two sprays per nostril twice daily (AM and PM)

The statistical analysis plan stipulated a gate-keeping strategy (in order to control for multiplicity) for the confirmatory test, i.e. comparing MP03-36 with placebo at first instance and then MP03-33 with placebo.

A total of 581 subjects were randomized at 42 sites. There was no obvious difference between the groups in the overall rate of premature discontinuations

Primary efficacy variable:

After 4 weeks of treatment, the LS mean improvement from baseline in the 12-hour reflective AM and PM combined TNSS was statistically significant for the MP03-36 group ( $p=0.0396$ ) when compared to the placebo group (Table 5). The difference between the MP03-33 group and placebo was not



statistically significant ( $p=0.1486$ ). The difference between MP03-36 and MP03-33 was also not statistically significant ( $p=0.4593$ ), however, MP03-36 performed numerically better than MP03-33.

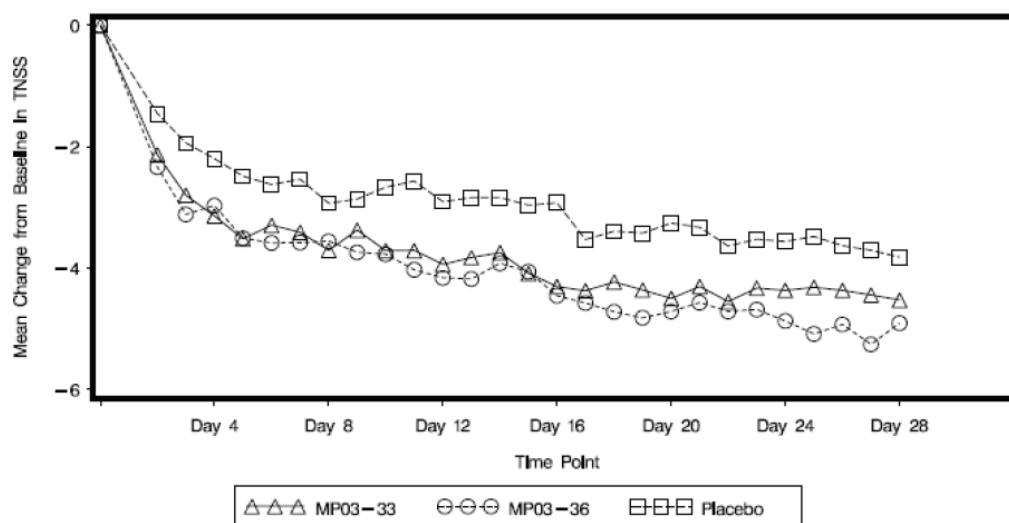
Table 5. Combined AM and PM 12 hour reflective TNSS, ITT

| Treatment groups <sup>a</sup> | Baseline, mean (SD) <sup>a</sup> | Change from baseline, LS mean (SE) <sup>b</sup> |                     |
|-------------------------------|----------------------------------|---|---------------------|
| MP03-36 (n=192)               | 15.90 (3.89)                     | -4.00 (0.273)                                   |                     |
| MP03-33 (n=193)               | 15.63 (3.80)                     | -3.75 (0.252)                                   |                     |
| Placebo (n=192)               | 14.82 (3.99)                     | -3.24 (0.273)                                   |                     |
| Pairwise comparison           | Point estimates <sup>b</sup>     | P-value <sup>b,c</sup>                          | 95% CI <sup>b</sup> |
| MP03-36 vs. placebo           | -0.76                            | 0.0396 <sup>d</sup>                             | -1.49, -0.04        |
| MP03-33 vs. placebo           | -0.51                            | 0.1486  | -1.19, 0.18         |
| MP03-36 vs. MP03-33           | -0.26                            | 0.4593  | -0.94, 0.43         |

It should be noted that for this particular study originally a non-significant difference between MP03-36 and placebo was reported ( $p=0.06$ ). Only on re-analyses in accordance to the protocol and statistical analysis plan (SAP), was it shown to be significant. However the results of sensitivity analysis support the conclusions of the re-analyses.

The time course of AM and PM combined reflective TNSS is shown in Figure 2. The difference between the two active treatments (MP03-36 and MP03-33) and placebo were significant only on single days during the 28-day treatment period.

Figure 2. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT



#### Secondary efficacy variables:

Overall, all secondary variables showed at least numerical superiority of the active treatments compared to placebo. Some significant results of secondary efficacy analyses are presented below.

**Instantaneous TNSS:** The least-squares (LS) mean changes from baseline in instantaneous AM and PM combined TNSS demonstrated similar response profiles as the 12-hour reflective scores, i.e. with a significant superiority of MP03-36 over placebo ( $p=0.044$ ), but not for MP03-33 over the entire 28-day study period.

**Reflective SSCS:** The overall changes in the reflective SSCS (consisting of itchy eyes, postnasal drip, cough, and headache) also demonstrated significant improvements in the MP03-36 group when compared to placebo ( $p=0.002$ ).

**Study 3 (SAR):**

The objective of this study was to evaluate the efficacy and safety of MP03-36 and MP03-33 compared to placebo in subjects with SAR. The efficacy and safety of MP03-36 was also compared to MP03-33. After the 1-week placebo run-in period, subjects who were eligible were randomized in a 1:1:1 ratio to:

- MP03-33
- MP03-36
- Placebo

All administered at a dose of two sprays per nostril twice daily for 14 days.

The SAP stipulated a gate-keeping strategy (in order to control for multiplicity) for the confirmatory test, i.e. comparing MP03-36 with placebo at first instance and then MP03-33 with placebo. Overall, 526 subjects were randomized at 29 sites and there was no obvious difference between the groups in the rates of premature discontinuations.

**Primary efficacy variable:**

After 2 weeks of treatment, the LS mean improvement from baseline in the 12-hour reflective AM and PM combined TNSS were significant ( $p < 0.001$ ) for both the MP03-36 and the MP03-33 groups when compared to the placebo group. The improvements in the MP03-36 group were numerically greater than those seen in the MP03-33 group. The difference between MP03-36 and MP03-33 did not reach significance ( $p = 0.0869$ ), however, providing a trend favouring MP03-36.

Table 6. Combined AM and PM 12 hour reflective TNSS, ITT

| <b>Treatment groups<sup>a</sup></b> | <b>Baseline, mean (SD)<sup>a</sup></b> | <b>Change from baseline, LS mean (SE)<sup>b</sup></b> |                           |
|-------------------------------------|--|---|---------------------------|
| MP03-36 (n=176)                     | 17.86 (3.28)                           | -5.23   | (0.369)                   |
| MP03-33 (n=169)                     | 18.28 (3.23)                           | -4.41   | (0.324)                   |
| Placebo (n=177)                     | 17.90 (3.30)                           | -2.34   | (0.273)                   |
| <b>Pairwise comparison</b>          | <b>Point estimates<sup>b</sup></b>     | <b>P-value<sup>b,c</sup></b>                          | <b>95% CI<sup>b</sup></b> |
| MP03-36 vs. placebo                 | -2.89                                  | <0.0001   | -3.77, -2.02              |
| MP03-33 vs. placebo                 | -2.07                                  | <0.0001   | -2.88, -1.26              |
| MP03-36 vs. MP03-33                 | -0.83                                  | 0.0869  | -1.78, 0.12               |

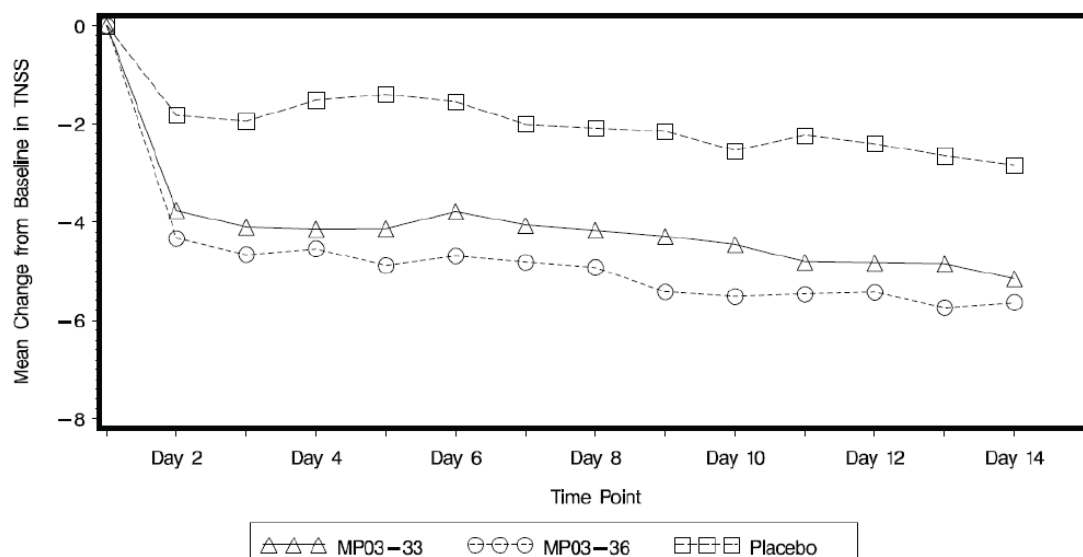
The results obtained in the re-analyses for the primary efficacy variable confirmed the results of the original report.

Sensitivity analyses including a treatment by site interaction term ( $p < 0.0001$ ), based on raw data ( $p < 0.0001$ ) and the overall analysis based on the Per-Protocol set ( $p < 0.0001$ ) yielded similar results for both active groups, confirming the efficacy of MP03-36 and MP03-33.

The time course of AM and PM combined reflective TNSS is shown in Figure 3. The differences between the two active treatments (MP03-36 and MP03-33) and placebo were significant at each treatment day



Figure 3. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT

**Secondary efficacy variables:**

Overall, all secondary variables showed at least numerical superiority of the active treatments compared to placebo. Some significant results of secondary efficacy analyses are presented below.

**Instantaneous TNSS:** The LS mean changes from baseline in instantaneous AM and PM combined TNSS were similar to the changes seen in the 12-hour reflective scores. Both the MP03-36 and MP03-33 groups demonstrated statistically significant ( $p < 0.001$ ) improvements over the entire 14-day study period and the improvements in the MP03-36 group were numerically greater than in the MP03-33 group.

**Reflective SSCS:** The overall changes in the reflective SSCS and each of its individual symptoms (itchy eyes, postnasal drip, cough, and headache) demonstrated significant improvements in the MP03-36 group when compared to placebo ( $p < 0.001$  for overall and each individual symptom). The improvements in the MP03-36 group were greater than in the MP03-33 group.

This is a pivotal study which demonstrated conclusively the efficacy of MP03-33 and MP03-36 in patients with SAR based on the statistically significant results on the primary efficacy variable. These observations are supported by significant results in some of the secondary efficacy variables and a numerical superiority over placebo in other secondary variables.

However, there was no significant difference between MP03-33 and MP03-36, though it is accepted that in most parameters MP03-36 was numerically superior to MP03-33.

**Study 4 (PAR):**

The objective of this study was to evaluate the efficacy and safety of MP03-36 and MP03-33 compared to placebo at a dosage of 1 spray per nostril twice daily in children of 6 to 11 years with PAR. The efficacy and safety of MP03-36 was also compared to MP03-33. After the 1-week placebo run-in period, subjects who were eligible were randomized in a 1:1:1 ratio to

- MP03-36, 1 spray per nostril twice daily (AM and PM)
- MP03-33, 1 spray per nostril twice daily (AM and PM)
- Placebo, 1 spray per nostril twice daily (AM and PM)

The treatment duration was 4 weeks.

The SAP stipulated a gate-keeping strategy (in order to control for multiplicity) for the confirmatory test, i.e. comparing MP03-36 with placebo at first instance and then MP03-33 with placebo. A total of 489 subjects were randomized at 25 sites and premature discontinuations were slightly lower in active treatment groups compared to placebo but this is not considered significant to affect the results.

#### Primary efficacy variable:

After 4 weeks of treatment, the LS mean improvement from baseline in the 12-hour reflective AM and PM combined TNSS was statistically significant for both, the MP03-36 group ( $p=0.005$ ) and the MP03-33 group ( $p=0.015$ ) when compared to the placebo group (Table 7). The difference between MP03-36 and MP03-33 was not statistically significant ( $p=0.82$ ).

