7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted with this application consists of three pivotal studies. The relatively small clinical program is acceptable given that Astelin is an approved product and that the intent of the clinical program was to establish comparability of ——— to Astelin. Some characteristics of these pivotal clinical studies that form the basis of the regulatory decision are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

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Table 1. Pivotal clinical studies

ID	Disease *Study type*	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
MP 430	SAR *Efficacy and safety* *Comparability*	2 weeks	12-83	1 spray BID 2 sprays BID A 1 spray BID A 2 sprays BID Pbo 1 spray BID Pbo 2 sprays BID	139 146 137 138 137 138	2006	USA
MP 432	Allergic rhinitis Nonallergic rhinitis *Long term safety* *Comparability*	52 weeks (6 month Interim)	12-82	2 sprays BID 2 sprays BID	281 278	On-going	Australia, Europe
———							

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* ——— = ——— Nasal Spray; A = Astelin Nasal Spray; Pbo = Placebo Nasal spray; MF = mometasone furoate nasal spray (Nasonex);
# Year study subject enrollment ended

b. Design and conduct of the studies

Study MP 430 was a randomized, double-blind, placebo-controlled, parallel-group design study conducted in patients 12 years of age and older with SAR. The study had a 7 day placebo run-in period followed by a 2 week double-blind treatment period. The primary efficacy endpoint was change from baseline in morning plus evening reflective total nasal symptoms score (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) averaged over 2 weeks of treatment. Secondary efficacy variable included the instantaneous recording of the same four symptoms (iTNSS) and the Rhinoconjunctivits Quality of Life Questionnaire (RQLQ). Safety assessments included recording of adverse events, vital signs, physical examinations, and clinical laboratory measurements.

Study MP 432 was a randomized, open-label active-controlled, parallel-group design study conducted in patients 12 years of age and older with perennial allergic rhinitis and non-allergic rhinitis. The study had a 7 day screening period followed by a 52 week open label treatment period. Safety assessments included recording of adverse events, vital signs, and physical examination with a focused nasal examination. Efficacy was assessed

by the Mini RQLQ. The applicant submitted results from a 6 months interim analysis with the NDA and submitted a 4-month safety update during the NDA review period.

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c. Efficacy findings and conclusions

The submitted clinical studies, along with the known findings of Astelin, are adequate to support the efficacy of [redacted] for SAR in patients 12 years of age and older. The clinical studies do not support approval of [redacted] for SAR in patients 5 to 11 years of age, and also do not support approval of the VMR indication. The applicant contends that [redacted] should have indications and dosage and administration recommendations for various ages identical to Astelin. The applicant's contention is based on their determination that the submitted data has demonstrated comparability between [redacted] and Astelin, and therefore, all indications and dosage and recommendation for various ages should be carried over from Astelin to [redacted] The Division disagrees with the applicant's contention. In subsequent sections three areas – SAR in patients 12 years of age and older, SAR in patients 5 to 11 years of age and older, and VMR in patients 12 years of age and older – are discussed.

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SAR in patients 12 years of age and older, and comment on comparability

In study MP 430 the 2 spray doses of [redacted] and Astelin were both statistically significantly superior to placebo for the primary efficacy endpoint, but the 1 spray dose of both products did not statistically significantly separate from placebo (Table 2). Secondary efficacy variables generally trended in a similar direction for both products and for both doses (data not shown in this review). This single study conducted in patients with SAR ages 12 years and above is sufficient to support efficacy in SAR for ages 12 years and older. The Agency typically relies on findings from replicate studies as substantial evidence of efficacy, but in this specific instance a single study is adequate because of previous findings with Astelin, and the fact that both Astelin and [redacted] are solution formulations with similar container and closure systems and in vitro characteristics. The dosing recommendation of both 2 sprays and 1 spray can be carried over to [redacted]. Although the data from this study shows that 1 spray of both formulations did not statistically significantly separate from placebo, the efficacy trends for both 2 sprays and 1 spray favored [redacted] over Astelin (Table 2). There is no reason to believe that [redacted] at 1 spray per nostril would not be efficacious in SAR, as previous placebo controlled studies have shown a statistically significant difference between Astelin at 1 spray per nostril twice daily and placebo.

