CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211746Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123164

MEETING PRELIMINARY COMMENTS

Glenmark Specialty S.A.
750 Corporate Drive
Mahwah, NJ 07430

Attention: Ed Lee, Senior Director
Regulatory Affairs

Dear Mr. Lee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSP 301(olopatadine hydrochloride and mometasone furoate) Nasal Spray.

We also refer to your May 15, 2017, correspondence, received May 15, 2017, requesting a meeting to discuss the content and format of the clinical and nonclinical sections of the proposed New Drug Application (NDA) for GSP 301 for the treatment of seasonal allergic rhinitis (SAR).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (240) 402-4483.

Sincerely,

{See appended electronic signature page}

Linda Ebonine, PA-C
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	July 13, 2017 12:00-1:00 pm
Meeting Location:	White Oak Building 22, Conference Room: 1421
Application Number:	123164
Product Name:	GSP 301(olopatadine hydrochloride and mometasone furoate)
Indication:	Treatment of seasonal allergic rhinitis (SAR)
Sponsor/Applicant Name:	Glenmark

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 13, 2017 at 12pm at the White Oak Campus Building 22, Conference Room 1421 between Glenmark and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Glenmark submitted the initial IND 123164 on October 17, 2014 and had the End of Phase 2 Meeting on September 10, 2015. On May 15, 2017, Glenmark submitted a Type B Pre-NDA meeting request for the purpose of discussing the proposed content and format of the clinical and nonclinical sections of a New Drug Application (NDA) for GSP 301 to support the proposed indication, the treatment of symptoms associated with seasonal allergic rhinitis in adults and adolescents 12 years of age and older. GSP 301 Nasal Spray contains olopatadine hydrochloride (H1 receptor antagonist) and mometasone furoate (anti-inflammatory corticosteroid). . A

separate meeting will be requested to discuss the format and content of the manufacturing- and quality-related sections of the NDA.

The briefing package was received on June 13, 2017.

2.0 DISCUSSION

Glenmark's questions from the briefing package are noted in *italic font* and the FDA's responses are provided in normal font.

2.1. REGULATORY AND LABELING

Question 1: *Does the agency agree that the nonclinical and clinical data to be submitted in the proposed NDA via the 505(b)(2) pathway provide an adequate basis for assessment to support this indication?*

FDA Response*:*
We agree with your plan to use the 505(b)(2) regulatory pathway. See additional guidance regarding the 505(b)(2) pathway below.

Question 2: *The proposed format and table of contents for the GSP 301 NS NDA for seasonal allergic rhinitis (SAR) is provided in the meeting information package. Does the Agency agree with the format and content of the proposed GSP 301 NS NDA?*

FDA Response:
We agree.

2.2. CLINICAL

Question 3: *Does the Agency concur that the unique subject exposure numbers in adult and adolescent subjects in the GSP 301 NS clinical program are sufficient to support the proposed NDA filing?*

FDA Response:
In general, the subject exposure numbers in adults and adolescent subjects in the GSP 301 clinical development program appear adequate to support your filing. However, if new safety signals are identified, more safety data may be required.

Question 4: *The Sponsor has conducted three adequate, well-controlled, double-blind clinical studies that evaluated the safety and efficacy of GSP 301 NS in accordance with the "combination rule" (21 CFR 300.50) to support the approval of GSP 301 NS for the treatment of seasonal allergic rhinitis (SAR). The Sponsor has analyzed the primary endpoint in accordance with the pre-specified statistical analysis plans (SAP) for the three pivotal studies (GSP 301-201, GSP 301-301, and GSP 301-304). The pre-specified primary analysis in the SAPs was the Analysis of Covariance (ANCOVA) for study GSP 301-201 and the mixed model repeated measures (MMRM) for studies GSP 301-301 and GSP 301-304.*

The Sponsor believes that the data from these three adequate, well-controlled, double-blind clinical studies provide replicate evidence to support the approval of GSP 301 NS for the treatment of SAR. Does the Agency agree?

FDA Response:
From a clinical standpoint, we agree that the totality of the evidence presented in the three studies (201, 301, and 304) provide sufficient evidence to support the review of GSP 301 NS for the treatment of SAR; but from a statistical perspective, Study 201 should be considered as supportive rather than independent when establishing efficacy due to statistical issues in multiple testing for combination rule and missing data handling, despite otherwise rigorous and appropriate statistical plan. Whether the clinical studies provide adequate evidence to support approval will be a review issue.