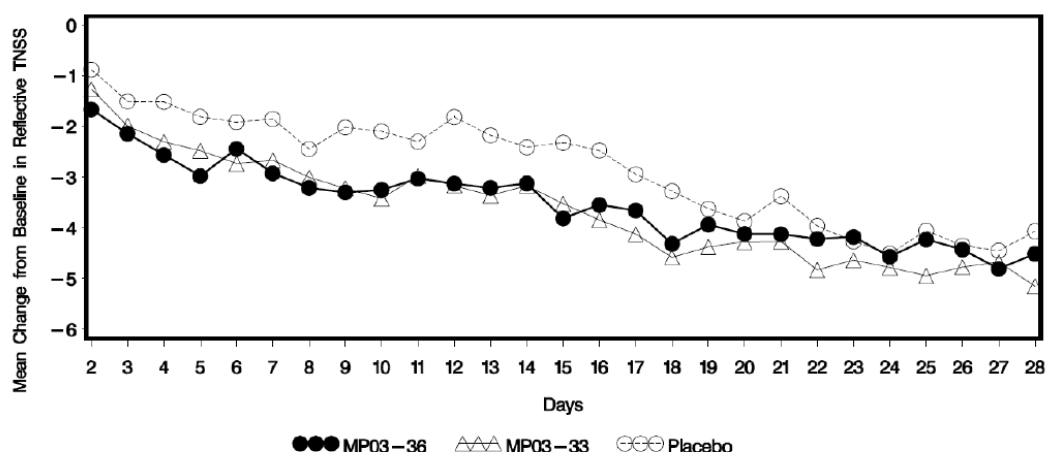
Table 7. Combined AM and PM 12 hour reflective TNSS, ITT

| Treatment groups    | Baseline, mean (SD) | Change from baseline, LS mean |             |
|---------------------|---------------------|-------------------------------|-------------|
| MP03-36 (n=159)     | 16.68 (3.39)        | -3.45                         |             |
| MP03-33 (n=166)     | 16.53 (3.40)        | -3.37                         |             |
| Placebo (n=161)     | 16.27 (3.09)        | -2.48                         |             |
| Pairwise comparison | Point estimates     | P-value                       | 95% CI      |
| MP03-36 vs. placebo | -0.97               | 0.005                         | -1.65,-0.29 |
| MP03-33 vs. placebo | -0.89               | 0.015                         | -1.61,-0.17 |
| MP03-36 vs. MP03-33 | -0.08               | 0.820                         | -0.76, 0.60 |

Sensitivity analyses included a treatment by site interaction term ( $p=0.001$  and  $p=0.004$  for MP03-36 and MP03-33, respectively), a treatment by age interaction term ( $p=0.004$  and  $0.008$ ) and an analysis based on the PP set ( $p=0.007$  and  $0.012$ ). These analyses yielded similar results for both active groups, confirming the efficacy of MP03-36 and MP03-33

The time course of AM and PM combined reflective TNSS is shown in Figure 4. The difference between MP03-36 and placebo were significant on some days (Days 2, 4, 5, 7, 9, 10, 12, and 15).

Figure 4. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT



#### Secondary efficacy variables:

Treatment differences between MP03-36 and placebo in secondary variables were not statistically significant. Some results of the secondary efficacy analysis are:

**Reflective TOSS (key secondary variable):** No statistically significant differences between any of the treatment groups. Each active group performed numerically better than placebo

**Instantaneous TNSS:** No statistically significant differences between any of the treatment groups; this holds true for combined, AM alone, and PM alone. Each active group performed numerically better than placebo.

The protocol scheduled several subgroup analyses, to be performed on the primary variable. These subgroups were separated by SAR negative (total N = 123) or SAR positive (total N = 252), by age (<9: total N = 211; ≥9: total N = 275), by sex (male: total N = 280; female: total N = 206), by race (white: total N = 379; non-white = 107), and by baseline TNSS (below median: total N = 245; above median: 241). For the latter three subgroups (by sex, race, and TNSS), only descriptive statistics were calculated, for the first two also inferential statistics.

All subgroup analyses supported results of the primary, namely at least numerical superiority for both actives over placebo.

### **Summary of studies with twice daily (BID) regimen**

Table 8. Main results of BID regimen studies

| Treatment arm                                 | ITT/<br>completed | Primary                          |                 | Secondary                              |                                  |                                  |                     |
|---|-------------------|----------------------------------|-----------------|--|----------------------------------|----------------------------------|---------------------|
|   |                   | Reflective TNSS <sup>AM+PM</sup> |                 | Instantaneous<br>TNSS <sup>AM+PM</sup> | Reflective SSCs <sup>AM+PM</sup> | Reflective TOSS <sup>AM+PM</sup> | RQLQ: Overall score |
|   |                   | LS mean (SE)                     | P-value vs. PLA | P-value vs. PLA                        | P-value vs. PLA                  | P-value vs. PLA                  | P-value vs. PLA     |
| MP03-36 <sup>AM+PM</sup>                      | 153/144           | -4.32 (0.29)                     | 0.002           | 0.160                                  | Not assessed                     | Not assessed                     | 0.021               |
| MP03-36 <sup>AM</sup> + Placebo <sup>PM</sup> | 158/154           | -3.97 (0.28)                     | 0.022           | 0.554                                  | Not assessed                     | Not assessed                     | 0.052               |
| Astelin <sup>AM+PM</sup>                      | 153/148           | -3.91 (0.35)                     | 0.055           | 0.088                                  | Not assessed                     | Not assessed                     | 0.004               |
| Placebo <sup>AM+PM</sup>                      | 153/147           | -3.02 (0.32)                     |                 |  |                                  |                                  |                     |
| MP03-36                                       | 192/180           | -4.00 (0.27)                     | 0.0396          | 0.044                                  | 0.002                            | Not assessed                     | 0.292               |
| MP03-33                                       | 194/180           | -3.75 (0.25)                     | 0.1486          | 0.102                                  | 0.226                            | Not assessed                     | 0.040               |
| Placebo                                       | 192/175           | -3.24 (0.27)                     |                 |  |                                  |                                  |                     |
| MP03-36                                       | 177/172           | -5.23 (0.37)                     | <0.001          | <0.001                                 | <0.001                           | Not assessed                     | <0.001              |
| MP03-33                                       | 169/166           | -4.41 (0.32)                     | <0.001          | <0.001                                 | 0.002                            | Not assessed                     | 0.238               |
| Placebo                                       | 177/171           | -2.34 (0.27)                     |                 |  |                                  |                                  |                     |
| MP03-36                                       | 159/148           | -3.45 <sup>a</sup>               | 0.005           | 0.435                                  | Not assessed                     | 0.249                            | 0.384               |
| MP03-33                                       | 166/156           | -3.37 <sup>a</sup>               | 0.015           | 0.160                                  | Not assessed                     | 0.157                            | >0.999              |
| Placebo                                       | 162/146           | -2.48 <sup>a</sup>               |                 |  |                                  |                                  |                     |

### **Studies with once daily (OD) regimen**

Each of the placebo-controlled efficacy studies of the OD regimen showed a homogenous distribution of the randomisation groups with respect to demographic and baseline characteristics. No obvious difference in the overall drop-out rates was found. There is a slightly higher drop out rate in placebo group, but this is not considered significant. Drop-outs due to treatment failure tended to occur more frequently in the placebo group.

Table 9. Premature discontinuations in MP03-36 and placebo groups from OD studies

| MP03-36, N (%) |          |         |          |          | Placebo, N (%) |          |         |         |          |
|----------------|----------|---------|----------|----------|----------------|----------|---------|---------|----------|
| Rand.          | All      | TF      | AE       | Oth      | Rand.          | All      | TF      | AE      | Oth      |
| 239 (100)      | 6 (2.5)  | 0       | 2 (0.8)  | 4 (1.7)  | 242 (100)      | 8 (3.3)  | 3 (1.2) | 1 (0.4) | 4 (1.7)  |
| 268 (100)      | 19 (7.1) | 3 (1.1) | 4 (1.5)  | 12 (4.5) | 268 (100)      | 18 (6.7) | 2 (0.7) | 3 (1.1) | 13 (4.9) |
| 251 (100)      | 13 (5.2) | 2 (0.8) | 5 (2.0)  | 6 (2.4)  | 255 (100)      | 15 (5.9) | 2 (0.8) | 4 (1.6) | 9 (3.5)  |
| 105 (100)      | 4 (3.8)  | 0       | 1 (1.0)  | 3 (2.9)  | 51 (100)       | 3 (5.9)  | 2 (3.9) | 0       | 1 (2.0)  |
| 863 (100)      | 42 (4.9) | 5 (0.6) | 12 (1.4) | 25 (2.9) | 816 (100)      | 44 (5.4) | 9 (1.1) | 8 (1.0) | 27 (3.3) |

### **Study 5 (PAR):**

This is a proof-of-concept or a pilot study to determine effect size and explore the appropriate timing (AM or PM) of the once daily dosing regimen. The study evaluated MP03-36 two sprays per nostril administered once daily (AM or PM) as compared to placebo in patients with PAR.

The study was initiated during the winter to avoid the possibility of symptoms due to seasonal pollens. A total of 156 subjects were randomized at 14 sites. After a 1-week placebo run-in period, eligible subjects were randomized in a 2:2:1:1 ratio to:

- MAM: MP03-36, two sprays per nostril once daily (AM)
- MPM: MP03-36, two sprays per nostril once daily (PM)

- PAM: Placebo, two sprays per nostril once daily (AM)
- PPM: Placebo, two sprays per nostril once daily (PM)

There was no obvious difference between the groups in the rates of premature discontinuations

Originally intended as a confirmatory trial, an amended protocol, dated 11 January 2007 (before study start), reduced the sample size and made clear that this study (with the reduced sample size) was only a proof of concept study. Therefore, no adjustments for multiplicity were planned.

#### Primary efficacy variable:

In this study, the changes from baseline to Day 28 in AM and PM combined 12-hour reflective TNSS for morning dosing (MAM vs. PAM) and evening dosing (MPM vs. PPM) of MP03-36, two sprays per nostril in the Intention-To-Treat (ITT) population were numerically greater than those seen in the respective placebo groups. As anticipated, the differences did not reach statistical significance due to the small sample size (Table 10). The two active groups yielded similar results.

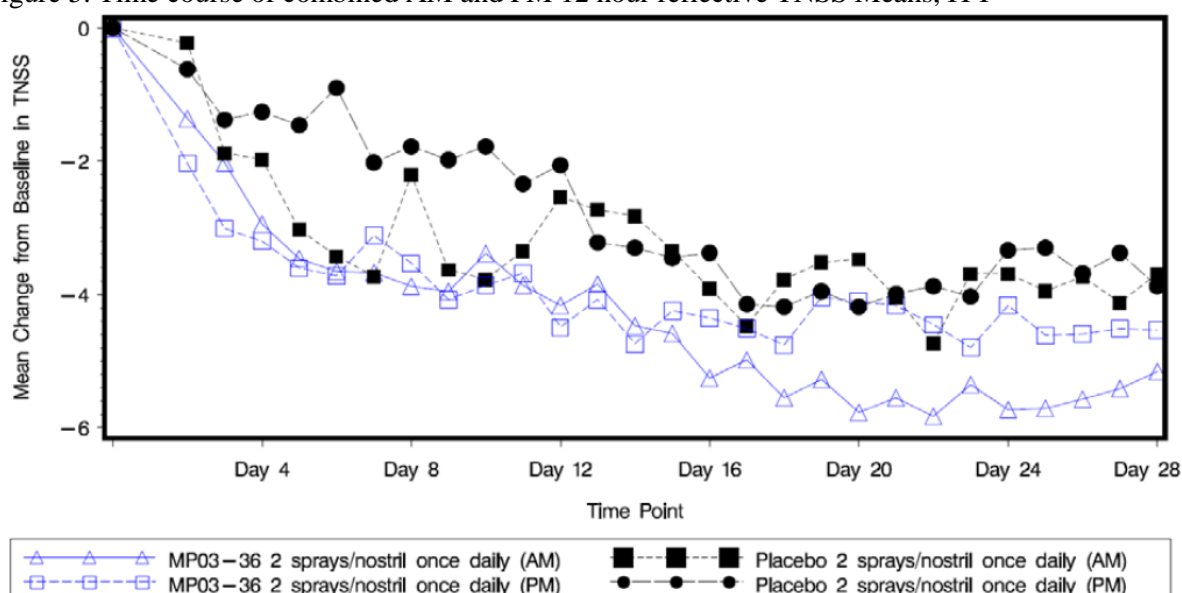
Table 10. Combined AM and PM 12 hour reflective TNSS, ITT

| Treatment groups <sup>a</sup> | Baseline, mean (SD) <sup>a</sup> | Change from baseline, LS mean (SE) <sup>b</sup> |                     |
|-------------------------------|----------------------------------|---|---------------------|
| MAM (n=51)                    | 15.30 (4.65)                     | -3.85 (0.42)                                    |                     |
| PAM (n=23)                    | 16.17 (3.34)                     | -2.77 (0.62)                                    |                     |
| MPM (n=49)                    | 15.28 (4.27)                     | -3.69 (0.48)                                    |                     |
| PPM (n=26)                    | 14.54 (3.40)                     | -2.53 (0.48)                                    |                     |
| Pairwise comparison           | Point estimates <sup>b</sup>     | P-value <sup>b,c</sup>                          | 95% CI <sup>b</sup> |
| MAM vs. PAM                   | -1.08                            | 0.378   | -10.30, 8.15        |
| MPM vs. PPM                   | -1.15                            | 0.323   | -9.29, 6.98         |
| MAM vs. MPM                   | -0.16                            | 0.834   | -7.69, 7.37         |

Sensitivity analyses, including a treatment by site-interaction term, based on raw data and the overall analysis, based on the PP set, yielded similar results

The time course indicated that both active regimens were similar during the first 2 weeks of treatment, but the AM regimen appeared to provide better efficacy after 14 days of treatment (Figure 5). The statistical analyses yielded no consistent statistical significant superiority to placebo of either treatment in any period

Figure 5. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT



Secondary efficacy variables:

