

## 2.4 Analytical Section

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. All bioanalytical assays fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

Azelastine and desmethylazelastine have been measured by a validated LC-MS-MS method, which achieved chromatographic separation after liquid-liquid extraction with an organic solvent after the addition of sodium carbonate solution to human EDTA plasma containing azelastine, desmethylazelastine and internal standards of  . The dynamic calibration range was   µg/mL for both analytes. Interday precision and accuracy of the method were evaluated using the results of the quality control samples assayed daily alongside the clinical samples. Table 4 summarizes the findings from the in-study validation of the method.

b(4)

**Table 4.** Assay performance (in-study validation) for azelastine and desmethylazelastine

	Azelastine	Desmethylazelastine
<b>Linearity</b>	Satisfactory: Standard curve ranged from <span style="border: 1px solid black; padding: 0 20px;"> </span>	Satisfactory: Standard curve ranged from <span style="border: 1px solid black; padding: 0 20px;"> </span>
<b>Accuracy</b>	Satisfactory: % Bias: <span style="border: 1px solid black; padding: 0 20px;"> </span>	Satisfactory: % Bias: <span style="border: 1px solid black; padding: 0 20px;"> </span>
<b>Inter-day Precision</b>	Satisfactory: % CV: <span style="border: 1px solid black; padding: 0 20px;"> </span> at <span style="border: 1px solid black; padding: 0 20px;"> </span>	Satisfactory: % CV: <span style="border: 1px solid black; padding: 0 20px;"> </span>
<b>Specificity</b>	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**4.2. OCP Filing/Review Form**

Office of Clinical Pharmacology  
New Drug Application Filing Form

General Information About the Submission

	Information		Information
NDA Number	22-203	Brand Name	
OCP Division	DCP2	Generic Name	Azelastine Hydrochloride (sweetened)
Medical Division	DPAP (OND-570)	Drug Class	H <sub>1</sub> -histamine receptor antagonist
OCP Reviewer	Partha Roy	Proposed Indication(s)	Seasonal allergic rhinitis for adults and children ≥5 years; vasomotor rhinitis for adults and children ≥12 years
OCP Team Leader (Acting)	Wei Qiu	Dosage Form	Nasal Spray
		Dosing Regimen	1 to 2 sprays (137 mcg each) per nostril twice daily
Date of Submission	30 July 2007	Route of Administration	Intranasal
Estimated Due Date of OCP Review	26 Mar 2008	Sponsor	MedPointe Pharmaceuticals
PDUFA Due Date	30 May 2008	Priority Classification	Standard
Division Due Date	28 Mar 2008		

b(4)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	1		
<b>1. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>4 Healthy Volunteers:-</b>				
single dose:	x	1		
multiple dose:				
<b>5 Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:	x			
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		2		
6				
<b>7 Filability and QBR comments</b>				
<b>8</b>	<b>"X" if yes</b>	<b>9 Comments</b>		
Application filable?	x	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		None		
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> <li>Demonstration of comparative bioavailability between (b) (4)S and Astelin.</li> <li>Acceptability of bioanalytical methods and analysis of azelastine and desmethylazelastine.</li> </ol>			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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this page is the manifestation of the electronic signature.**  
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/s/

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Partha Roy  
3/28/2008 10:30:54 PM  
BIOPHARMACEUTICS

Wei Qiu  
3/28/2008 10:39:15 PM  
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