Question 5: *The Sponsor plans to commercialize a 240-spray presentation of GSP 301 NS, which is* (b) (4) *to the 120-spray presentation used in the clinical development plan. Consistent with the Agency's advice at the EOP2 meeting (Question 14), the Sponsor proposes to demonstrate the comparability between the 120-spray and 240-spray presentations by providing a comparative in vitro product performance assessment in Module 3 of the NDA. Does the Agency agree that this approach is sufficient for supporting the commercialization of the 240-spray presentation of the GSP 301 NS drug product?*

FDA Response:
Our advice at the EOP2 meeting on September 10, 2015, was based on the expectation that the 240-spray presentation would be used in two of the four phase 3 studies (refer to EOP2 meeting minutes dated October 5, 2015, Question 14, response and discussion). The current briefing package indicates that none of the studies in the clinical development program utilized the 240-spray presentation. Therefore, you may provide a comparative in vitro product performance assessment as discussed at the EOP2 meeting. As the 240-spray presentation was not utilized in any clinical studies, you should also include in vitro data that mimic patient misuse scenarios (e.g., failing to shake before use), if possible. Whether this data will be sufficient to support the commercialization of the 240-spray presentation will be a review issue at the time of NDA submission.

2.3 BIOSTATISTICS

Question 6: *The Sponsor has provided a comprehensive draft Integrated Summary of Effectiveness Analysis Plan in the meeting information package. Does the Agency agree with the proposed draft ISE Analysis Plan?*

FDA Response:
We agree with the proposed draft ISE SAP.

Question 7*: The Sponsor has provided a comprehensive draft Integrated Summary of Safety (ISS) Analysis Plan in the meeting information package. Does the Agency agree with the proposed draft ISS Analysis Plan?*

FDA Response:
We agree.

2.4 CLINICAL PHARMACOLOGY

Question 8: *A PK bridge between GSP 301 NS and the marketed individual monotherapies (NASONEX and PATANASE) has been established in healthy volunteer studies. Additionally, in accordance with the Agency's recommendation at the End of phase 2 meeting, the Sponsor has generated PK data in subjects with SAR to derive exposure estimates for olopatadine and mometasone furoate at the proposed dose and dose regimen of GSP 301 NS. Does the Agency agree that the PK data generated are adequate to characterize the PK profile of GSP 301 NS?*

FDA Response:
Based on the information provided in the meeting package, we agree that the PK data generated are adequate for the GSP 301 NS NDA submission. The adequacy of the data will be a review issue.

Question 9: *The Sponsor intends to reference the literature and the approved monotherapy labeling In accordance with the 505(b)(2) pathway. Accordingly, the Sponsor does not plan to perform drug-drug interaction studies or generate additional PK data in special populations for the GSP 301 NS NDA submission. Does the Agency concur with this approach?*

FDA Response:
We agree that no additional DDI studies or PK data in hepatic/renal impairment patients are needed for the GSP 301 NS NDA submission.

2.5 NONCLINICAL

Question 10: *The Sponsor provided a justification in the EoP 2 Chemistry Manufacturing Control Meeting Information Package (SN0009) for the proposed concentration of dibasic sodium phosphate (NaPD) heptahydrate in the GSP 301 NS drug product in response to the Agency's request. The Sponsor believes that a concentration of (b) (4)% NaPD heptahydrate in the GSP 301 NS drug product is acceptable and does not pose a safety risk. Does the Agency agree?*

FDA Response:
We agree.

Question 11: *The level of the excipient carboxymethyl cellulose (CMC) sodium per spray of GSP 301 NS ((b) (4)% w/w) is approximately (b) (4) times the levels listed in the FDA's IID for Approved Products (b) (4)% w/w) administered via the nasal route; however, the total daily intake of this excipient is almost equivalent ((b) (4)% versus 0.(b) (4)%) to the total CMC content specified for FDA-approved products administered by the intranasal route. Furthermore, the placebo for the GSP 301 NS nasal formulation containing (b) (4)% w/w CMC content level was qualified in a 13-week intranasal rat toxicity study. Accordingly, the Sponsor believes that a*

concentration of (b)(4)% w/w CMC sodium in the GSP 301 NS drug product has been adequately supported. Does the Agency agree?

FDA Response:
We agree.

Question 12: *All the excipients used in the GSP 301 NS formulation are listed in FDA's IID for Approved Products for nasal administration. The Sponsor has calculated the TDD using their published LD50 values and a default safety factor of 1000 (10 for each interspecies and inter-individual variation and an additional 10 for short-term study). A wide safety margin was obtained for each excipient. Does the Agency agree with this approach?*

FDA Response:
Your NDA submission should include justification for the safety qualification of all excipients. As you have done for the excipients specified in Questions 10 and 11, we recommend that you compare the daily exposure levels for each excipient in GSP 301 NS to those present in other approved nasal products and in your 13-week intranasal rat study. Your proposal to consider safety margins based on additional toxicology data available for the excipients is also reasonable. The agency will review and evaluate the excipients used in the GSP 301 formulation during the NDA review process.

Question 13: *The accelerated stability data for GSP 301 NS showed no increase in impurities over 24 months and no individual impurity was present in the product at greater than (b)(4)%. Based on these data, the Sponsor believes that all potential drug product impurities have been qualified and are below acceptance criteria as per ICH Q3(R2) requirements. Therefore, no additional qualification or identification of individual impurities is required. Does the Agency agree?*

FDA Response:
It is premature to conclude that no additional qualification or identification of individual impurities is required prior to our detailed evaluation of your NDA application, although we encourage you to follow all of the ICH Q3 guidances.