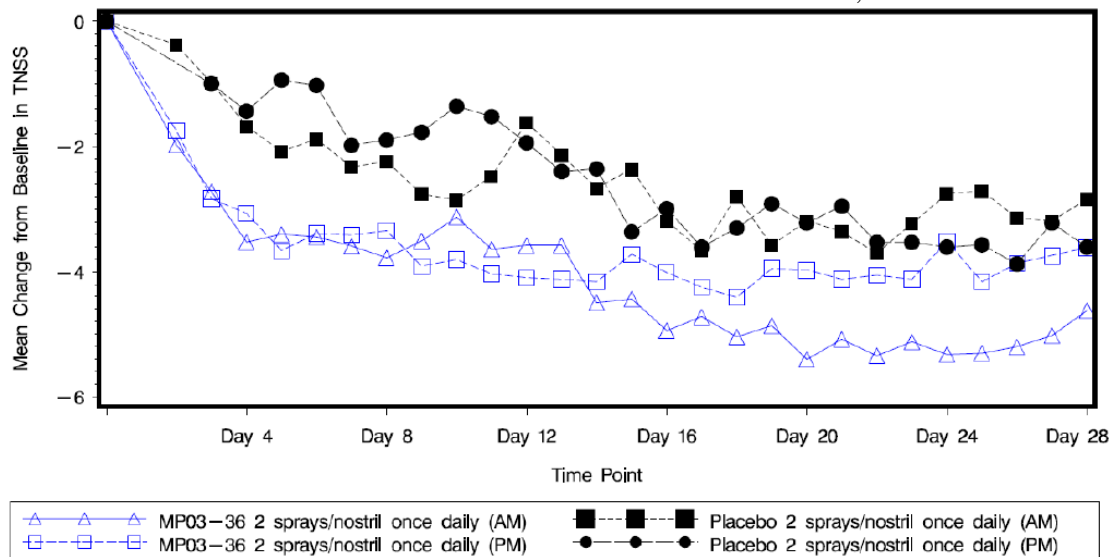
Overall, all secondary variables showed at least numerical superiority of MP03-36, though statistical significance was not consistent. Some results on the secondary efficacy analysis including the key secondary efficacy variable are presented below.

**AM and PM instantaneous TNSS (end of 24-hour dosing interval, key secondary variable):** The LS mean changes from baseline in AM and PM instantaneous TNSS with MP03-36 over the entire 28-day study period were numerically greater than those seen with placebo for both AM and PM dosing but did not achieve statistical significance when compared to placebo ( $p=0.094$  for AM dosing;  $p=0.452$  for PM dosing).

**Instantaneous TNSS:** The LS mean changes from baseline in instantaneous AM and PM combined TNSS demonstrated similar response profiles to the 12-hour reflective scores. However, neither of the active dosage groups (MAM or MPM) demonstrated statistical significance compared to placebo in the overall score from baseline to Day 28 ( $p=0.089$  for AM dosing;  $p=0.388$  for PM dosing).

The time course of instantaneous TNSS also indicated that both active regimens were similar during the first 2 weeks of treatment, but the AM regimen appeared to provide better efficacy after 14 days of treatment (Figure 6).

Figure 6. Time course of combined AM and PM instantaneous TNSS Means, ITT



It should be noted that based on the original results of this study, the AM dosing regimen was chosen for further development. The results of this study were used as basis for calculation of sample sizes of pivotal OD studies.

Though this study is technically not a pivotal study, the study has been included under main studies as the study design and efficacy endpoints are similar to the main studies. The sample size of the study was such that statistical significance was not expected. However, numerical superiority was seen for the treatment arms of AM or PM dosing as compared to the respective placebo treatment.

When AM and PM dosing was compared between them, it was seen that AM dosing had a slight numerical advantage to the PM dosing and further the time course of changes in TNSS suggested a better efficacy for the AM regimen as compared to the PM regimen after 14 days of treatment. Based on the results of the study, a selection of AM dosing for the OD dosing regimen is endorsed.

**Study 6 (SAR):**

The objective of this study was to evaluate the safety and efficacy of MP03-36 at a dosage of two sprays per nostril once daily (AM) compared to placebo two sprays per nostril once daily (AM) in subjects with SAR. After a 1-week placebo run-in period, eligible subjects were randomized to the double-blind treatment period in a 1:1 ratio to the following treatment arms.

MP03-36 – two sprays per nostril once daily in the morning (AM)

Placebo - two sprays per nostril once daily in the morning (AM)

The treatment duration was 2 weeks.

A total of 481 subjects were randomized at 35 sites. There was no obvious difference between the groups in the rates of premature discontinuations.

**Primary efficacy variable:**

After 2 weeks of treatment, the LS mean improvement from baseline in the 12-hour AM and PM combined reflective TNSS were significantly ( $p=0.0017$ ) greater for the MP03-36 group compared to the placebo group

Table 11. Combined AM and PM 12 hour reflective TNSS, ITT

| <b>Treatment groups<sup>a</sup></b> | <b>Baseline, mean (SD)<sup>a</sup></b> | <b>Change from baseline, LS mean (SE)<sup>b</sup></b> |                           |
|-------------------------------------|--|---|---------------------------|
| MP03-36 (n=238)                     | 17.74 (3.54)                           | -3.48   | (0.259)                   |
| Placebo (n=241)                     | 17.73 (3.31)                           | -2.42   | (0.246)                   |
| <b>Pairwise comparison</b>          | <b>Point estimates<sup>b</sup></b>     | <b>P-value<sup>b,c</sup></b>                          | <b>95% CI<sup>b</sup></b> |
| MP03-36 vs. placebo                 | -1.05                                  | 0.0017  | -1.70,-0.40               |

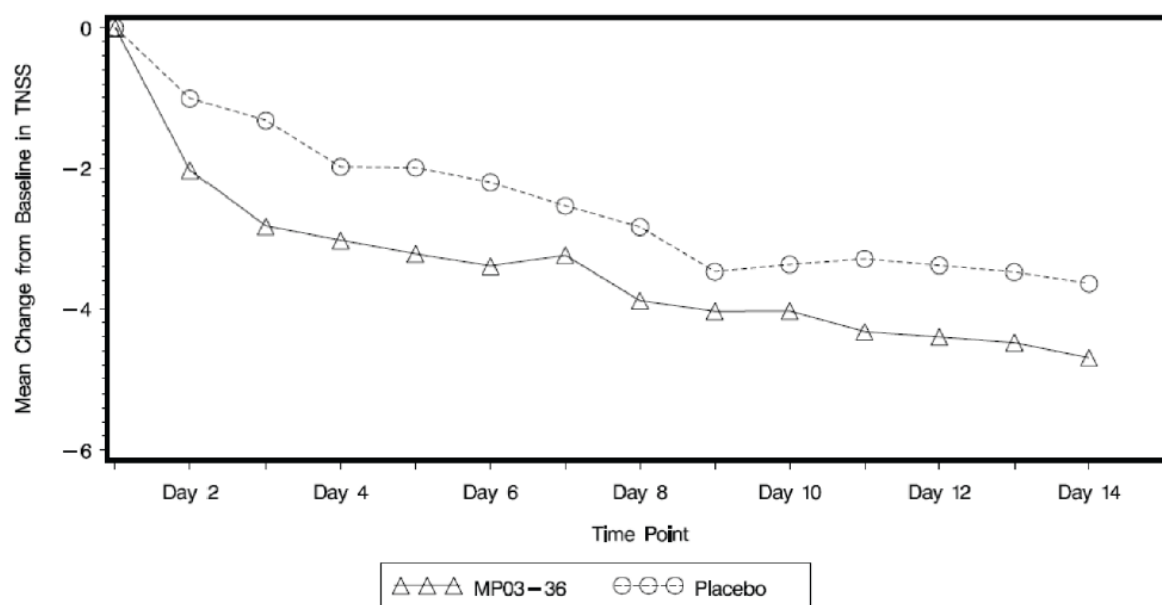
The results obtained in the re-analyses for primary and key secondary efficacy variable confirmed the results of the original report.

Sensitivity analyses including a treatment by site interaction term ( $p=0.0013$ ), based on raw data ( $p=0.0016$ ) and the overall analysis based on the PP set ( $p=0.0022$ ) yielded similar results

The time course of AM and PM combined reflective TNSS is shown in Figure 7. The difference between MP03-36 and placebo was significant at each treatment day except Day 7 ( $p=0.1030$ ), Day 9 ( $p=0.1865$ ), and Day 10 ( $p=0.1477$ )



Figure 7. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT

Secondary efficacy variables:

Overall, all secondary variables showed at least numerical superiority of MP03-36. Some secondary efficacy analyses including the key secondary variable are presented below

**AM instantaneous TNSS (end of 24-hour dosing interval, key secondary variable):** The instantaneous AM TNSS showed a trend-like superiority of MP03-36 vs. placebo in the overall analysis ( $p=0.0885$ , 95% CI: -0.62 to 0.04). The same was found in the sensitivity analyses. The difference between MP03-36 and placebo was significant at Day 6 and Day 12.

**Instantaneous TNSS:** The LS mean change from baseline in the instantaneous AM and PM combined TNSS demonstrated statistically significant improvement ( $p=0.023$ ) in the MP03-36 group when compared to the placebo group over the entire 14-day study period.

**Reflective SSCS:** The overall changes in the reflective SSCS (consisting of itchy eyes, postnasal drip, cough, and headache) demonstrated significant improvements ( $p=0.025$ ) in the MP03-36 group when compared to placebo

The results of this pivotal study using the MP03-36 dose regimen show that this dose is efficacious as compared to placebo on the primary efficacy variable of symptom control. A significant result on the key secondary variable was not demonstrated, though statistical significance was achieved on some of the other secondary variables.

Study 7 (SAR):

The objective of this study was to evaluate the efficacy and safety of MP03-36 at a dosage of two sprays per nostril once daily (AM) compared to placebo two sprays per nostril once daily (AM) in subjects with SAR. After a 1 week placebo run-in period, eligible subjects were randomized to the double-blind treatment period in a 1:1 ratio to the following treatment arms.

MP03-36 – two sprays per nostril once daily in the morning (AM)

Placebo - two sprays per nostril once daily in the morning (AM)

The treatment duration was 2 weeks

A total of 536 subjects were randomized at six sites. There was no obvious difference between the groups in the rates of premature discontinuations.

#### Primary efficacy variable:

After 2 weeks of treatment, the LS mean improvement from baseline in the 12-hour reflective AM and PM combined TNSS was statistically significant for the MP03-36 group ( $p < 0.001$ ) when compared to the placebo group.

Table 12. Combined AM and PM 12 hour reflective TNSS, ITT

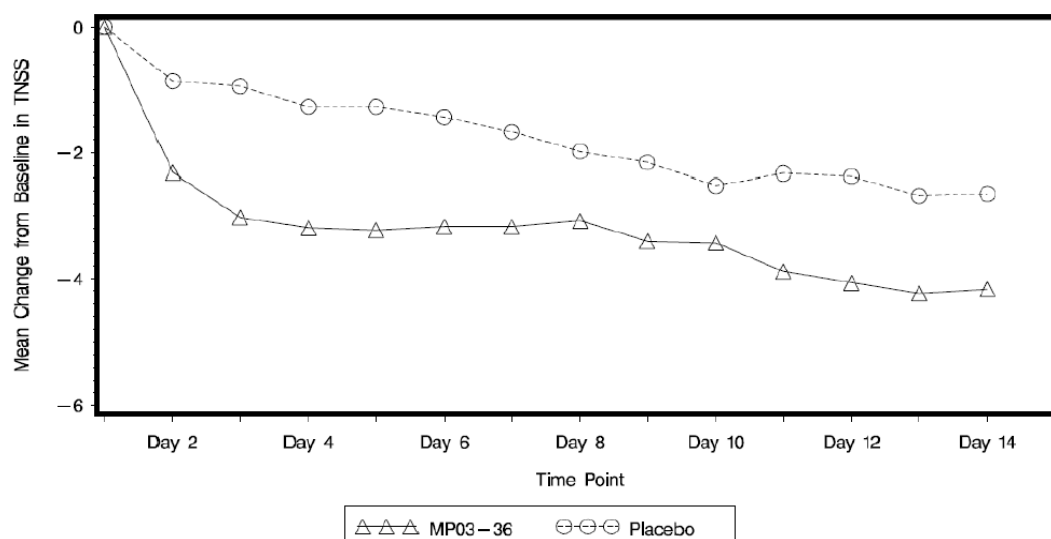
| Treatment groups <sup>a</sup> | Baseline, mean (SD) <sup>a</sup> | Change from baseline, LS mean (SE) <sup>b</sup> |                     |
|-------------------------------|----------------------------------|---|---------------------|
| MP03-36 (n=266)               | 18.50 (3.283)                    | -3.35 (0.243)                                   |                     |
| Placebo (n=266)               | 18.00 (3.334)                    | -1.85 (0.205)                                   |                     |
| Pairwise comparison           | Point estimates <sup>b</sup>     | P-value <sup>b,c</sup>                          | 95% CI <sup>b</sup> |
| MP03-36 vs. placebo           | -1.50                            | <0.0001   | -2.10,-0.91         |

The results obtained in the re-analyses for the primary and the key secondary efficacy variable confirmed the results of the original report.