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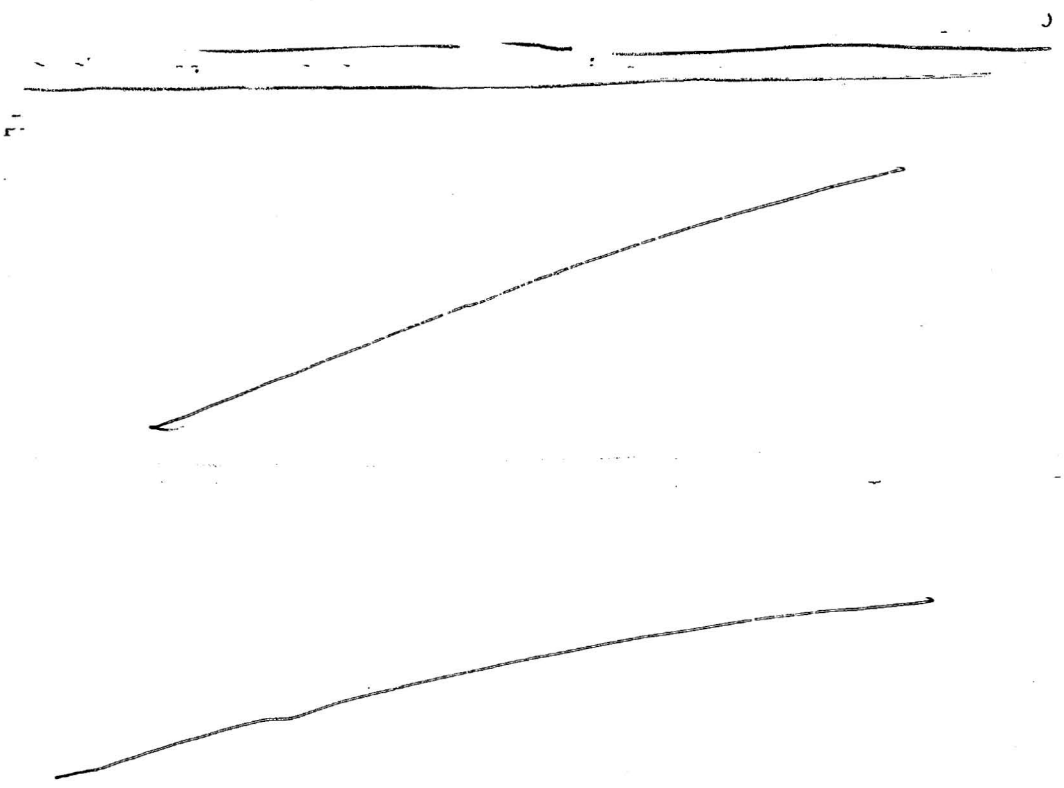

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Comment on Comparability:

The decision to approve the SAR indication for ages 12 years of older is based on the reasoning stated above and is not based on demonstration of comparability. For this specific decision one does not even need to conclude whether comparability of the two products has been demonstrated. Nevertheless, it is worth commenting on comparability because the applicant has concluded that comparability between / ——— , and Astelin has been demonstrated through study MP 430. b(4)

As mentioned above in section 2 of this review above, the Agency Draft Guidance on Allergic Rhinitis mentions a comparability approach to support approval of changes in formulation.[2] This Draft Agency Guidance recommends demonstration of comparability

[2] Guidance for Industry. Allergic Rhinitis: Clinical Development Program for Drug Products. Draft Guidance. Available at www.fda.gov/cder/guidance

in a single study using two doses of each formulation and demonstration of comparability of the dose-response curves. This principle was conveyed to the applicant on a meeting dated May 3, 2005. The single study MP 430 was conducted to show comparability but failed to show dose-response because the 1 spray per nostril twice daily dose, which is an approved dose for SAR, did not statistically separate from placebo (Table 2). Without demonstration of dose-response, comparability cannot be assessed. Therefore, based on this approach, the submitted study has failed to show comparability between [redacted] and Astelin. b(4)