In addition, we note that a chemistry/manufacturing pre-submission meeting will be requested. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

In your NDA application, provide a detailed report of any genotoxic impurity assessments (i.e., as specified in ICH M7 Guideline, Assessment, and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk [May 2015]); including structures assessed, QSAR analysis methods and results, and expert assessment leading to the conclusion that a given structure has a negative prediction for genotoxicity.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that

supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

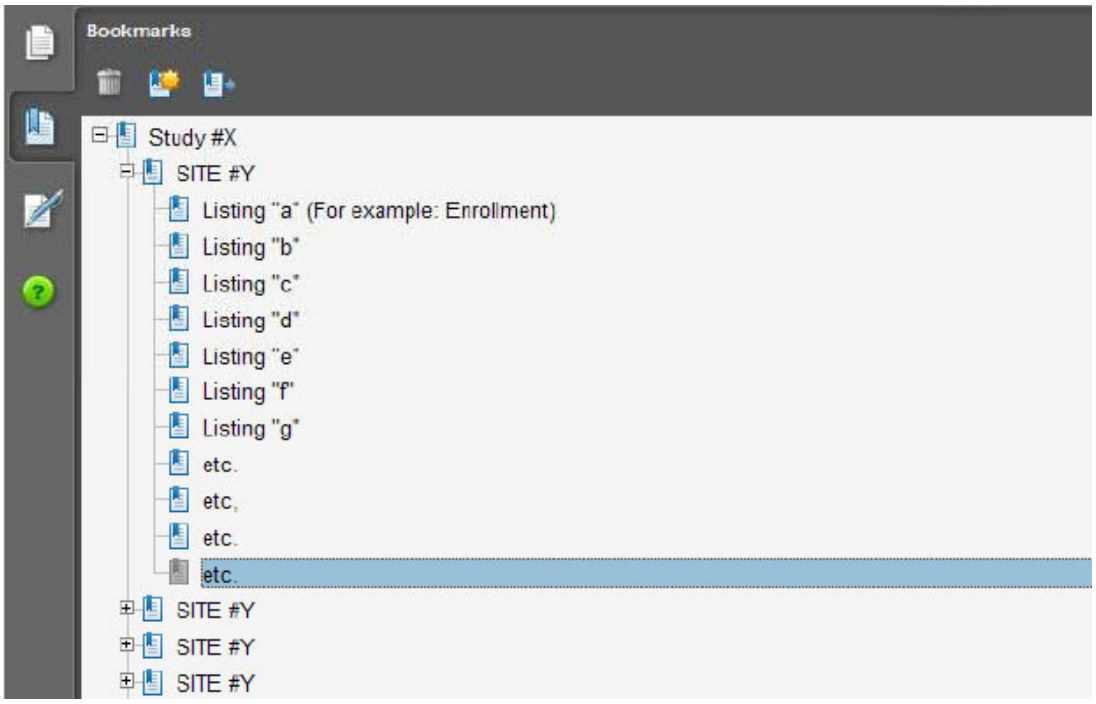
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

LINDA EBONINE
07/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123164

MEETING MINUTES

Glenmark Pharmaceuticals
750 Corporate Drive
Mahwah, New Jersey 07430

Attention: Axel Perlwitz, Ph.D.
VP Regulatory Affairs

Dear Dr. Perlwitz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for olopatadine hydrochloride and mometasone furoate.

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2015. The purpose of the meeting was to meeting to discuss your proposed phase 3 clinical development program, proposed at the pre-IND meeting, and the results from the studies conducted to date .

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 10, 2015, 9:00-10:00 am
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	123164
Product:	GPS 301
Indication:	SAR (b) (4) in adults and adolescents 12 years of age and older
Sponsor/Applicant Name:	Glenmark Pharmaceuticals Limited
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder:	Laura Musse, R.N., M.S., C.R.N.P

FDA ATTENDEES
Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, And Rheumatology Products (DPARP)
Banu Karimi-Shah, M.D., Clinical Team Leader, DPARP
Kathleen Donohue, M.D., Clinical Reviewer, DPARP
Sheetal Agarwal, Ph.D., RAC., Clinical Pharmacology Reviewer, OCP/OTS
Timothy Robison, Ph.D., Nonclinical Team Leader, DPARP
Brett Jones, Ph.D., Nonclinical Reviewer, DPARP
Craig M. Bertha, Ph.D., CMC Lead, Branch IV, Division of New Drug Products II (DNDP II)
David Petullo, Ph.D., Statistical Team Leader, Division of Biometrics II (DBII)
Lan Zeng, Ph.D., Statistical Reviewer, DBII

SPONSOR ATTENDEES
Patrick Keohane, MBBS, President Clinical R&D, Chief Medical Officer
Sudeesh Tantry, Ph.D., Vice President, Clinical R&D
Yacine Salhi, Ph.D., Director of Statistical Science, Clinical Project
Girish Gudi, Ph.D., Vice President, Drug Metabolism & Pharmacokinetics
Zona Godsafe, M.Sc., Vice President, Toxicology
Axel Perlwitz, Ph.D., Vice President, Regulatory Affairs, N. America Respiratory
Fiona Mortimer, Ph.D., Director, Global Clinical Regulatory Affairs

1.0 BACKGROUND

Glenmark Pharmaceuticals requested an End of Phase 2 meeting to discuss their product's (GSP 301 NS), proposed phase 3 clinical development program and to present the results from the studies conducted to date. GSP 301 is a nasal spray, containing olopatadine hydrochloride and mometasone furoate, and it is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The meeting was granted on September 10, 2015 and the background information package was received on August 3, 2015.