Sensitivity analyses including a treatment by site interaction term ( $p < 0.0001$ ), based on raw data ( $p < 0.0001$ ) and the overall analysis based on the PP set ( $p < 0.0001$ ) yielded similar results

The time course of AM and PM combined reflective TNSS is shown in Figure 8. The difference between MP03-36 and placebo was significant at each treatment day except Day 10 ( $p = 0.0814$ ).

Figure 8. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT



#### Secondary efficacy variables:

Overall, all secondary variables showed at least numerical superiority of MP03-36. Some results of the secondary efficacy analysis including the key secondary efficacy variable are provided below.

**AM instantaneous TNSS (end of 24-hour dosing interval, key secondary variable):** The instantaneous AM TNSS showed a significant superiority of MP03-36 vs. placebo in the overall analysis ( $p < 0.0001$ , 95% CI: -0.99 to -0.39). The same was found in the sensitivity analyses. The difference between MP03-36 and placebo was significant at each treatment day.

**Instantaneous TNSS:** The LS mean change from baseline in the instantaneous AM and PM combined TNSS demonstrated statistically significant improvement ( $p < 0.001$ ) in the MP03-36 group when compared to the placebo group over the entire 14-day study period



**Reflective SSCS:** The overall changes in the reflective SSCS and each of its individual symptoms (itchy eyes, postnasal drip, cough, and headache) demonstrated significant improvements ( $p \leq 0.005$ ) in the MP03-36 group when compared to placebo

This study showed consistent statistically significant results on both the primary and key secondary efficacy variable as well as in the sensitivity analyses.

#### **Study 8 (SAR):**

The objective of this study was to evaluate the efficacy and safety of MP03-36 at a dosage of two sprays per nostril once daily (AM) compared to placebo two sprays per nostril once daily (AM) in subjects with SAR.

This study was conducted because one of the two earlier pivotal OD studies failed to demonstrate a statistically significant difference between MP03-36 and placebo for AM instantaneous scores, which was intended to assess the efficacy of MP03-36 at the dose trough and demonstrate the adequacy of the proposed dosing interval. One pivotal study did show a statistically significant difference for this key secondary endpoint but there was a need of replication to confirm the efficacy of OD dosing regimen.

After a 1-week placebo run-in period, eligible subjects were randomized to the double-blind treatment period in a 1:1 ratio to the following treatment arms.

MP03-36 – two sprays per nostril once daily in the morning (AM)

Placebo - two sprays per nostril once daily in the morning (AM)

The treatment duration was 2 weeks

Overall, 506 subjects were randomized at seven sites. There was no obvious difference between the groups in the rates of premature discontinuations.

#### **Primary efficacy variable:**

After 2 weeks of treatment, the LS mean improvement from baseline in the 12-hour reflective AM and PM combined TNSS was statistically significant for the MP03-36 group ( $p < 0.0001$ ) when compared to the placebo group

Table 13. Combined AM and PM 12 hour reflective TNSS, ITT

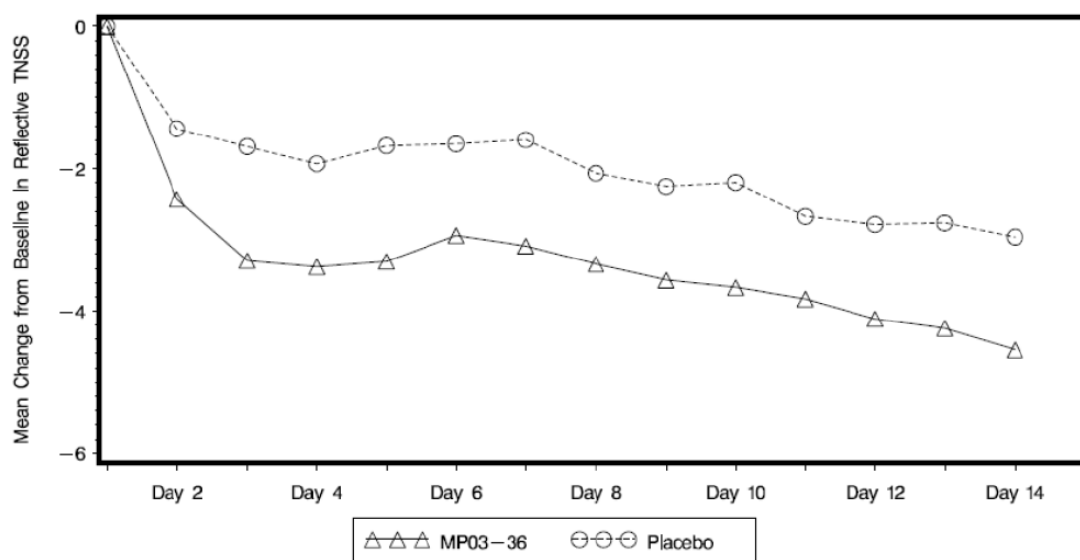
| <b>Treatment groups<sup>a</sup></b> | <b>Baseline, mean (SD)<sup>a</sup></b> | <b>Change from baseline, LS mean (SE)<sup>b</sup></b> |                           |
|-------------------------------------|--|---|---------------------------|
| MP03-36 (n=251)                     | 18.48 (3.23)                           | -3.48 (0.259)   |                           |
| Placebo (n=254)                     | 18.76 (3.30)                           | -2.17 (0.211)   |                           |
| <b>Pairwise comparison</b>          | <b>Point estimates<sup>b</sup></b>     | <b>P-value<sup>b,c</sup></b>                          | <b>95% CI<sup>b</sup></b> |
| MP03-36 vs. placebo                 | -1.32                                  | <0.0001   | -1.95, -0.68              |

The results obtained in the re-analyses for the primary and the key secondary efficacy variable confirmed the results of the original report.

Sensitivity analyses including a treatment by site interaction term ( $p < 0.0001$ ), based on raw data ( $p < 0.0001$ ) and the overall analysis based on the PP set ( $p = 0.0001$ ) yielded similar results

The time course of AM and PM combined reflective TNSS is shown in Figure 9. The difference between MP03-36 and placebo was significant at each treatment day.

Figure 9. Time course of combined AM and PM 12 hour reflective TNSS Means, ITT

**Secondary efficacy variables:**

Overall, all secondary variables showed at least numerical superiority of MP03-36 compared to placebo. Some secondary efficacy analysis results including the key secondary efficacy variable are provided below.

**AM instantaneous TNSS (end of 24-hour dosing interval, key secondary variable):** The instantaneous AM TNSS showed a significant superiority of MP03-36 vs. placebo in the overall analysis ( $p=0.0004$ , 95% CI: -0.89 to -0.26). The same was found in the sensitivity analyses. The difference between MP03-36 and placebo was significant at each treatment day with the exception of Day 6 ( $p=0.0714$ ) and Day 9 ( $p=0.0734$ ).

**Instantaneous TNSS:** The LS mean change from baseline in the instantaneous AM and PM combined TNSS demonstrated statistically significant ( $p<0.001$ ) improvements in the MP03-36 group when compared to the placebo group over the entire 14-day study period

**TOSS:** In this study also ocular symptoms were specifically documented and analysed as TOSS. The overall changes in the reflective TOSS as well as instantaneous TOSS were significantly superior ( $p<0.001$ ) after MP03-36 when compared to placebo. All individual symptoms (itchy eyes, watery eyes, and red eyes) of the TOSS contributed to this result with significant differences

**Post nasal drip (PND):** The overall improvement in PND (included in other studies as a symptom of SSCS) were after MP03-36 also significantly superior to placebo ( $p=0.002$ )

The results of this study were consistent with the results of the previous pivotal study. The results were statistically significant both for the primary and key secondary efficacy variable, as well as in the sensitivity analyses. The results provide conclusive evidence of the efficacy of a once daily dosing regimen of MP03-36 as compared to placebo.

**Summary of studies with once daily (OD) regimen**

Table 14. Main results of OD regimen studies

| Treatment arm | ITT/ completed | Main results, absolute changes from baseline, ITT sets |                 |                                    |                 |                                     |                                  |                                  |                     |
|---------------|----------------|--|-----------------|------------------------------------|-----------------|-------------------------------------|----------------------------------|----------------------------------|---------------------|
|               |                | Primary  |                 | Key secondary                      |                 | Secondary                           |                                  |                                  |                     |
|               |                | Reflective TNSS <sup>AM+PM</sup>                       | P-value vs. PLA | Instantaneous TNSS <sup>EoDI</sup> | P-value vs. PLA | Instantaneous TNSS <sup>AM+PM</sup> | Reflective SSCS <sup>AM+PM</sup> | Reflective TOSS <sup>AM+PM</sup> | RQLQ: Overall score |
|               |                | LS mean (SE)   |                 | LS mean (SE)                       |                 | P-value vs. PLA                     | P-value vs. PLA                  | P-value vs. PLA                  | P-value vs. PLA     |
| MP03-36 AM    | 53/53          | -3.85 (0.42)   | 0.378           | -1.97 (n.av.)                      | 0.094           | 0.089                               | 0.418                            | Not assessed                     | 0.104               |
| Placebo AM    | 23/22          | -2.77 (0.62)   |                 | -1.12 (n.av.)                      |                 |                                     |                                  |                                  |                     |
| MP03-36 PM    | 50/48          | -3.69 (0.48)   | 0.323           | -1.70 (n.av.)                      | 0.452           | 0.388                               | 0.464                            | Not assessed                     | 0.501               |
| Placebo PM    | 27/26          | -2.53 (0.48)   |                 | -1.33 (n.av.)                      |                 |                                     |                                  |                                  |                     |
| MP03-36       | 238/233        | -3.48 (0.26)   | 0.0017          | -1.34 (0.13)                       | 0.0885          | 0.023                               | 0.025                            | Not assessed                     | 0.048               |
| Placebo       | 242/234        | -2.42 (0.25)   |                 | -1.05 (0.12)                       |                 |                                     |                                  |                                  |                     |
| MP03-36       | 266/249        | -3.35 (0.24)   | <0.0001         | -1.32 (0.12)                       | <0.0001         | <0.001                              | <0.001                           | Not assessed                     | 0.023               |
| Placebo       | 266/250        | -1.85 (0.21)   |                 | -0.62 (0.11)                       |                 |                                     |                                  |                                  |                     |
| MP03-36       | 251/238        | -3.48 (0.26)   | <0.0001         | -1.38 (0.13)                       | 0.0004          | <0.001                              | Not assessed                     | <0.001                           | <0.001              |
| Placebo       | 254/240        | -2.17 (0.21)   |                 | -0.81 (0.11)                       |                 |                                     |                                  |                                  |                     |

**Clinical studies in special populations**

The applicant is proposing this higher strength Azelastine S 0.15% for use in children aged 6 years and above. The only data of this strength in this age group is provided by study 4 (above). In this study 159 children aged 6-11 years were exposed to MP03-36 1 spray per nostril BID for 4 weeks. This study showed that this dosing regimen was better than placebo on the primary efficacy variable, though none of the secondary efficacy variable reached statistical significance.

No significant safety concerns emerged from this study. The safety profile in children as seen from this study is comparable to the safety profile in adults. The availability of oral azelastine used in some EU countries in children reassures on systemic safety. Therefore, the only safety concern for which direct clinical data is not available is the “topical safety during long-term use” in children aged 6-11 years. The applicant has, therefore, included the following sentence in the SmPC: “Use longer than 4 weeks is not recommended in children 6-11 years due to lack of clinical data”.

**Analysis performed across trials (pooled analyses AND meta-analysis)****Pooled analysis on the BID regimen**

This clinical development programme allowed for reasonable pooling of two of the BID studies for the comparison MP03-36 BID with placebo; both studies were performed in SAR. Pooling of PAR with SAR studies was not considered reasonable because of the different severity of symptoms and the duration of the trials. Furthermore, the two PAR studies were not pooled because of different patient populations and dosages regimen (one versus two sprays per nostril BID) among them.

This pooled analysis sums up the data of 330 SAR patients treated with two sprays per nostril MP03-36 BID and 330 patients treated with matching placebo (also BID).