Another approach to assess comparability of two nasal spray products is to use the principle outlined in another related Agency Guidance document.[3] This guidance is on the development of generic nasal spray products. This guidance requires that the two products be qualitatively and quantitatively the same, meaning that they both contain same active and inactive ingredients and the amount of each be within 5%. [redacted] and Astelin are qualitatively and quantitatively different because of the presence of two excipients in [redacted] that are not present in Astelin; however, because these two are solution formulationswith the same container and closure system and similar in vitro characteristics, one can assume that the differences in excipients will not impact the rate and extent of availability of the active moiety at the site of action on the nasal mucosa. Therefore, the criteria of bioequivalence described for clinical study in the guidance document are not unreasonable to apply here as a test of comparability. The design and conduct of study MP 430 are similar to the study recommended in the guidance document and allows for such analyses. Our statistical team performed equivalence analysis for [redacted] and Astelin, which shows that the two products fail the bioequivalence test (Table 3). The guidance document recommends testing at the lowest labeled dose to optimize sensitivity. In study MP 430 the lowest labeled dose, 1 spray each nostril twice daily, did not even statistically separate from placebo and should not be tested. Nevertheless, both the 1 spray and the 2 sprays doses were tested and both failed. For the 2 sprays dose, with which both Astelin and [redacted] statistically significantly separated from placebo, [redacted], tended to be numerically better than Astelin (Table 3). b(4) b(4)

It appears that adding the two excipients has changed the efficacy of azelastine. The efficacy of [redacted], may be better than Astelin in treating SAR, but the efficacy of [redacted], and Astelin is certainly not comparable.

Table 3. Equivalence analysis for the change from baseline of rTNSS* (study MP 430) b(4)

Treatment comparisons	Baseline Mean	Baseline Median
	90% CI for the ratio of means	90% CI for the ratio of means
Astelin and [redacted], 2 sprays	0.986, 1.466	0.986, 1.464
Astelin and [redacted], 1 spray	0.866, 1.324	0.867, 1.323
* To pass BE equivalence test the 90% CI must fall between 0.8 and 1.25		

[3] Guidance for Industry. Bioavailability and bioequivalence studies for nasal aerosol and nasal spray for location action. Available at www.fda.gov/cder/guidance

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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8. Safety

a. Safety database

The safety assessment of [redacted] was based on the studies MP 430 and MP 432 (Table 1). A total of 564 patients 12 years of age and older were exposed to [redacted] in these two studies 2 weeks and 6 months in duration. The overall safety database was adequate.

b(4)

[5] Adkinson F. Middleton's Allergy. Principles and Practice, 6th ed, pg 1405.

[6] Dykewiza M, Fineman S. Executive Summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis. Ann Allergy Asthma Immunol 1998; 81: 463-468

[7] Product labels for Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, and ProAir HFA Inhalation Aerosol.

b. Safety findings and conclusion

The submitted data support the safety of [redacted] 12 years of age and older. As mentioned above the application does not support safety for ages 5 to 11 years. There were no deaths in the clinical program. Serious adverse events were few and did not suggest a new safety signal. The majority of the adverse events were mild and generally similar between [redacted] and Astelin. Common adverse events that occurred more in drug treated groups compared to placebo in the 2 week study were bitter taste, epistaxis, headache, nasal discomfort, fatigue, and somnolence. In the long-term safety study reporting of adverse events was similar. Nasal mucosal ulcerations and epistaxis were seen in both active treatment arms in similar frequency. b(4)

Addition of the two sweetening agents did not seem to mask the bitter taste of azelastine. In the 2 week study, bitter taste was the commonest adverse event reported for both formulations, with a frequency of 7% and 6% with [redacted] 2 prays per nostril twice daily and 1 spray per nostril once daily, respectively, and 8% and 10% with Astelin 2 prays per nostril twice daily and 1 spray per nostril once daily respectively. This is not surprising because bitter taste receptors are in the back of the tongue whereas sweet taste receptors are mostly at the tip of the tongue. A nasal spray formulation drips to the back of the tongue and does not reach the tip of the tongue in any substantial amount. b(4)

c. REMS/RiskMAP

Not relevant because (b) (4) will not be approved in this cycle. Other antihistamines do not have REMS and RiskMAP, and, barring any new safety findings [redacted] will not require REMS or RiskMap when approved. b(4)

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Azelastine is not a new molecular entity. Antihistamines, including nasal antihistamines, are a well studied drug class, and efficacy and safety of this class of drug, including azelastine, is fairly well understood. The efficacy and safety findings seen in the clinical program were fairly obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

This NDA does not trigger PREA because there is no new active ingredient, no new indication, no new dosage form, no new dosing regimen, or no new route of administration. The applicant has a reasonable pediatric development plan for azelastine nasal spray. During approval of Astelin supplement (NDA 20-114, February 17, 2006) for 1 spray per nostril twice daily dosing for SAR, studies in children 2 years of age and older was deferred, and studies below 2 years of age was waived. The Division has taken the position that SAR does not occur in children below 2 years of age. Although the lower age cut-off is somewhat arbitrary, there is literature support for the lower age bound (J Allergy Clin Immunol 2000; 106:832). The deferred pediatric studies will adequately address all pediatric drug development for azelastine nasal spray down to the age of 2 years.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was requested for this application because azelastine nasal spray is a well studied product, and the two clinical studies conducted with [redacted] were fairly routine standard studies. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards. b(4)

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There were 3 investigators with significant equity interest in MEDA or its predecessor. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC.

