

Discussion:

MedPointe asked the Division to clarify its PK requirements. The Division stated that the purpose of the study is to support the safety of the drug since the proposed pivotal trial is only 2 weeks. MedPointe needs to show whether the new formulation has an effect on the bioavailability of the drug. The Agency stated that although bioequivalence between the new formulation and the old formulation is not being pursued, 90% confidence intervals of the ratio of relevant PK parameters between the formulations should be reported, At least 12 patients per subgroup would be needed, and it is recommended that blood samples to describe the full PK profile be taken on all groups due to the fact that the drug has a long half life. It is acceptable to use healthy subjects.

Pediatric Program

Question A. In order to comply with PREA, MedPointe proposes to use the study design options described in your September 20, 2002 Astelin® Pediatric Written Request as the basis of our sweetened formulation pediatric study. Does the Division agree with this approach?

Question B. Assuming a pediatric study (as outlined in September 20, 2002 Pediatric Written Request) is conducted and leads to an approved SAR indication in children ≥ years of age and older, would there be an additional 6-months of pediatric exclusivity?

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Response: Our responses to your questions regarding your Pediatric Program are not included here. If available before the meeting, we will forward our responses to you.

Discussion:

The Division stated that we will defer this discussion until a later time. The Division did note that for any drug product, it is necessary to conduct studies down to the age where the disease exists.

Toxicology Requirements

Question: Does the Division agree that no additional toxicology evaluations are required for the sweetened formulation?

Response: No, the Division does not agree. Additional toxicology evaluations are required in order to qualify the safety of inhaled sucralose and the significant change in the product formulation. To adequately evaluate the product, the following studies are needed:

- 1. One (1) 6-month intranasal toxicity study of sucralose and one (1) 3-month bridging intranasal toxicity study of the sweetened formulation in the most appropriate species, or*

2. *One (1) 6-month intranasal toxicity study of the sweetened formulation in the most appropriate species.*

Additional toxicity studies may be needed pending the results of the recommended studies. For example, the observation of proliferative or preneoplastic changes in chronic toxicity studies with sucralose may warrant the conduct of a carcinogenicity study via the intranasal route.

The studies should be designed to adequately evaluate the toxicity profile of sucralose and the sweetened formulation in the respiratory tract. An adequate evaluation should include establishment of a no-observed-adverse-effect-level (NOAEL) for sucralose via the intranasal route, sufficient safety margins for sucralose in humans based on the animal data, and an evaluation of potential toxicological interactions between sucralose and the active ingredient.

Species selection for these 6- and 3-month studies should be based on the results of shorter term studies (generally 2-4 weeks in duration) in 2 species which include at least one non-rodent species. Consultation with the Division regarding the study designs prior to study initiation is encouraged.

Intranasal toxicity studies of the sweetened formulation with a treatment duration at least equal to that of intended clinical trials should be completed prior to the initiation of such trials. Therefore, studies of at least 2 weeks duration using the proposed formulation in 2 species should be submitted to support the proposed 2-week clinical trial. The recommended 3- and 6-month studies should be submitted to support any longer duration clinical trials and an NDA submission.

The safety qualification of impurities, degradants, leachables and extractables, if applicable, should be addressed in the NDA submission.

The above recommendations are based on our determination that the rationales provided in the briefing package for not conducting additional toxicity studies are insufficient to support the safety of chronic intranasal use of the sweetened formulation. The rationales include: 1) The toxicity of Astelin® is well characterized in NDA 20-114; 2) Sucralose is safe to use as a food additive. The material safety data sheet (MSDS) of sucralose does not identify any special risk for inhalation exposure. A 2-week intranasal irritation study with 0.15% sucralose in rats did not reveal any significant adverse reactions; and 3) Clinical studies will evaluate the safety of the formulation. These rationales are insufficient to support the safety of chronic clinical use of the sweetened formulation due to the lack of animal toxicity studies to adequately evaluate the intranasal use of the formulation and its components for the reasons described below.

Data obtained from the development of Astelin Nasal Spray is not sufficient to support the safety of the sweetened formulation because the

two formulations have significantly different compositions. The sweetened formulation contains three ingredients (i.e., 0.15% sucralose, 0.15% sorbitol and 0.15% sodium chloride) that are not present in the Astelin[®] nasal spray. Significant formulation differences may alter the safety profile of the final drug product. The safety profile of the sweetened formulation is unknown because no toxicity studies have been completed with the sweetened formulation. Consequently, the nonclinical program for Astelin[®] Nasal Spray is considered insufficient to support the safety of the sweetened formulation.

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The safety of the chronic intranasal use of sucralose, a component of the sweetened formulation, has not been established. Sucralose has not been approved for any intranasal products although it is considered safe to be used as a food additive and for oral consumption. The difference in routes of administration might affect the toxicity of sucralose, especially regarding the local toxicity. The lack of special cautionary measures to prevent inhalation exposure of sucralose as indicated in the MSDS is not adequate to alleviate concerns about the safety of chronic intranasal use of the compound. Also, the completed 2-week intranasal study in rats (Study No. 16365) suggests that sucralose may enhance the irritation induced by azelastine HCl as the addition of 0.15% sucralose to Astelin[®] nasal spray increased the incidence of acute multi-focal inflammation in males and goblet cells hypertrophy/hyperplasia in females. These findings are a potential safety concern and additional toxicity studies are needed to alleviate this concern. Therefore, the safety of chronic intranasal use of sucralose needs to be supported by adequate nonclinical data using the appropriate route of administration.

The sorbitol concentration in the sweetened formulation is significantly higher than that in approved intranasal drug products. Clinical evaluation alone is not considered adequate to evaluate the safety profile of a drug product. The nonclinical safety of the sweetened formulation must be demonstrated and the recommended animal toxicity studies should be designed to achieve this goal.