The Division (FDA) sent Preliminary Comments to Glenmark Pharmaceuticals on September 8, 2015.

2. DISCUSSION

Following introductions, Dr. Sudeesh Tantry commenced the meeting with a slide presentation containing the sponsor's clarification remarks for questions 9, 11, 12, 16 and 18. Dr. Tantry then stated that they were in concurrence with the Division's responses to the remaining questions.

2.1 Nonclinical Development

Question 1: *Given the lack of any irritancy with GSP 301 NS or any significant alteration in systemic toxicity with the GSP 301 NS FDC compared to the individual components, the 13 week comparative toxicity study conducted by the Sponsor is considered acceptable to support the Phase 3 clinical program and subsequent NDA approval of GSP 301 NS (665 mcg olopatadine hydrochloride/25 mcg mometasone furoate per 100 mcL). No further toxicity studies are proposed. In addition, no reproductive or developmental toxicity studies are proposed.*

Does the Agency concur?

Response:
Pending review, the 13-week rat intranasal combination toxicology study listed in the meeting package appears adequate to support the proposed phase 3 clinical trials. For an NDA submission, refer to comments regarding impurities in the pre-IND meeting minutes dated August 15, 2014.

We agree that no additional reproductive or developmental toxicity studies with the drug combination product are required.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

2.2 Clinical Development

Question 2: *Does the Agency agree that the results of the Phase 1 pharmacokinetic (PK) studies (GSP-301-101 and 102) are sufficient for the characterization of the PK of GSP 301Nasal Spray in healthy subjects and that these results can be extrapolated to the anticipated patient population?*

Response:
We concur.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 3: *Does the Agency agree that the results of the PK studies (GSP-301-101 and 102) are adequate to allow for extrapolation of results from the currently marketed individual components of the Fixed Dose Combination (FDC) (PATANASE and NASONEX) as supportive (establishing an appropriate bridge) for the proposed GSP 301 Nasal Spray clinical program?*

Response:
Studies GSP-301-101 and 102 are adequate to provide a PK bridge to the marketed, approved products for 505(b)(2) bridging purposes.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 4: *Does the Agency agree that the results of the Phase 1 pharmacokinetic (PK) studies (GSP-301-101 and 102) with a single dose are sufficient to extrapolate to the proposed BID regimen of GSP-301?*

Response:
We recommend that you provide PK data with your final to-be-marketed formulation at the dosing regimen at which the product will be labeled. To obtain this PK data, you may employ a population PK analysis approach or obtain extensive samples from a sub-set of subjects in the impending trials. For more guidance on this topic, see the following link to the FDA Guidance for Population Pharmacokinetics:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred**.**

Question 5: *Does the Agency agree that no additional adult, adolescent or pediatric PK studies (either in healthy subjects or Allergic Rhinitis (AR) patients) are needed for the proposed GSP 301 Nasal Spray clinical program?*

Response:
See response to Question 4 for obtaining additional PK data in adults and adolescents with the final choice of dosing regimen. We defer our response to the need for PK data in pediatric subjects until the time when a pediatric study plan is discussed for your drug product. In addition, we recommend that you plan to submit a comprehensive label for your drug product including information for dosing in special populations (for e.g., dosing in renal or hepatic impairment subjects etc.) as well as addressing drug-drug interaction potential (for e.g., interactions with transporters and CYP enzymes etc.). You may either conduct the assessments yourself (through dedicated studies or through population PK analysis in impending trials) or obtain information from published literature as permitted by the 505 (b) (2) regulatory pathway. For general guidance on this topic, see the following link to the FDA Guidance for Drug Interaction Studies:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 6: *Based on the results of the Phase 2 efficacy and safety study (GSP-301-201), does the Agency agree that GSP 301 Nasal Spray (olopatadine hydrochloride 665 µg and mometasone furoate 25 µg nasal spray, twice daily (BID)) is the single optimal dosage regimen appropriate for further evaluation in the Phase 3 program for adults and adolescents (12 years of age and older) for* (b) (4) *Seasonal Allergic Rhinitis (SAR)* (b) (4) *indications (subjects with SAR* (b) (4) *)?*

Response:
Based on the data provided, the proposed doses in the FDC product appear reasonable. In addition to the efficacy of the combination product, we expect that your phase 3 program will also demonstrate the efficacy of each single ingredient over placebo. See response to Question 7 and Question 16.

Discussion:
Sponsor acknowledged the Division's response and requested further clarification in relation to Question 16.