MP03-36 showed a clear-cut and statistically significant difference when compared to placebo

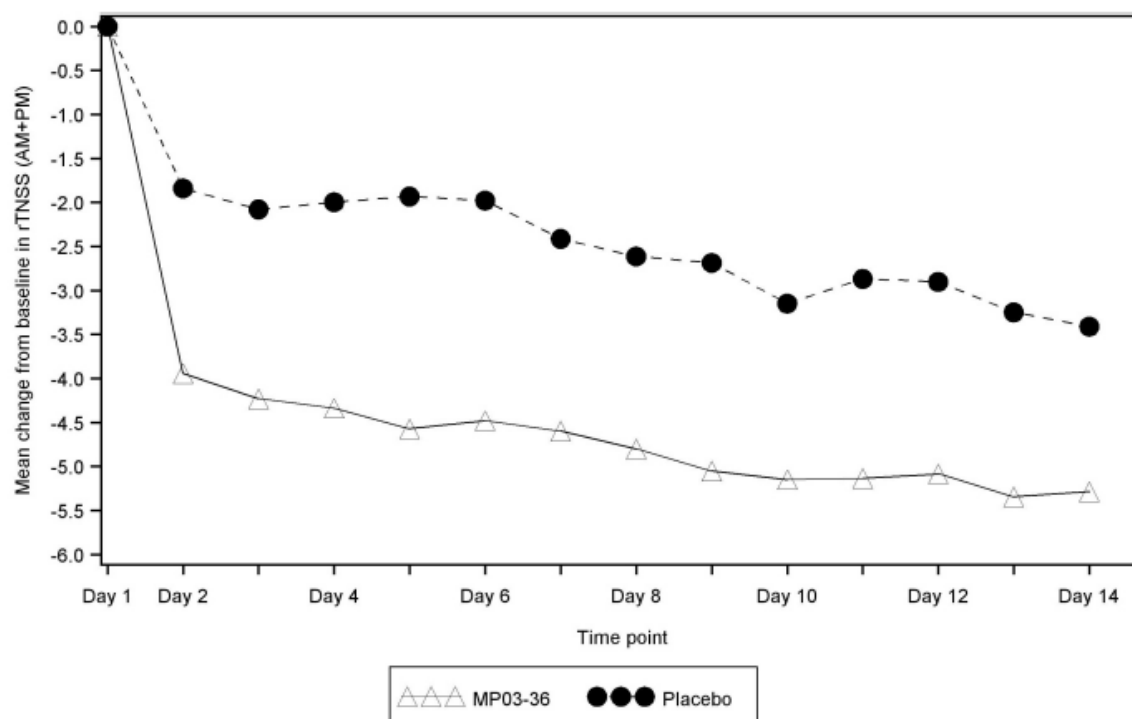
Table 15. Pooled analysis, SAR, BID: Combined AM and PM 12 hour reflective TNSS

**Table 13 Pooled analysis, SAR, BID: Combined AM and PM 12-h reflective TNSS**

| Treatment groups    | Baseline, mean (SD) | Change from baseline, LS mean (SE) |              |
|---------------------|---------------------|------------------------------------|--------------|
| MP03-36 BID         | 18.1 (3.1)          | -4.58 (0.240)                      |              |
| Placebo BID         | 18.0 (3.2)          | -2.58 (0.208)                      |              |
| Pairwise comparison | Point estimates     | P-value                            | 95% CI       |
| MP03-36 vs. placebo | -1.99               | <0.0001                            | -2.59, -1.40 |

The time course indicated significant differences between MP03-36 and placebo already on Day 2 and each of the following time points (all  $p < 0.0001$ ). Overall, there was no evidence for tachyphylaxis.

Figure 10. Pooled analysis, SAR, BID: Time course of combined AM and PM 12 hour reflective TNSS Means



Because individual studies were not designed to differentiate treatments in secondary variables, the pooled data provided more robust results.

Each individual nasal variable and each nasal symptom score showed statistically significant differences between MP03-36 and placebo (Table 16). The data indicate that the overall effect was well balanced, i.e. not driven by a large effect on a limited number of symptoms and no effect or even worsening in the other symptoms.

Table 16. Pooled analysis, SAR, BID: Overview on secondary nasal variables

|  | MP03-36 BID<br>Change from BL<br>LSmean (SE) | Placebo BID<br>Change from BL<br>LSmean (SE) | MP03-36 vs. Placebo |                          |             |
|--|--|--|---------------------|--------------------------|-------------|
|  |  |  | P-value             | Estimate<br>for $\Delta$ | 95% CI      |
| 12-h refl. TNSS <sup>AM</sup>                | -2.25 (0.12)                                 | -1.32 (0.10)                                 | <0.0001             | -0.93                    | -1.23,-0.63 |
| 12-h refl. TNSS <sup>PM</sup>                | -2.32 (0.12)                                 | -1.26 (0.11)                                 | <0.0001             | -1.06                    | -1.37,-0.75 |
| C. 12-h refl. itchy nose <sup>AM+PM</sup>    | -1.13 (0.07)                                 | -0.56 (0.06)                                 | <0.0001             | -0.57                    | -0.74,-0.40 |
| C. 12-h refl. nas. congest. <sup>AM+PM</sup> | -0.92 (0.06)                                 | -0.59 (0.05)                                 | <0.0001             | -0.33                    | -0.50,-0.17 |
| C. 12-h refl. runny nose <sup>AM+PM</sup>    | -1.17 (0.07)                                 | -0.68 (0.06)                                 | <0.0001             | -0.49                    | -0.66,-0.31 |
| C. 12-h refl. sneezing <sup>AM+PM</sup>      | -1.39 (0.07)                                 | -0.75 (0.06)                                 | <0.0001             | -0.64                    | -0.83,-0.46 |
| C. instant. TNSS <sup>AM</sup>               | -4.04 (0.25)                                 | -2.43 (0.21)                                 | <0.0001             | -1.62                    | -2.24,-1.00 |
| Instant. TNSS <sup>PM</sup>                  | -2.01 (0.13)                                 | -1.19 (0.11)                                 | <0.0001             | -0.82                    | -1.13,-0.51 |
| Instant. TNSS <sup>AM+PM</sup>               | -2.06 (0.14)                                 | -1.30 (0.12)                                 | <0.0001             | -0.76                    | -1.11,-0.41 |
| C. instant. itchy nose <sup>AM+PM</sup>      | -1.04 (0.07)                                 | -0.54 (0.06)                                 | <0.0001             | -0.50                    | -0.68,-0.32 |
| C. instant. nas. congest. <sup>AM+PM</sup>   | -0.83 (0.07)                                 | -0.57 (0.06)                                 | 0.0023              | -0.26                    | -0.42,-0.09 |
| C. instant. runny nose <sup>AM+PM</sup>      | -1.00 (0.07)                                 | -0.62 (0.06)                                 | <0.0001             | -0.38                    | -0.56,-0.20 |
| C. instant. sneezing <sup>AM+PM</sup>        | -1.25 (0.07)                                 | -0.64 (0.07)                                 | <0.0001             | -0.62                    | -0.81,-0.42 |

In the pooled analysis of the BID data, each domain of the RQLQ as well as the overall score showed statistically significant differences between MP03-36 and placebo.

Table 17. Pooled analysis, SAR, BID: Overview on RQLQ

| Domain               | MP03-36 BID<br>Change from BL<br>LSmean (SE) | Placebo BID<br>Change from BL<br>LSmean (SE) | MP03-36 vs. Placebo |                          |             |
|----------------------|--|--|---------------------|--------------------------|-------------|
|                      |  |  | P-value             | Estimate<br>for $\Delta$ | 95% CI      |
| Activity             | -1.49 (0.09)                                 | -1.09 (0.08)                                 | 0.0008              | -0.40                    | -0.63,-0.17 |
| Sleep                | -1.33 (0.08)                                 | -0.84 (0.08)                                 | <0.0001             | -0.48                    | -0.69,-0.28 |
| Eye symptoms         | -1.51 (0.09)                                 | -0.90 (0.08)                                 | <0.0001             | -0.61                    | -0.84,-0.38 |
| Practical problems   | -1.52 (0.08)                                 | -1.01 (0.08)                                 | <0.0001             | -0.52                    | -0.74,-0.30 |
| Nasal symptoms       | -1.51 (0.08)                                 | -1.02 (0.08)                                 | <0.0001             | -0.49                    | -0.70,-0.27 |
| Nonhayfever symptoms | -1.23 (0.07)                                 | -0.86 (0.07)                                 | 0.0002              | -0.37                    | -0.57,-0.18 |
| Emotions             | -1.32 (0.08)                                 | -0.91 (0.08)                                 | 0.0002              | -0.41                    | -0.62,-0.19 |
| Overall              | -1.37 (0.07)                                 | -0.93 (0.07)                                 | <0.0001             | -0.44                    | -0.63,-0.26 |

Taking in to account the overall efficacy results of the BID dosing regimen, the efficacy results in patients with SAR is convincing on efficacy based on the change in the efficacy variables.

#### Pooled analysis on the OD regimen

This clinical development programme allowed for reasonable pooling of the three OD confirmatory studies; all these studies were performed in SAR. The pilot study was not pooled because it was conducted in PAR, consequently with different severity of symptoms and duration of the trial.

This pooled analysis (ITT) sums up the data of 755 SAR patients treated with two sprays per nostril MP03-36 OD and 762 SAR patients treated with matching placebo (also OD).

MP03-36 showed a clear-cut and statistically significant difference when compared to placebo.

Table 18. Pooled analysis, SAR, OD: Combined AM and PM 12 hour reflective TNSS

| Treatment groups    | Baseline, mean (SD) | Change from baseline, LS mean (SE) |             |
|---------------------|---------------------|------------------------------------|-------------|
| MP03-36             | 18.3 (3.4)          | -3.38 (0.144)                      |             |
| Placebo             | 18.2 (3.3)          | -2.14 (0.127)                      |             |
| Pairwise comparison | Point estimates     | P-value                            | 95% CI      |
| MP03-36 vs. placebo | -1.24               | <0.0001                            | -1.59,-0.88 |

The time course indicated significant differences between MP03-36 and placebo already on Day 2 and each of the following time points (all  $p < 0.0001$ ). Overall, there was no evidence for tachyphylaxis.

The change from baseline in the AM instantaneous TNSS (end of 24-hour dosing interval, key secondary variable) for the entire 14-day study period showed a clear-cut and statistically significant difference when compared to placebo (Table 19) demonstrating the adequacy of the proposed dosing interval. The point estimate for the difference between MP03-36 OD and matching placebo (-0.51) was lower than that observed in the combined reflective TNSS due to the reduced baseline level of about 9.7 score points.

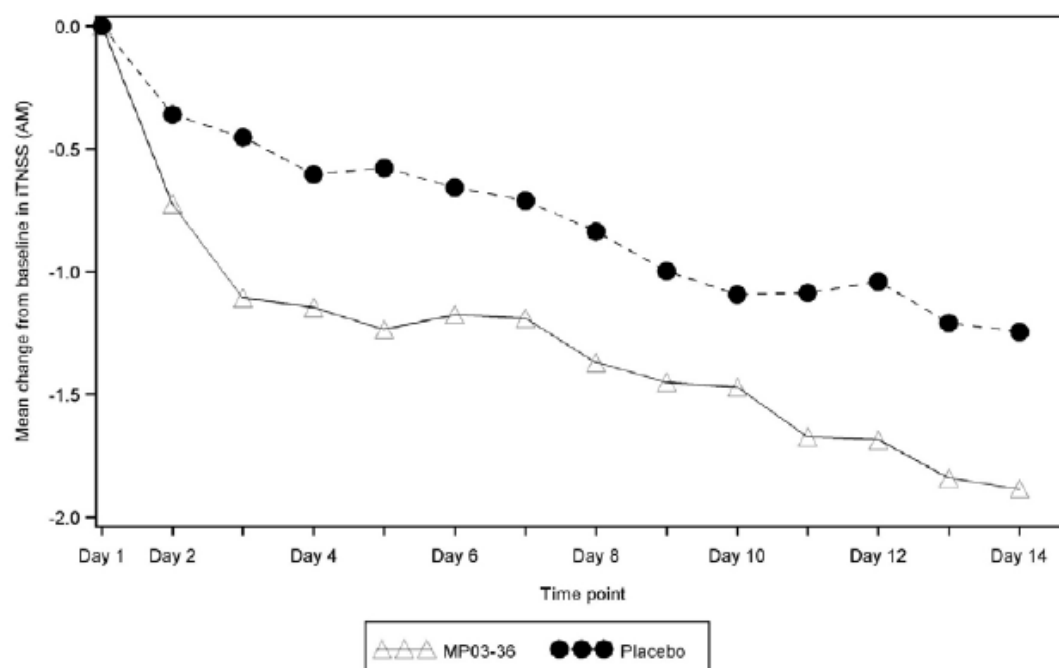
Table 19. Pooled analysis, SAR, OD: Instantaneous AM TNSS

| Treatment groups    | Baseline, mean (SD) | Change from baseline, LS mean (SE) |             |
|---------------------|---------------------|------------------------------------|-------------|
| MP03-36             | 8.59 (2.02)         | -1.31 (0.071)                      |             |
| Placebo             | 8.54 (1.95)         | -0.79 (0.064)                      |             |
| Pairwise comparison | Point estimates     | P-value                            | 95% CI      |
| MP03-36 vs. placebo | -0.51               | <0.0001                            | -0.69,-0.33 |

The time course of the instantaneous AM TNSS also indicated significant differences between MP03-36 and placebo already on Day 2 and each of the following time points (all  $p < 0.005$ ), again without evidence for tachyphylaxis.



Figure 11. Pooled analysis, SAR, OD: Time course of the instantaneous AM TNSS Means



Because individual studies were not designed to differentiate treatments in secondary variables, the pooled data provided more robust results.

In the pooled analysis of the OD data each individual nasal variable and each nasal symptom score showed statistically significant differences between MP03-36 and placebo (Table 20). The data again indicated that the overall effect was well balanced and it was not driven by a large effect on a limited number of symptoms and no effect or even worsening in the other symptoms.