12. Labeling

a. Proprietary Name

The applicant proposed the trade name [redacted], for this product. DMEDP reviewed this trade name and found it unacceptable. The applicant submitted two additional trade names, [redacted] and [redacted], both of which were not acceptable to DMEDP. The problem with these trade names is that the root name for the product is the same, and the suffix contains an abbreviation that does not convey any specific meaning. Subsequently the applicant submitted two other trade names, Astepro and [redacted] DMEDP has not rendered a final decision on acceptability of these two trade names. b(4)

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and by DDMAC, and DMEDP. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have not agreed to the final version of the label because of a lack of agreement on the VMR indication and SAR indication in patients 5 to 11 years of age.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, DDMAC, and DMEP, and the last version was found to be acceptable.

d. Patient Labeling and Medication Guide

The patient instructions for use was reviewed by various disciplines of this Division, and DSRCS, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

b(4)

The applicant has submitted adequate data to support approval of ——— for the relief of symptoms of SAR in patients 12 years of age and older. The submitted data do not support approval for SAR in patients 5 to 11 years of age, and VMR for 12 years of age and older. The action on this application will be Not Approval.

The following two comments can be used to create the action letter.

1. The data from the submitted clinical studies are not adequate to establish efficacy and safety of ——— for the relief of symptoms of vasomotor rhinitis for patients 12 years of age and older. ———

b(4)

2. The data from the submitted clinical studies are not adequate to establish efficacy and safety of ———, for relief of symptoms of seasonal allergic rhinitis for patients 5 to 11 years of age.

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efficacy and safety of ———, for relief of symptoms of seasonal allergic rhinitis for ages 12 years and above, ———

3. ———

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b. Risk Benefit Assessment

The overall risk and benefit assessment of ——— support its approval for relief of symptoms of SAR in patients 12 years of age and older without any specific restrictions, but not for patients with SAR ages 5 to 11 years of age and not patients with VMR. The submitted clinical study showed efficacy in SAR patients ages 12 years and older, and the safety profile was acceptable for this age group. The major safety findings of clinical concern were somnolence, fatigue, epistaxis, and nasal mucosal ulcerations. Sedation manifesting as somnolence and fatigue is common with some antihistamines, and was also seen with Astelin Nasal Spray. Local nasal mucosal irritation manifesting as epistaxis and ulceration is common with nasal spray formulation, and was also seen with Astelin.

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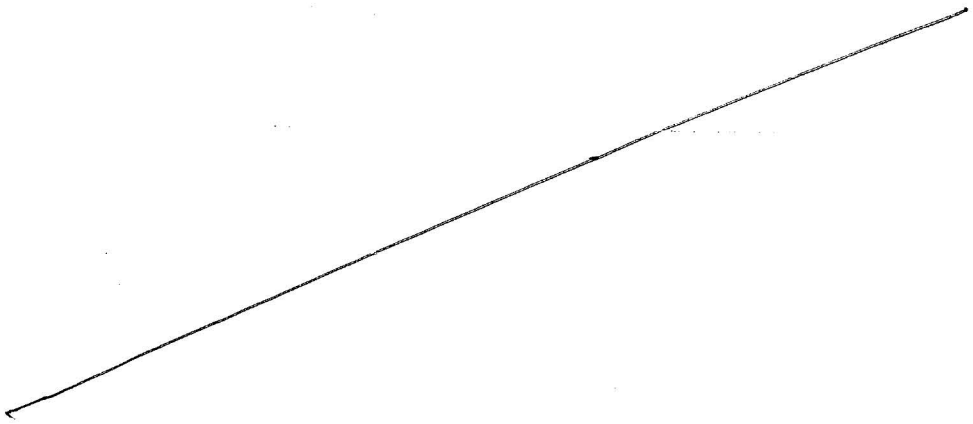

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c. Post-marketing Risk Management Activities
Not relevant because the application will not be approved.

d. Post-marketing Study Commitments
Not relevant because the application will not be approved.

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/s/

Badrul Chowdhury
5/30/2008 11:37:58 AM
MEDICAL OFFICER
Div Dir summary review