Question 7: *Based on the results of the Phase 2 efficacy and safety study (GSP-301-201), does the Agency concur that additional formal dose-ranging studies are not required for either GSP 301 Nasal Spray or its individual monotherapy components to support the clinical program in adults and adolescents (12 years of age and older)?*

Response:
We concur. As noted during the pre-IND meeting, we remain uncertain whether dose-ranging results from a mountain cedar-sensitive population will be predictive (b) (4); however the proposed approach is generally acceptable. See response to Question 6.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 8: *The Sponsor recognizes the requirement for replicate SAR studies to establish adequate efficacy (reflective Total Nasal Symptom Score (rTNSS) and instantaneous TNSS (iTNSS)) and safety for the approval of a SAR indication. However:*

a. Does the Agency require that the SAR efficacy (rTNSS and iTNSS) and safety to be established in multiple seasonal models (e.g. Mountain cedar and spring or fall) for the approval of a SAR indication?

Response:
We do not require that safety and efficacy be established in multiple seasonal models.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

b. For the secondary endpoints such as Total Ocular Symptom Scores (rTOSS and iTOSS), onset of action and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), does the Agency require replicate SAR study data if the Sponsor desires to include the data in the product insert as a label claim? Do the data need to be from 2 different seasonal models (e.g. mountain cedar and spring or fall)?

Response:

1. Onset of action and ocular claims (e.g. rTOSS and iTOSS) require replicate evidence for inclusion in the product label. This replicate evidence may be derived from either SAR (b) (4) trials.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

2. RQLQ should be evaluated in all trials. You should analyze RQLQ using a responder analysis (using the MCID for the instrument). All patients (not just a subset as identified in Question 18) should be included in the primary analysis. The analysis should be conducted for the combination versus each of the single ingredients, as well as placebo. Pending review, the RQLQ analysis would be included in

labeling to inform providers, regardless of a positive/negative result.

Discussion:
Sponsor acknowledged Division's response and requested further clarification in relation to Question 18.

3. Data from two different seasonal models is not necessary.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 9: (b) (4)

Discussion:
The Sponsor requested clarification on whether the phase 2 SAR study was intended to read as phase 3 SAR study. The Division responded that this was a typographical error and that phase 2 will be revised to read as phase 3.

Question 10: *Does the Agency concur with the proposed overall safety evaluation approach?*

Response:
We concur.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 11: *Does the Agency concur that the outlined Phase 3 clinical program (study designs, sample sizes, statistical analysis and endpoints) is adequate to support the indications of* (b) (4) *SAR* (b) (4) *in adults and adolescents 12 years of age and older?*

Response:
While the outlined phase 3 clinical program is adequate, the Division recommends that the Sponsor consider a more streamlined approach. Given the positive results of the phase 3 study in SAR, two additional studies (one in SAR and one (b) (4)), with extensions to obtain long-term safety data, would be adequate to support approval of GPS-301 for both indications.

Discussion:

The Sponsor stated that their reasons for not conducting the two additional studies with extensions to obtain long-term safety data were due to timing, logistical issues and other considerations. The sponsor reiterated that they will not be conducting extension studies for (b) (4) SAR (b) (4). The sponsor indicated that they would like to discuss further the low pH of the formulation since they have now modified their PDP in consideration to the Divisions comments.

Following the above discussion the sponsor then provided the rationale as to why they would like to exclude study subjects with nasal structural abnormality, stating that the main concern is that there may be suboptimal drug delivery which may impact the safety and efficiency. The sponsor affirmed their willingness to include these subjects if the Division strongly recommended it. However, the sponsor reiterated that they would like to exclude subjects with a history of nasal ulceration and erosions, indicating that these pre-existing conditions may manifest in the AE profile. The sponsor presented their modified exclusion criteria and inquired if their proposal was acceptable to the Division.

The Division asked if their product were to be approved, is the sponsor proposing to exclude these patients from real-life use. The Division requested clarification on their rationale for excluding study subjects with a history of nasal ulcerations and erosions. The Division stated that study subjects with a history of nasal ulcerations and erosions are at risk for nasal perforations and that it is known that steroids can cause perforations, and that adding antihistamines along with a low pH pose additional risks. The Division recommended that patients with nasal ulcerations and erosions be included.

The Division noted that earlier programs that had excluded patients with nasal ulcerations and erosions later were required to perform additional studies including them so as to adequately characterize the safety profile of the drug in these higher-risk patients. The Division encouraged the sponsor to include all-comers in order to avoid the need for an additional study. The sponsor addressed the Division's comments on the low pH of their formulation. The Sponsor proposed to formulate a placebo with a higher pH and (b) (4) (b) (4) (b) (4) with a 12-month long-term safety study comparing GSP 301 NS vs 2 different formulations of the placebo.

The (b) (4) (b) (4) Sponsor did not plan to collect the safety comparison data versus Nasonex in their clinical development program. The sponsor asked if this proposal was acceptable to the Division and if the Division had any concerns with the start of the (b) (4) study at any other time other than winter.