Table 20. Pooled analysis, SAR, OD: Overview on secondary nasal variables

|  | MP03-36                       | Placebo                       | MP03-36 vs. Placebo |                          |             |
|--|-------------------------------|-------------------------------|---------------------|--------------------------|-------------|
|  | Change from BL<br>LSmean (SE) | Change from BL<br>LSmean (SE) | P-value             | Estimate<br>for $\Delta$ | 95% CI      |
| 12-h refl. TNSS <sup>AM</sup>                | -1.64 (0.07)                  | -1.11 (0.06)                  | <0.0001             | -0.53                    | -0.71,-0.36 |
| 12-h refl. TNSS <sup>PM</sup>                | -1.75 (0.08)                  | -1.03 (0.07)                  | <0.0001             | -0.71                    | -0.91,-0.52 |
| C. 12-h refl. itchy nose <sup>AM+PM</sup>    | -0.84 (0.04)                  | -0.49 (0.04)                  | <0.0001             | -0.35                    | -0.46,-0.25 |
| C. 12-h refl. nas. congest. <sup>AM+PM</sup> | -0.73 (0.04)                  | -0.51 (0.03)                  | <0.0001             | -0.22                    | -0.31,-0.13 |
| C. 12-h refl. runny nose <sup>AM+PM</sup>    | -0.90 (0.04)                  | -0.58 (0.04)                  | <0.0001             | -0.32                    | -0.43,-0.21 |
| C. 12-h refl. sneezing <sup>AM+PM</sup>      | -0.95 (0.04)                  | -0.57 (0.04)                  | <0.0001             | -0.38                    | -0.49,-0.27 |
| C. instantaneous TNSS <sup>AM+PM</sup>       | -2.87 (0.14)                  | -1.67 (0.13)                  | <0.0001             | -1.20                    | -1.56,-0.84 |
| Instant. TNSS <sup>AM</sup>                  | -1.31 (0.07)                  | -0.79 (0.06)                  | <0.0001             | -0.51                    | -0.69,-0.33 |
| Instant. TNSS <sup>PM</sup>                  | -1.60 (0.08)                  | -0.90 (0.07)                  | <0.0001             | -0.70                    | -0.90,-0.50 |
| C. instant. itchy nose <sup>AM+PM</sup>      | -0.74 (0.04)                  | -0.38 (0.04)                  | <0.0001             | -0.36                    | -0.46,-0.25 |
| C. instant. nas. congest. <sup>AM+PM</sup>   | -0.64 (0.04)                  | -0.45 (0.03)                  | <0.0001             | -0.19                    | -0.29,-0.10 |
| C. instant. runny nose <sup>AM+PM</sup>      | -0.78 (0.04)                  | -0.50 (0.04)                  | <0.0001             | -0.28                    | -0.39,-0.18 |
| C. instant. sneezing <sup>AM+PM</sup>        | -0.74 (0.04)                  | -0.37 (0.04)                  | <0.0001             | -0.37                    | -0.48,-0.25 |

The SSCS was documented in two SAR/OD studies. In the pooled analysis of these OD data each score of the SSCS showed statistically significant differences between MP03-36 and placebo.

Table 21. Pooled analysis, SAR, OD: Overview on SSCS

|  | MP03-36                       | Placebo                       | MP03-36 vs. Placebo |                   |             |
|--|-------------------------------|-------------------------------|---------------------|-------------------|-------------|
|  | Change from BL<br>LSmean (SE) | Change from BL<br>LSmean (SE) | P-value             | Estimate<br>for Δ | 95% CI      |
| C. 12-h refl. SSCS <sup>AM+PM</sup>        | -2.54 (0.16)                  | -1.56 (0.15)                  | <0.0001             | -0.98             | -1.38,-0.58 |
| 12-h refl. SSCS <sup>AM</sup>              | -1.28 (0.08)                  | -0.78 (0.07)                  | <0.0001             | -0.49             | -0.69,-0.29 |
| 12-h refl. SSCS <sup>PM</sup>              | -1.28 (0.09)                  | -0.78 (0.08)                  | <0.0001             | -0.50             | -0.72,-0.28 |
| C. 12-h refl. cough <sup>AM+PM</sup>       | -0.59 (0.05)                  | -0.34 (0.05)                  | 0.0003              | -0.25             | -0.39,-0.12 |
| C. 12-h refl. postn. drip <sup>AM+PM</sup> | -0.71 (0.05)                  | -0.48 (0.05)                  | 0.0008              | -0.22             | -0.35,-0.09 |
| C. 12-h refl. itchy eyes <sup>AM+PM</sup>  | -0.79 (0.05)                  | -0.44 (0.05)                  | <0.0001             | -0.35             | -0.48,-0.21 |
| C. 12-h refl. headache <sup>AM+PM</sup>    | -0.49 (0.05)                  | -0.29 (0.05)                  | 0.0032              | -0.20             | -0.33,-0.07 |

In the pooled analysis of the OD data each domain of the RQLQ as well as the overall score showed statistically significant differences between MP03-36 and placebo.

Table 22. Pooled analysis, SAR, OD: Overview on RQLQ

| Domain               | MP03-36                       | Placebo                       | MP03-36 vs. Placebo |                   |             |
|----------------------|-------------------------------|-------------------------------|---------------------|-------------------|-------------|
|                      | Change from BL<br>LSmean (SE) | Change from BL<br>LSmean (SE) | P-value             | Estimate<br>for Δ | 95% CI      |
| Activity             | -1.19 (0.06)                  | -0.91 (0.06)                  | 0.0005              | -0.27             | -0.43,-0.12 |
| Sleep                | -0.97 (0.05)                  | -0.66 (0.05)                  | <0.0001             | -0.31             | -0.45,-0.16 |
| Eye symptoms         | -1.12 (0.05)                  | -0.82 (0.05)                  | <0.0001             | -0.30             | -0.45,-0.15 |
| Practical problems   | -1.21 (0.05)                  | -0.83 (0.05)                  | <0.0001             | -0.39             | -0.53,-0.24 |
| Nasal symptoms       | -1.14 (0.05)                  | -0.84 (0.05)                  | <0.0001             | -0.30             | -0.44,-0.16 |
| Nonhayfever symptoms | -0.82 (0.05)                  | -0.64 (0.05)                  | 0.0046              | -0.18             | -0.31,-0.06 |
| Emotions             | -0.98 (0.05)                  | -0.70 (0.05)                  | 0.0001              | -0.28             | -0.42,-0.14 |
| Overall              | -1.03 (0.05)                  | -0.75 (0.04)                  | <0.0001             | -0.28             | -0.41,-0.16 |

The pooled analysis shows significant results for the treatment arm as compared to placebo.

## Supportive studies

### Study 9 (PAR)

This study evaluated the long-term efficacy and also the long term safety of MP03-36. The aim of this study was to evaluate the long-term safety and tolerability of the highest suggested dose with MP03-36 (two sprays per nostril BID) over a 1-year period in subjects with PAR.

This is the only efficacy/safety study that was not the standard (randomized, double-blind, placebo-controlled, parallel group study) and therefore its design is described in more detail.

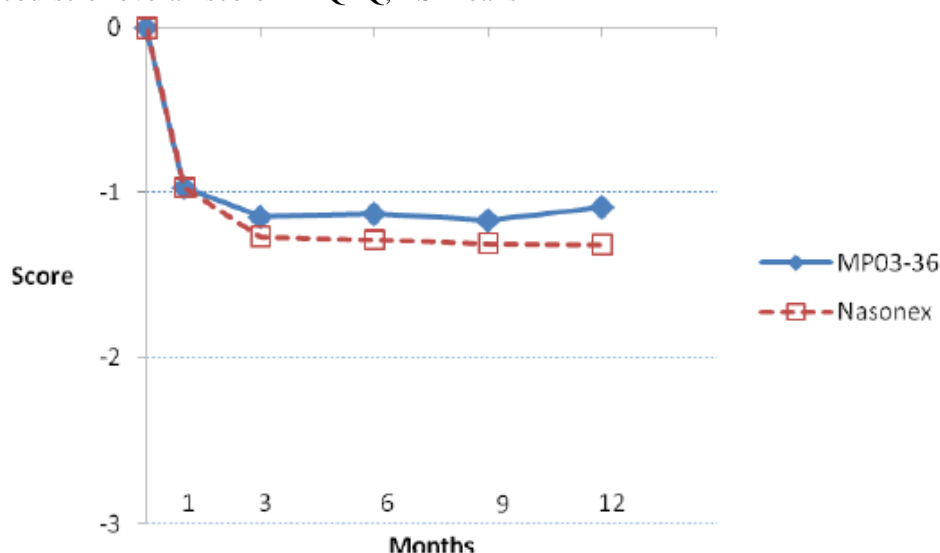
This was a randomized, open-label, active-controlled parallel-group study in subjects with PAR. Subjects who participated in either Study 2 or Study 5 above (safety and efficacy of MP03-36 in treating PAR) were eligible to participate in this study. Subjects who participated in these studies fulfilled their Day 28 final visit and the randomization visit for this study in the same visit. Every effort was made to randomize subjects directly from Study 2 or Study 5 into this study on the day of their last visit or within 14 days after completing these studies. Alternatively, newly identified subjects not participating in Study 2 or Study 5 who met the study entry criteria were enrolled following an initial 2 to 7 day screening period. This screening period applied only to newly identified subjects or to subjects who had completed their final visit for Study 2/Study 5 more than 14 days prior to the first visit for this study. Qualified subjects were randomized in a 2:1 ratio to treatment with MP03-36, 2 sprays per nostril twice daily or Nasonex® nasal spray two sprays per nostril once daily.

Efficacy evaluation was secondary; therefore, the only efficacy variable documented in this study was the RQLQ. Mometasone furoate (Nasonex®, two sprays per nostril OD) was included as an active control.

The applicant asserts that as the long-term efficacy of azelastine has already been established with lower dose strengths than which is proposed in this application, confirmatory long term efficacy data are not needed. The evaluation of RQLQ in this one year study is sufficient to monitor maintenance of effect. The open study design is considered acceptable because if there was any bias this would be expected to be in favour of the well established mometasone nasal spray.

At 1 year of treatment or early termination, the RQLQ indicated significant mean improvements (vs. baseline) in the overall score of 0.90 in the MP03-36 group and 1.11 in the Nasonex group ( $p=0.037$  between the groups). The difference between MP03-36 and Nasonex was small. All the individual dimensions of the RQLQ always showed significant improvements in both groups vs. baseline. Both treatments maintained efficacy over time as indicated in the time course of the overall score

Figure 12. Time course of overall score in RQLQ, LS Means



The significant improvements from baseline in RQLQ scores in both treatment groups indicated that subjects with PAR were compliant with medication and responsive to therapy. Although the RQLQ suggested more favourable outcome after Nasonex, this instrument indicated long-term efficacy of MP03-36. There was no evidence for tachyphylaxis.

**Safety Results:** In this study, MP03-36 was shown to be safe with long-term use. Most adverse events were of mild or moderate severity, and were primarily local effects, in particular dysgeusia. In addition to dysgeusia, the most common events ( $>5\%$  and  $<14\%$ ) in this group included nasal discomfort, sinusitis, upper respiratory tract infection, epistaxis, nasopharyngitis, and headache. There were no deaths, serious adverse events, or unexpected adverse events related to therapy in the MP03-36 group. No episodes of nasal ulceration, nasal septal perforation or episodes of moderate or severe epistaxis were observed in the MP03-36 group. Most findings on the focused head and neck evaluation were mild or moderate, and among subjects with severe findings for mucosal oedema and nasal discharge, there were moderate decreases following 12 months of MP03-36 treatment (from 23 subjects to 15 subjects and from 6 subjects to 4 subjects, respectively).

This is an open-label study and further there was no placebo-control arm. Therefore, any conclusions on long-term maintenance of efficacy from this study are not robust. This study provides useful information on the long-term safety of the higher dose strength, but again for the safety assessment, the lack of placebo control arm is a minor hindrance. The safety data is in comparison to Nasonex, which is a different class of drug. However, the safety data *per se* does not raise any new safety concerns.



**Overall conclusions on clinical efficacy**

Azelastine S 0.1% nasal spray is licensed for use in children aged 6 years and above. The applicant has applied for a line extension for a higher strength of 0.15%, as follows:

- a) Azelastine S 0.15% two sprays in each nostril BID in adults and adolescents 12 years and above
- b) Azelastine S 0.15% two sprays in each nostril OD in adults and children aged 12 years and above
- c) Azelastine S 0.15% one spray in each nostril BID in children aged 6 years and above

The first two dosage regimens are in adults and adolescents. There are three studies to support the first dose regimen, two in SAR patients and one in PAR patients. The efficacy results in SAR patients were more compelling than the efficacy results in PAR patients. All these studies met the primary efficacy endpoint. Though statistical significance on the secondary endpoints was not consistently met, they can be considered generally supportive of the conclusion of efficacy.

There are four studies in support of the second dose regimen. Of these one was a pilot study and the other three were pivotal studies. Two of the pivotal studies showed significant results on the primary efficacy variable and the key secondary efficacy variable. One study showed significant results on the primary efficacy variable only.

For the third dosage regimen, the applicant has submitted the results of a 4-week study in children aged 6 to 11 years with PAR. This study showed significant results in the primary efficacy variable and numerical superiority, but not significant results in the secondary efficacy variable. It is acknowledged that demonstration of efficacy in PAR is difficult. As well as this, the lower dose of Azelastine is already approved at this dosage regimen in this age group.