Discussion:

MedPointe stated that they understand the issues related to sucralose, and they do have their shorter term studies completed (1 rodent, 1 non-rodent) and they did not see any concerning findings. MedPointe asked the Division if the previously submitted rat study would satisfy one of the two studies required. The Division stated that the study as it was would not satisfy as one of the 2 studies required for 2 reasons:

1. The study did not appear to test the intended clinical formulation. The study report was not specific about the composition of the vehicle. It appeared that the vehicle was the old formulation (Astelin[®]) spiked with sucralose. Studies with

the intended clinical formulation are needed to support the clinical use of such formulations.

2. The study did not establish a NOAEL for the formulation. The rats treated with either 0.1% or 0.15% azelastine HC in presence of 0.15% sucralose showed increased incidences of nasal lesions than those treated with the vehicle, vehicle plus sucralose, or Astelin[®]. The finding suggests a potential synergistic toxicological interaction between sucralose and azelastine. Such an interaction is of safety concern. Consequently, a NOAEL for the formulation is needed for its safety evaluation.

MedPointe stated that the new formulation was used. MedPointe agreed to submit the composition of the formulation used in the study to the IND for review. The Division could follow up with a teleconference for further discussion, if necessary.

MedPointe disagreed with the Division's conclusion that the NOAEL for the formulation has not been established. MedPointe reasoned that the increased incidence of nasal lesions was seen in the groups of interest because the Astelin control groups, especially the females, showed unexpectedly low incidences of the lesion. Furthermore, the incidence and type of lesions observed in the groups with both azelastine and sucralose were well within the historic background values. MedPointe agreed to submit the histological data for the Division to review.

MedPointe sought clarifications on the establishment of a NOAEL for sucralose in rats. MedPointe stated that a NOAEL has been established because no nasal lesions were observed in the group treated with the vehicle in presence of sucralose. The Division agreed with the sponsor that 0.15% sucralose did not affect the toxicity of vehicle but disagreed with the conclusion that the NOAEL for sucralose was established because of toxicity associated with the formulation containing the same concentration of sucralose. The Division pointed out that the groups treated with sucralose and azelastine showed increased incidence of nasal lesions than the vehicle plus sucralose. The Division interpreted the above finding as a sign of potential synergistic toxicological interactions between sucralose and azelastine. Since the findings associated with the formulation are more relevant to the safety evaluation, the lack of NOAEL in the formulation would be translated into a lack of NOAEL for sucralose. Further, it is premature to conclude that a NOAEL for chronic use of sucralose has been established because the 2 week toxicity studies are not always predictive of the response to chronic exposure. Thus, MedPointe should design studies to attempt to establish a NOAEL for sucralose. Ideally, different doses of sucralose should be employed.

MedPointe agreed to submit all available evidence for the Division to review. The Division would determine that acceptability of the 2-week rat study upon reviewing additional data. If the additional data are deemed satisfactory, the completed 2-week in rats can be considered satisfactory to meet the requirement for the 2-week study in a rodent species. If the additional data are not considered adequate, MedPointe will have to perform an additional 2-week rodent study.

The Division encouraged MedPointe to submit the study protocols for comments. MedPointe stated they will put together a protocol and submit for a later discussion.

Once MedPointe clarifies and documents the formulations of the study, a later discussion can be held concerning the dog studies. The Division stated that once the formulation and histological data is submitted, a NOAEL can be evaluated.

MedPointe asked if the animal studies need to be conducted prior to the start of their clinical trials. The Division stated that the supporting animal studies should be conducted prior to the start of the clinical studies for the new formulation. Draft reports may be initially submitted followed by the finalized reports.

MedPointe stated that they do intend on having a CMC meeting at a later date. They understand the requirements for full characterizations needed and they will comply.

MedPointe summarized the major points of discussion:

1. MedPointe will use a comparability clinical study design, using 5 arms. They will compare active versus placebo and they will eyeball the dose response curves.
2. MedPointe will include baseline values as covariate in their model.
3. The PK data is supportive for safety. There is large variability in the PK data, and MedPointe will use 90% confidence interval limits in its comparisons. MedPointe will look for directional changes. The use of healthy volunteers and at least 12 subjects is acceptable for the purpose of PK comparisons between formulations.
4. MedPointe will provide clarification of the formulations used in the toxicology studies. MedPointe will provide a new protocol for the dog and will follow up with a future teleconference for discussion. MedPointe acknowledges the Division's requirement for a second toxicology study.
5. MedPointe will defer the pediatric discussion until a later time.

Minutes Preparer

Colette Jackson

Drafted by: CCJ/May 20, 2005

Initialed by: Pei/May 23, 2005
McGovern/ May 27, 2005
Suarez/ May 26, 2005
Fadiran/ May 26, 2005
Gebert/ May 23, 2005
Purohit-Sheth/ May 27, 2005
Gilbert-McClain/ May 27, 2005
Chowdhury/ June 9, 2005

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/s/

Colette Jackson
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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	<h2 style="margin: 0;">PRESCRIPTION DRUG USER FEE COVERSHEET</h2>
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A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS MEDPOINTE HEALTHCARE INC Richard Fosko 265 Davidson Avenue Suite 300 Somerset NJ 08873 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-203
2. TELEPHONE NUMBER 732-564- 2358	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

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3. PRODUCT NAME Nasal Spray (Azelastine Hydrochloride)	6. USER FEE I.D. NUMBER PD3007484
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7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY
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8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

OMB Statement:
 Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director Regulatory Affairs	DATE 7/24/07
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
 \$896,200.00

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