The Division acknowledged that the proposed revised study is acceptable in addressing the low pH of the formulation in relation to the safety evaluation. The Division stated that there is not a requirement to compare FDC with Nasonex in

order to gain approval and stated that the placebo controlled long-term safety study will become the basis of the safety labeling in Section 6 of the Prescribing Information, as opposed to the short term safety and efficacy studies. The Division emphasized, that if a signal were observed in the short-term studies it will be included in the label. The sponsor acknowledged the Division's responses. The sponsor's plan to address the low pH of the placebo (b) (4) was acceptable to the Division. Including two placebo arms, one with a low pH and one with a normal pH, should allow for a robust and effectively blinded efficacy comparison to the low pH arm and a robust safety comparison to the normal pH arm.

The Division then remarked that it appeared as if the sponsor still intends to do two SAR studies. The sponsor indicated that it was their intent to demonstrate replication of the evidence. They stated that in their phase 2 studies some of the secondary endpoints, onset of action and the ocular symptoms scores were not successful and therefore did not meet the Division's standards. The sponsor inquired if this would be a concern to the Division.

The Division stated that conducting the two additional studies with the replication of the secondary endpoints can occur in the SAR (b) (4) studies. The Division asked how important it is to obtain the ocular claim in section 14. The sponsor responded that it is their goal to obtain the ocular claim in the label.

The Division stated that if the sponsor is proposing a combination product versus single monotherapy entity then this may pose a higher hurdle to surpass. Adding that, in general, the QOL assessment for ocular symptoms, onset of action or other secondary measures would not necessarily be included in the label. The Division stated that the approval of a SAR only indication may not impact the utility of their product. The sponsor acknowledged that superiority of FDC vs the single monotherapy entities may not be achievable and acknowledged the Divisions remarks.

The sponsor proceeded with requesting assurance that it was the Divisions intention for the second sentence to read '*However, given the findings in your phase 2 SAR study, we do not believe multiple SAR studies in **Phase 3** are necessary to support a SAR indication for your product.*' and not phase 2. The Division affirmed this was a typographical error and the sponsor interpreted the response correctly.

In proceeding to the next clarification item, the sponsor stated that they intend to enroll study subjects within the shortest feasible timeframe to ensure the study is conducted within the relevant allergen season. The Sponsor also requested clarification on the Division's expectation for enrollment 'within a few days' with consideration to the logistics to enroll such subjects in these studies.

The Division emphasized that a reasonable effort should be made to ensure a uniform time-period with respect to allergen exposure.

Question 12: *Does the Agency require device ruggedness evaluations as part of the Phase 3 clinical program?*

Response:
Yes. With reference to the response to question 14 below, and regardless of the fact that subjects will administer the drug with supervision of the study personnel, we expect you to investigate any complaints related to the drug product or device ruggedness and to collect the necessary *in vitro* data to determine if there are issues that need correction. For specific information about systematic drug product characterization studies to be performed for device robustness, we refer you to our recommendations in the *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – CMC Documentation* (July 2002).

Discussion:
The sponsor indicated that they plan to investigate any complaints related to the drug product or device ruggedness and to collect the necessary *in vitro* data to determine if there are issues that need correction. Additionally, they do not plan to use a formal questionnaire or any additional studies to evaluate device ruggedness evaluations in their phase 3 program. The Sponsor inquired if the Division is in agreement with their proposal.

The Division agreed with the Sponsor's proposal.

Question 13: *Does the Agency concur that the overall subject exposure numbers in adult and adolescent subjects with Allergic Rhinitis (AR) outlined in the clinical program is sufficient for approval of this product?*

Response:
The overall exposure appears sufficient to support approval of your product; however, if new safety signals arise, further data may be required.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred

Question 14: *Does the Agency agree in principle that conducting only two of the four Phase 3 studies in the to-be-commercialized 240-spray bottle is sufficient to support the NDA for GSP 301 NS (assuming that adequate supportive in vitro data are provided in the Pharmaceutical Development and Stability sections of the NDA)?*

Response:
Generally we recommend that you use the final to-be-marketed version of the drug product in the critical clinical studies, but your plan to demonstrate comparable *in vitro* product performance during the shelf life for the 120 and

the 240 spray presentations is reasonable. Specifics of the supportive comparative data are expected to be a subject of the CMC end-of-phase 2 meeting.

Discussion:
The Sponsor acknowledged the Division's response. No discussion occurred.

2.3 Biostatistics

Question 15: *Does the Agency concur in that the Clinical Development Plan (CDP) is adequate to support the proposed indication(s)?*

Response:
See response to Question 11.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred.

Question 16: *Does the Agency concur that the sample size estimation of the GSP 301-301 study is adequate and acceptable to support the indication of SAR – (b) (4) in adults and adolescents 12 years of age and older?*

Response:
The proposed sample size appears appropriate based on the information provided. However, as your studies should also demonstrate the efficacy of each single ingredient over placebo (see response to Question 6) you may need to reevaluate the proposed sample size. Your studies should be reasonably sized and powered but it is important to note that a small statistically significant difference may not be clinically meaningful. Further, we expect that the single entities would demonstrate efficacy over placebo and that the combination product would demonstrate efficacy over the single entities with the same magnitude of treatment effect as seen for the single entities over placebo.