The aim of the development of the higher dose strength is to offer more treatment options to the treating physician to tailor to the needs of the individual patient before considering other treatment options. The applicant has presented and discussed the results of the pivotal studies, even in the absence of formal comparison to the lower dose-strength, to show that there was clear evidence that the rate of efficacy/response was higher with the higher-dose strength as compared to the lower-dose strength, supporting this regimen.

**Safety****Introduction**

The safety profile of azelastine 0.1% nasal spray is well established and has been accepted previously. Moreover the active substance has been available for a long time. An oral azelastine formulation has been marketed in some European countries for a longer time period than the nasal product.

In the clinical development of this higher strength (0.15%) nasal spray MP03-36, there were in total 10 clinical studies. There were eight placebo-controlled studies investigating clinical efficacy as primary objective and one active-controlled long-term (1 year) study investigating clinical safety as primary objective. All of the studies were randomized, parallel-group trials

All studies except one were conducted in adolescents and adults, while one was conducted in children of 6 to 11 years. This was also the only study that investigated the one spray per nostril, in this case BID, while all other studies investigated two sprays per nostril, either OD or BID.

**Patient exposure**

In the overall clinical development program of MP03-36 (including the healthy volunteers in the pharmacokinetic study), there were 4649 subjects who were evaluable for safety. Of these, 2189 received MP03-36, 551 received MP03-33, 171 received Astelin, 237 received Nasonex, and 1501

received placebo. Considering that 57 of 226 patients enrolled in one study were already exposed to MP03-36 in previous studies, over 2100 individual patients were exposed to MP03-36.

The clinical development programme allowed for reasonable pooling of the seven placebo-controlled studies in patients  $\geq 12$  years and a presentation by study duration of either two (SAR studies) or 4 weeks (PAR studies) and by dosage regimen (two sprays per nostril BID vs. two sprays per nostril OD).

This Safety Population consisted of a total of 2513 subjects with SAR and 737 subjects with PAR, who received at least one dose of study medication (excluding subjects who received Astelin). Of the 2513 subjects with SAR, 1247 were treated with MP03-36, 170 were treated with MP03-33, and 1096 were treated with placebo. More than 95% of the subjects in each treatment group completed the SAR studies.

Of the 737 subjects with PAR, 297 were treated with MP03-36, 197 were treated with MP03-33 and 243 were treated with placebo. More than 91% of the subjects in each treatment group completed the PAR studies. Overall, 1544 subjects received MP03-36 and 1339 subjects received placebo

The data of the children's study (Study 4) and the active-controlled long-term study (Study 9) were not pooled owing to the differences in study population, investigated dosage, design or duration and are presented separately.

The 703 subjects who were randomised to the long-term safety study included 146 (20.8%) subjects following their participation in Study 2, 80 (11.4%) subjects following their participation in Study 5, and 477 (67.9%) subjects who were enrolled only in the long term safety study (Study 9). However, because incidences of adverse events were separately evaluated in these studies, all subjects in Study 9 could be regarded as new patients for this summary of clinical safety. Of these 703 subjects, 466 received MP03-36 and 237 received Nasonex. 468 subjects completed the study, of these 290 (62.2%) were from the MP03-36 group and 178 (75.1%) were from the Nasonex group

Study 4 randomized 489 children (between 6 and 11 years) with PAR, to twice daily treatment with one spray per nostril for 4 weeks of either MP03-36 (n=161), MP03-33 (n=166), or placebo (n=162); all were evaluable for safety. More than 90% of the subjects in each treatment group completed the study. The mean duration of exposure differed only marginally between the groups (range between 27.7 and 28.3 days); the median exposure was 29 days in each group. While this study provides adequate short-term safety data in this subgroup, there is no data on long-term safety in children aged 6-11 years for the proposed higher dose strength.

### Adverse events

The table below provides an overview of the adverse events in the placebo controlled studies.

Table 1. Overview of adverse events in placebo-controlled studies

|                                       | MP03-36    |           |            | MP03-33   | Placebo    |           |           |
|---------------------------------------|------------|-----------|------------|-----------|------------|-----------|-----------|
|                                       | Any        | BID       | OD         | BID       | Any        | BID       | OD        |
| Safety evaluable (N)                  | 1544       | 523       | 1021       | 367       | 1339       | 523       | 816       |
| Number of AE reported                 | 453        | 146       | 307        | 130       | 251        | 118       | 133       |
| Number of "related" AE reported       | 284        | 95        | 189        | 80        | 91         | 45        | 46        |
| Number (%) subjects with any AEs      | 296 (19.2) | 98 (18.7) | 198 (19.4) | 85 (23.2) | 188 (14.0) | 90 (17.2) | 98 (12.0) |
| Number (%) subjects w. "related" AEs  | 195 (12.6) | 63 (12.0) | 132 (12.9) | 54 (14.7) | 72 (5.4)   | 36 (6.9)  | 36 (4.4)  |
| Number (%) subjects w. serious AEs    | 0          | 0         | 0          | 0         | 2 (0.1)    | 2 (0.4)   | 0         |
| Number (%) of deaths                  | 0          | 0         | 0          | 0         | 0          | 0         | 0         |
| Number (%) subjects who discontinued* | 73 (4.7)   | 27 (5.2)  | 46 (4.5)   | 21 (5.7)  | 74 (5.5)   | 30 (5.7)  | 44 (5.4)  |
| Number (%) discontinuations due to AE | 30 (1.9)   | 16 (3.1)  | 14 (1.4)   | 7 (1.9)   | 20 (1.5)   | 12 (2.3)  | 8 (1.0)   |

In the long-term (1-year) study, the percentage of subjects with adverse events was 75% (349/466) with MP03-36 administered 2 sprays per nostril twice daily and 69% (163/237) with Nasonex administered 2 sprays per nostril once daily. 11.6% of the subjects discontinued from the MP03-36 group due to

adverse events (dysgeusia and nasal discomfort were the most commonly reported adverse events), and 7.2% of the subjects discontinued from the Nasonex group.

In Study 4 more children discontinued due to adverse events from the placebo group (6/162, 3.7%) than from the active groups (MP03-36: 2/161, 1.2%; MP03-33: 0, 0%). The percentage of children with adverse events was 23.6% with MP03-36, 25.9% with MP03-33, and 23.5% with placebo.

The following table presents a summary of the adverse event data in the seven placebo-controlled studies and the long-term safety study.

Table 2. Most common adverse events in pooled analysis and long-term study

|  | Pooled analysis |            | Long-term safety study |                      |
|--|-----------------|------------|------------------------|----------------------|
|  | MP03-36         | Placebo    | MP03-36                | Nasonex <sup>®</sup> |
|  | N (%)           | N (%)      | N (%)                  | N (%)                |
| SAF                                      | 1544 (100)      | 1339 (100) | 466 (100)              | 237 (100)            |
| Any adverse event                        | 296 (19.2)      | 188 (14.0) | 349 (74.9)             | 163 (68.8)           |
| Dysgeusia                                | 69 (4.5)        | 9 (0.7)    | 62 (13.3)              | 3 (1.3)              |
| Nasal discomfort                         | 55 (3.6)        | 19 (1.4)   | 46 (9.9)               | 19 (8.0)             |
| Epistaxis                                | 26 (1.7)        | 21 (1.6)   | 43 (9.2)               | 24 (10.1)            |
| Sneezing                                 | 23 (1.5)        | 1 (0.1)    | 14 (3.0)               | 0 (0.0)              |
| Headache                                 | 19 (1.2)        | 21 (1.6)   | 41 (8.8)               | 30 (12.7)            |
| Upper respiratory tract infection        | 11 (0.7)        | 9 (0.7)    | 43 (9.2)               | 28 (11.8)            |
| Somnolence                               | 11 (0.7)        | 1 (0.1)    | 17 (3.6)               | 1 (0.4)              |
| Nasal mucosal disorder                   | 9 (0.6)         | 6 (0.4)    | 1 (0.2)                | 1 (0.4)              |
| Pharyngolaryngeal pain                   | 8 (0.5)         | 9 (0.7)    | 22 (4.7)               | 14 (5.9)             |
| Fatigue                                  | 8 (0.5)         | 2 (0.1)    | 19 (4.1)               | 2 (0.8)              |
| Sinusitis                                | 7 (0.5)         | 5 (0.4)    | 44 (9.4)               | 19 (8.0)             |
| Nausea                                   | 7 (0.5)         | 5 (0.4)    | 9 (1.9)                | 5 (2.1)              |
| Nasopharyngitis                          | 6 (0.4)         | 6 (0.4)    | 43 (9.2)               | 20 (8.4)             |
| Bronchitis                               | 6 (0.4)         | 1 (0.1)    | 19 (4.1)               | 6 (2.5)              |
| Cough                                    | 6 (0.4)         | 2 (0.1)    | 15 (3.2)               | 12 (5.1)             |
| Sinus headache                           | 6 (0.4)         | 6 (0.4)    | 15 (3.2)               | 4 (1.7)              |
| Gastroenteritis viral                    | 5 (0.3)         | 4 (0.3)    | 8 (1.7)                | 10 (4.2)             |
| Pyrexia                                  | 5 (0.3)         | 6 (0.4)    | 5 (1.1)                | 8 (3.4)              |
| Dizziness                                | 5 (0.3)         | 2 (0.1)    | 4 (0.9)                | 5 (2.1)              |
| Lacrimation increased                    | 5 (0.3)         | 0          | 2 (0.4)                | 3 (1.3)              |
| Back pain                                | 4 (0.3)         | 2 (0.1)    | 16 (3.4)               | 5 (2.1)              |
| Throat irritation                        | 4 (0.3)         | 1 (0.1)    | 4 (0.9)                | 1 (0.4)              |
| Blood pressure increased                 | 4 (0.3)         | 0          | 0                      | 1 (0.4)              |
| Influenza                                | 3 (0.2)         | 0          | 15 (3.2)               | 9 (3.8)              |
| Mucosal erosion                          | 0               | 0          | 13 (2.8)               | 6 (2.5)              |
| Rhinitis allergic (or rhinitis seasonal) | 0               | 1 (0.1)    | 11 (2.4)               | 4 (1.7)              |

Overall a relevant difference in the incidence of adverse events between MP03-36 and placebo were seen for the following events: Dysgeusia, nasal discomfort, sneezing, somnolence, fatigue, bronchitis, cough, lacrimation increased and blood pressure increased.

The below table provides an analysis of adverse events by dose.

Table 3. Incidence of adverse events by dose and regimen

|                          | <b>MP03-36 OD</b> |          | <b>MP03-36 BID</b> |          | <b>MP03-33 BID</b> |          | <b>Placebo (any)</b> |          |
|--------------------------|-------------------|----------|--------------------|----------|--------------------|----------|----------------------|----------|
|                          | <b>N</b>          | <b>%</b> | <b>N</b>           | <b>%</b> | <b>N</b>           | <b>%</b> | <b>N</b>             | <b>%</b> |
| SAF                      | 1021              | 100      | 523                | 100      | 367                | 100      | 1339                 | 100      |
| Dysgeusia                | 38                | 3.7      | 31                 | 5.9      | 27                 | 7.4      | 9                    | 0.7      |
| Nasal discomfort         | 37                | 3.6      | 18                 | 3.4      | 12                 | 3.3      | 19                   | 1.4      |
| Sneezing                 | 14                | 1.4      | 9                  | 1.7      | 1                  | 0.3      | 1                    | 0.1      |
| Somnolence               | 5                 | 0.5      | 6                  | 1.1      | 1                  | 0.3      | 1                    | 0.1      |
| Fatigue                  | 3                 | 0.3      | 5                  | 1.0      | 0                  | 0.0      | 2                    | 0.1      |
| Bronchitis               | 6                 | 0.6      | 0                  | 0.0      | 0                  | 0.0      | 1                    | 0.1      |
| Cough                    | 3                 | 0.3      | 3                  | 0.6      | 2                  | 0.5      | 2                    | 0.1      |
| Lacrimation increased    | 4                 | 0.4      | 1                  | 0.2      | 0                  | 0.0      | 0                    | 0.0      |
| Blood pressure increased | 3                 | 0.3      | 1                  | 0.2      | 0                  | 0.0      | 0                    | 0.0      |

Source: Module 2.7.4, Table 10.

\* Confined to those adverse events that obviously occurred more frequently after MP03-36 than after placebo

An analysis of adverse events as compared to placebo shows that most of the events were consistent with the established safety profile of azelastine. The only events that were not already described for azelastine S 0.1% spray include cough, lacrimation increased, bronchitis and increased blood pressure. However, for these events generally a dose-response was not seen and/or long-term safety data did not support their classification as adverse drug reaction. For bronchitis none of the cases were considered related to treatment by the investigator.

The below table displays the most common adverse events that occurred in the children's study in comparison to the incidence in the pooled analysis.

Table 4. Incidence of most common adverse events in Study 4 versus pooled analysis

|                                   | <b>Study 4</b>                 |                                |                | <b>Pooled analysis</b>      |                |
|-----------------------------------|--------------------------------|--------------------------------|----------------|-----------------------------|----------------|
|                                   | <b>MP03-36<br/>1 spr/n BID</b> | <b>MP03-33<br/>1 spr/n BID</b> | <b>Placebo</b> | <b>MP03-36<br/>Any dose</b> | <b>Placebo</b> |
|                                   | <b>N (%)</b>                   | <b>N (%)</b>                   | <b>N (%)</b>   | <b>N (%)</b>                | <b>N (%)</b>   |
| SAF                               | 161 (100)                      | 166 (100)                      | 162 (100)      | 1544 (100)                  | 1339 (100)     |
| Any adverse event                 | 38 (23.6)                      | 43 (25.9)                      | 38 (23.5)      | 296 (19.2)                  | 188 (14.0)     |
| Nasal discomfort                  | 7 (4.3)                        | 1 (0.6)                        | 0              | 55 (3.6)                    | 19 (1.4)       |
| Epistaxis                         | 7 (4.3)                        | 8 (4.8)                        | 5 (3.1)        | 26 (1.7)                    | 21 (1.6)       |
| Dysgeusia                         | 6 (3.7)                        | 4 (2.4)                        | 1 (0.6)        | 69 (4.5)                    | 9 (0.7)        |
| Upper respiratory tract infection | 4 (2.5)                        | 4 (2.4)                        | 3 (1.9)        | 11 (0.7)                    | 9 (0.7)        |
| Sneezing                          | 4 (2.5)                        | 3 (1.8)                        | 2 (1.2)        | 23 (1.5)                    | 1 (0.1)        |
| Oropharyngeal pain <sup>c</sup>   | 3 (1.9)                        | 1 (0.6)                        | 2 (1.2)        | 1 (0.1)                     | 2 (0.2)        |
| Abdominal discomfort              | 2 (1.2)                        | 0                              | 0              | 0                           | 0              |
| Pyrexia                           | 2 (1.2)                        | 2 (1.2)                        | 3 (1.9)        | 5 (0.3)                     | 6 (0.4)        |
| Nasopharyngitis                   | 1 (0.6)                        | 5 (3.0)                        | 3 (1.9)        | 6 (0.4)                     | 6 (0.4)        |
| Headache                          | 1 (0.6)                        | 3 (1.8)                        | 4 (2.5)        | 19 (1.2)                    | 21 (1.6)       |
| Rash                              | 0                              | 2 (1.2)                        | 1 (0.6)        | 2 (0.1)                     | 0              |

The incidence of adverse events was higher in children as compared to the pooled analysis. The data in the pooled analysis includes shorter treatment period of 2 weeks, which could bias the results in its favour.

### Serious adverse events and deaths

There were two serious adverse events in the SAR studies, both of which were in the placebo group, and there were no serious adverse events in any of the placebo-controlled PAR studies. In the long-term (1-year) study, eight patients (four patients of the MP03-36 group and four of the Nasonex group) experienced one or two serious adverse events; none was attributed to study treatment. There were no deaths in the SAR and PAR studies.

### Cardiac safety

Historically, there were concerns with cardiac adverse reactions caused by antihistamines. Therefore, earlier studies had investigated the effect of azelastine on QTc. However, minimal QTc prolongation was only found after **oral** administration of azelastine at doses 2- to 4-fold higher than that recommended, but not with nasal administration, which results in far lower systemic exposure.

In the placebo-controlled studies in patients  $\geq 12$  years, only two isolated adverse events of the System Organ Class Cardiac Disorders occurred. These were one case of moderate palpitations and one case of mild tachycardia, both occurred in the MP03-36 BID group and none was attributed to study medication.

In the long-term study, two adverse events of the System Organ Class Cardiac Disorders occurred in the MP03-36 group (0.4%) and two in the Nasonex group (0.8%). All were isolated occurrence. One severe and serious case of angina pectoris and one severe and serious case of coronary artery disorder occurred in the MP03-36 group; both were classified as unlikely related to study medication.

### Safety in special populations

Elderly patients, i.e. above 65 years of age, represented a relatively small proportion (about 3%) of the Safety Population of the pooled placebo-controlled studies (MP03-36: 49 patients; placebo: 48 patients). The incidence of adverse events – overall and for specific terms - was lower than in the main group aged 18 to 65 years. Only four isolated occurrences of adverse events were reported in the MP03-36 group. The long-term study provided similar data, i.e. lower rate of adverse events compared to the main adult group.

Adolescents patients, i.e. patients 12-17 years of age, represented about 10% of the Safety Population of the pooled placebo-controlled studies (MP03-36: 150 patients; placebo: 140 patients). The incidence of adverse events (overall) and of treatment “related” adverse events was lower in this subset than in the group of adults aged 18-65 years. Also on a preferred term level, no term obviously occurred more often in adolescents than adults aged 18-65.

In the children’s study, more patients withdrew from the study due to an adverse events in the placebo group (3.7 %) than in the MP03-36 treatment group (1.2 %).

Overall, the incidence of any adverse events was comparable between MP03-36 and placebo groups (23.6 and 23.5%, respectively); however, the incidence of treatment-related adverse events (as considered by the investigator) was higher in the MP03-36 (13.7%) than in placebo group (4.9%). This difference was driven by higher incidences in the MP03-36 group for *nasal discomfort*, *dysgeusia*, *epistaxis*, and *sneezing*. Other treatment-related adverse events were reported in isolated cases only.

Compared with data of adults and adolescents, the incidence of specific terms did not show obvious differences, with the exception of *epistaxis* and *URTI*, that occurred more frequently in the children’s study including the placebo group (*epistaxis*: 4.3% for MP03-36 and 3.1% for placebo, *URTI*: 2.5% and 1.9% respectively). Of note, *headache*, *vomiting*, and *nausea* occurred more frequently in the placebo group.

### Discontinuation due to adverse events

Discontinuations due to adverse events occurred with a similar incidence in the MP03-36 and the placebo group in the placebo-controlled SAR studies in patients  $\geq 12$  years (1.8% and 1.6%, respectively). Respective figures for the PAR studies were 2.7% and 1.2%. Treatment related adverse events (as assessed by the investigator) leading to discontinuations of MP03-36 included two cases of dysgeusia, four cases of nasal discomfort, three cases of sneezing, and single cases of nausea, fatigue, pharyngeal hypoaesthesia, sinus headache, sinusitis, dyspepsia, upper respiratory infection, and lacrimation increased (watery eye).

Premature discontinuations due to adverse events were more frequent in the long-term study, 54 (11.6%) of the patients discontinued from the MP03-36 group, and 17 (7.2%) patients discontinued from the

Nasonex group. The most common adverse events occurring in the MP03-36 group that resulted in discontinuation were *dysgeusia* (12 subjects or 2.6%) and *nasal discomfort* (10 subjects or 2.1%). Other adverse events occurring by more than one subject in the MP03-36 group that resulted in discontinuation were *headache*, *fatigue* (each in four subjects), *somnolence*, *increased appetite*, *pharyngolaryngeal pain* (3 subjects), *sneezing*, *weight increased*, *dry mouth*, and *throat irritation* (two subjects). Of note, the overall incidence of *headache* and *pharyngolaryngeal pain* in MP03-36 was lower than that reported for Nasonex and also lower or comparable to that reported for placebo (Table 2).

In Study 4, only two children discontinued from MP03-36 due to adverse events (one *nasal discomfort* and one *sinusitis*), no child from MP03-33, but six children from placebo.

### Post marketing experience

The first international Periodic Safety Update Report (PSUR) for azelastine hydrochloride (azelastine HCl) was issued for azelastine nasal spray and covered the period January 1991 until December 1996. Meanwhile, the 9th PSUR on all formulations of azelastine hydrochloride was issued in February 2012 covering the period of 1 January 2009 to 31 December 2011.

This PSUR also covers experiences with the two product licences in the US for the sucralose and sorbitol containing azelastine nasal sprays, Astepro 0.1% (denoted as Azelastine S 0.1% nasal spray, i.e. MP03-33) and Astepro 0.15% (denoted as Azelastine S 0.15% nasal spray, i.e. MP03-36).

It was estimated that overall about 29 million packs of azelastine nasal spray were sold or distributed as samples worldwide between October 2008 and September 2011. From the new Azelastine S 0.1% product about 4 million packs and from the new Azelastine S 0.15% product about 9.5 million packs were sold or distributed. In all categories, the number of medically confirmed cases reported after Azelastine S 0.15% nasal spray was lower than that reported for Azelastine S 0.1% nasal spray indicating that increasing the azelastine concentration from 0.1% to 0.15% does not incrementally increase the risk for medical events.

Safety data of Azelastine S 0.15% nasal spray from market experiences are as follows:

Two cases derived from spontaneous reporting were classified as serious and unlisted; none were classified as serious listed reactions. One case described a tachyarrhythmia that occurred in a 51-year-old male. Concomitant medication included lisinopril that is known to cause tachycardia. The available information precludes a reasonable causality assessment. The other case described atrial fibrillation that occurred in a 60-year-old male. Various factors including patient's medical history with atrial fibrillation triggered the final causality assessment as "unlikely".

Thirty-eight (38) non-serious unlisted reactions were recorded from spontaneous reporting. Among the most frequently reported unlisted adverse drug reactions (ADRs) in this PSUR for all azelastine nasal spray formulations, the following occurred after azelastine S 0.15 % nasal spray: nasal congestion (1), throat irritation (2), dyspnoea (4), headache (1), condition aggravated (1). There was no case of drug intolerance.

The reporting frequency of listed ADRs was estimated at  $43 / 9,531,719$  patients =  $0.05 / 10,000$  patients for Azelastine S 0.15% nasal spray. Considering in addition the listed ADRs reported from consumers (483) the total reporting frequency of listed ADRs was estimated at  $526 / 9,531,719$  patients =  $0.55 / 10,000$  patients, i.e. very low.

Four hundred and sixty-nine (469) non-medically confirmed consumer reports were registered during the period covered by this report. No cases were serious, and none were fatal. All of these consumer reports originate from the US market. Among the most frequently reported unlisted ADRs for azelastine nasal spray (all formulations), the following occurred after Azelastine S 0.15% nasal spray: headache (40), condition aggravated (12), nasal congestion (9) and nasal dryness (12). There was no case of drug ineffectiveness or drug effect decreased.

Meda Pharmaceuticals Limited committed to monitor the occurrence of anosmia. No medically confirmed case of anosmia were reported for Azelastine S 0.15% nasal spray. No case of anosmia was reported in 2189 patients treated with Azelastine S 0.15% nasal spray in clinical studies discussed in this document. However, the company will continue to closely monitor further reports on anosmia.

The PSUR concluded that the data were in accordance with the known safety profile of azelastine nasal spray as described in the Reference Safety Information. There was no evidence of a changed safety profile of azelastine nasal spray (all formulations and dosages). No change of the Reference Safety Information or other safety action was considered necessary. No new adverse drug reaction has been identified.

### **Overall conclusions on clinical safety**

The safety data from the clinical studies is considered adequate for the proposed higher dose strength (0.15%) and is supported by post marketing safety data from the USA. In addition, there is considerable safety data for the lower dose (0.1%) strength and the oral formulation in the literature.

The safety data available for the higher dose strength (0.15%) in children aged 6-11 years comes only from a study where the treatment duration was 4 weeks. Therefore, use longer than 4 weeks is not recommended in children aged 6-11 years.

The most common adverse events are dysgeusia, nasal discomfort, epistaxis, and sneezing. In addition, somnolence and fatigue were reported in some cases. The safety profile in children as seen from a 4-week study is comparable to the safety profile in adults.

The data on serious adverse events and cardiac safety are very reassuring. The treatment discontinuation rates due to adverse events is higher in longer-term treatment studies (4 weeks or 1 year) as compared to placebo, but the events *per se* does not raise any significant safety concerns.

The post marketing safety data also does not raise any new safety signals.

The available safety information is consistent with the known safety profile of azelastine and does not raise any new concerns.

### **SmPC, PIL and Labels**

The SmPCs, PILs and text versions of the labels are acceptable from a clinical perspective.

### **Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product. This application concerns a well-known medicinal product which has been on the market for more than 20 years. The safety profile of the product is, therefore, well established.

### **Clinical Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

### **Conclusion**

The grant of Marketing Authorisations is recommended.



#### **IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY**

The important quality characteristics of Rhinolast S/Astepro 0.15% Nasal Spray are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

#### **NON-CLINICAL**

As the pharmacodynamic and pharmacokinetic properties of azelastine hydrochloride are well-known and as these applications concern a higher strength of a known product, no further pharmacodynamic and pharmacokinetic studies are required and none have been provided. The applicant has submitted four new repeated-dose toxicity studies, which demonstrate that no additional local toxicity is associated with the introduction of this higher strength in comparison to currently marketed nasal spray formulations of azelastine. There are no objections to the approval of these products from a non-clinical viewpoint.

#### **CLINICAL**

A number of studies have been provided, which adequately demonstrate the efficacy of Rhinolast S/Astepro 0.15% Nasal Spray in improving the symptoms of allergic rhinitis in adults and adolescents. Clinical experience of up to 4 weeks duration showed good efficacy in children 6 years and older; however, there is no current clinical experience regarding topical safety for a longer duration of treatment in children. Therefore, longer than 4 weeks of treatment is not recommended in children 6-11 years.

#### **SAFETY**

The available safety information is consistent with the known safety profile of azelastine and does not raise any new concerns.

#### **PRODUCT LITERATURE**

The SmPCs, PILs and text versions of the labelling are satisfactory.

#### **BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with azelastine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.



## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|----------------|------------------|-------|---------|
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