Additionally, your gate keeping strategy proposed to adjust for multiplicity for the primary efficacy analyses should include comparisons of the single entities against placebo as well as the combination product compared to the single entities.

Discussion:
In regards to the Combination Rule, the sponsor requested clarification of the statement that the combination should demonstrate efficacy over the single entities with the same magnitudes of effect as seen between the single entities over placebo. The Sponsor inquired if a statistically significant treatment effect size of reasonable magnitude be acceptable to the Agency.

The Division reinforced that each monotherapy must demonstrate superiority to placebo, and that in turn the combination show superiority to each monotherapy.

A statistically significant and clinically meaningful difference on all four endpoints would be necessary to support approval. As to the magnitude of the treatment difference from combination over monotherapies vs. monotherapies over placebo, the Division reinforced that the key point was that treatment differences must be clinically meaningful, and not just statistically significant. The point estimate does not have to be identical for the four endpoints.

Question 17: *Does the Agency agree with the selection of the Last Observation Carried Forward (LOCF) as method to impute missing rTNSS value in the primary analysis of efficacy?*

Response:
No. While the amount of missing data is expected to be minimal in this type of study, we do not recommend single imputation methods such as LOCF. As discussed in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, LOCF is generally not based on reasonable scientific assumptions and is also statistically inappropriate because it is does not take into account the uncertainty in the imputation process. More importantly, steps should be taken to prevent missing data by continuing to collecting safety and efficacy data regardless of treatment adherence. The only reason for withdrawal from the study should be a patient's withdrawal of consent to contribute additional information. We also recommend your sensitivity analyses should include "tipping point" multiple imputation analyses that include the possibility that patients on active drug have worse outcomes than patients on placebo. The methods for handling missing data in the primary efficacy analysis should be pre-specified in the protocol and SAP.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred

Question 18: *Does the Agency agree that RQLQ population will be the primary analysis set for RQLQ endpoint?*

Response:
All patients (not just the RQLQ population) should be included in the primary set. See response to Question 8b.

Discussion:
(b) (4)

(b) (4)

The Division did not agree, and reinforced that the RQLQ included in the label would be for the entire analysis set, with no exclusions by age, language or baseline score.

Question 19: Does the Agency agree that for subjects who discontinue prior to Day 15, the RQLQ score at their withdrawal visit will be used?

Response:
Different methods should be considered to handle patients who discontinued prior to Day 15. See response to Question 17.

Discussion:
Sponsor acknowledged the Division's response. No discussion occurred

Post Meeting Comments:
If nasal exams are to be performed by nonspecialists, the Division encouraged the Sponsor to perform baseline imaging of nasal mucosa so as to allow pre- and post-treatment comparisons for adverse events.

3.0

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should

include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*

3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor slide presentation.

Question 9:

(b) (4)

Question 11: *Does the Agency concur that the outlined Phase 3 clinical program (study designs, sample sizes, statistical analysis and endpoints) is adequate to support the indications of* (b) (4) *SAR* (b) (4) *in adults and adolescents 12 years of age and older?*

Agency's Response:

While the outlined phase 3 clinical program is adequate, the Division recommends that the Sponsor consider a more streamlined approach. Given the positive results of the phase 2 study in SAR, two additional studies (one in SAR and one in (b) (4)), with extensions to obtain long-term safety data, would be adequate to support approval of GPS-301 for both indications.

Sponsor's Response:

The Sponsor acknowledges the response from the Agency but is proposing to conduct the SAR (b) (4) phase 3 studies without an extension for safety. This is in consideration to the proposed long-term safety study, as discussed below, to address the issue raised to take into account the low pH of the formulation in the safety analyses.

Agency's Response:

We have the following additional comments regarding the study design:

1. We note the proposed exclusion of participants with a history of nasal surgery, polyposis, nasal septal deviation, or nasal structural abnormalities in your phase 3 program. These patients should not be excluded from your program, as this would limit the generalizability and external validity of your development program.

Sponsor's Response:

The rationale for the proposed exclusion was to avoid any sub-optimal nasal spray delivery and absorption due to nasal structural abnormalities, which may impact the efficacy and safety assessments. However, if the Agency strongly recommends the Sponsor should include these subjects then subjects with a history of nasal surgery, polyposis, nasal septal deviation or nasal structural abnormality will be included. However, the Sponsor proposes to exclude subjects with a history of nasal ulceration and nasal erosion as these pre-existing conditions are likely to interfere with the interpretation of the safety data.

The modified exclusion Criteria would read as follows:

(b) (4)

Does the Agency Agree?

Agency's Response:

2. We note the low pH of the investigational products (actives and placebo) to be used in the phase 3 clinical development program. While matching pH of the products to be used in each of the treatment arms is essential to maintain blinding for efficacy purposes, the low pH in the placebo group may impact the interpretability of the safety data, as commonly occurring adverse reactions may be underestimated when compared to the low pH of the placebo treatment arm. You should propose a plan to account for this issue in your safety analyses.

Sponsor's Response:

To satisfy the above recommendation on safety analyses the Sponsor proposes to formulate a placebo with a higher pH.

As a result the Sponsor proposes (b) (4) (b) (4) (b) (4) a 12-month long-term safety study comparing GSP 301 NS vs 2 different formulations of the placebo.

The proposed study design will be a double-blind, randomized, 12-month safety study assessing safety at 1 month, 3 months, 6 months and 12 months.

Proposed treatment arms will be:

- GSP 301 NS – 400 subjects
- GSP 301 NS Placebo (low pH) – 200 subjects
- GSP 301 NS Placebo (alternate higher pH) – 200 subjects

Safety assessments will be done similar to the planned safety endpoints for the (b) (4) study (b) (4) but at 1 month, 3 months, 6 months and 12 months. Additionally, some efficacy data will also be collected as part of the secondary endpoints.

(b) (4) (b) (4) the Sponsor is not planning to collect the safety comparison data vs. Nasonex in the clinical development program.

Is this proposal acceptable to the Agency?

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Agency's Response:

3. We note the low pH of the investigational products (actives and placebo) to be used in the phase 3 clinical development program. While matching pH of the products to be used in each of the treatment arms is essential to maintain blinding for efficacy purposes, the low pH in the placebo group may impact the interpretability of the safety data, as commonly occurring adverse reactions may be underestimated when compared to the low pH of the placebo treatment arm. You should propose a plan to account for this issue in your safety analyses.

Sponsor's Response:

The Sponsor wishes to confirm that the repeat of point 2 is a typographical error only and that no additional point has been omitted in this document.

Agency's Response:

As outlined in "*Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products*":

1. Pollen counts should be measured regularly at participating study sites.

Sponsor's Response:

The Sponsor acknowledges the response from the Agency.

Agency's Response:

2. We note that Study GSP 301-302 (b) (4) is slated to begin in August 2016, and will exclude patients with anticipated SAR during the time of study conduct. (b) (4)

Sponsor's Response:

The Sponsor wishes to seek clarification from the Agency (b) (4)
(b) (4)

Agency's Response:

3. For SAR studies, you should randomize all patients at a given study site within a few days to reduce variability in allergen exposure.

Sponsor's Response:

It is the intention of the Sponsor to enroll subjects in these studies within the shortest feasible timeframe to ensure study conduction within the relevant allergen season. The Sponsor requests clarification on the expectation of the Agency for enrollment 'within a few days' with consideration to the logistics to enroll such subjects in these studies.

Question 12: *Does the Agency require device ruggedness evaluations as part of the Phase 3 clinical program?*

Agency's Response:

Yes. With reference to the response to question 14 below, and regardless of the fact that subjects will administer the drug with supervision of the study personnel, we expect you to investigate any complaints related to the drug product or device ruggedness and to collect the necessary *in vitro* data to determine if there are issues that need correction. For specific information about systematic drug product characterization studies to be performed for device robustness, we refer you to our recommendations in the *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – CMC Documentation* (July 2002).

Sponsor's Response:

The Sponsor acknowledges the response from the Agency and is planning to investigate any complaints related to the drug product or device ruggedness and to collect the necessary *in vitro* data to determine if there are issues that need correction. However, no further device ruggedness evaluations will be performed in this phase 3 program.

Does the Agency agree with this proposal?

Question 16: *Does the Agency concur that the sample size estimation of the GSP 301-301 study is adequate and acceptable to support the indication of SAR – [redacted] (b) (4) in adults and adolescents 12 years of age and older?*

Agency's Response:

The proposed sample size appears appropriate based on the information provided. However, as your studies should also demonstrate the efficacy of each single ingredient over placebo (see response to Question 6) you may need to reevaluate the proposed sample size. Your studies should be reasonably sized and powered but it is important to note that a small statistically significant difference may not be clinically meaningful. Further, we expect that the single entities would demonstrate efficacy over placebo and that the combination product would demonstrate efficacy over the single entities with the same magnitude of treatment effect as seen for the single entities over placebo.

Additionally, your gate keeping strategy proposed to adjust for multiplicity for the primary efficacy analyses should include comparisons of the single entities against placebo as well as the combination product compared to the single entities.

Sponsor's Response:

The Sponsor acknowledges that the single entities are expected to demonstrate efficacy over placebo. However, the Sponsor would like to clarify the statement that the combination should demonstrate efficacy over the single entities with the same magnitudes of treatments as seen between the single entities over placebo. It is the intention of the Sponsor to comply with the Combination Rule to confirm statistical superiority of GSP 301 NS against each single entity. Although the Sponsor will make every effort to establish that the combination product demonstrates efficacy over the single entities with the same magnitude of treatment effect as seen for the single entities over placebo, would a statistically significant treatment effect size of reasonable magnitude be acceptable to the Agency?

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA MUSSE
10/05/2015