Dear Mr. Pangu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NER1006 Powder for Oral Solution.

We also refer to your November 20, 2015 correspondence, received November 20, 2015, requesting a meeting to discuss:

- the adequacy of the nonclinical information and reference data to support the NDA
- the adequacy of the proposed phase 3 clinical studies to demonstrate efficacy and safety of NER1006 for the proposed indication in the NDA
- the adequacy of the planned integrated analyses of safety and efficacy in the NDA
- timing for submission and Agency review
- The adequacy of the regulatory filing strategy for the NDA

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, call me, Regulatory Project Manager at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

CDR James Carr, MPAS, PA-C
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 2, 2016, 9:00AM EST-10:00AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 120089
Product Name: NER1006
Indication: bowel preparation before colonoscopy
Sponsor/Applicant Name: Norgine Limited

FDA ATTENDEES (tentative)
Julie Beitz, M.D., Director, Office of Drug Evaluation III
Amy Egan, M.D., M.P.H., Deputy Director (acting), Office of Drug Evaluation III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy Director, Division of Gastroenterology and Inborn Errors Products
Dragos Roman, M.D., Deputy Director, Division of Gastroenterology and Inborn Errors Products
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products
Joette Meyer, Pharm.D., Acting Associate Director of Labeling, Division of Gastroenterology and Inborn Errors Products
Juli Tomaino, M.D., MSCR, Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Charles McQueen, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs, Office of Drug Evaluation III
Wes Ishihara, Regulatory Scientist, Office of Drug Evaluation III
Danuta Gromek-Woods, Ph.D., CMC Lead, Office of New Drug Quality Assessments (ONDQA)
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology and Inborn Errors Products
Dinesh Gautam, Ph.D., Pharmacology Reviewer, Division of Gastroenterology and Inborn Errors Products
Sue-Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3

Reference ID: 3878563
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 February 2, 2016, 9:00AM EST-10:00AM EST, 10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903 between Norgine Limited and the

Reference ID: 3878563
Division of Division of Gastroenterology and Inborn Errors 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. 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). Contact the Regulatory Project Manager (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

NER1006 is being developed for cleansing of the colon in preparation for colonoscopy in adults. IND 120089 for NER1006 was submitted to FDA on December 18, 2013. The phase 1 and phase 2 study reports have been submitted to the IND. An end-of-phase 2 (EOP2) meeting was held on April 16, 2014 to gain FDA guidance on the ongoing developmental program and proposed phase 3 studies. Norgine plans to submit a 505(b)(1) NDA for the proposed indication. Based on the results from the phase 3 clinical studies, Norgine requested this pre-NDA Meeting.

2.0 DISCUSSION

2.1. Non Clinical

**Question 1:** Based on provision of a complete nonclinical package with all nonclinical reports provided, does the Agency agree that no additional nonclinical studies/data are needed to support a 505(b)(1) NDA for NER1006?

**FDA Response to Question 1:** The non-clinical package appears to be adequate to support the NDA. However, if you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you (e.g., published literature, FDA’s finding of safety and/or effectiveness for a listed drug) and for which you have not obtained a right of reference, then your marketing application will be a 505(b)(2) NDA. You must establish a “bridge” between your proposed product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. You must also establish that reliance on studies described in the published literature is scientifically appropriate.

See the 505(b)(2) REGULATORY PATHWAY section below for additional information on submitting a 505(b)(2) NDA.

Reference ID: 3878563
2.2. Clinical

**Question 2:** Does the Agency agree that adequate data have been generated in Phase III to support the proposed 2-day split dosing and 1-day morning split dosing regimens for NER1006 in adults?

**FDA Response to Question 2:** We cannot agree. We have the following concerns regarding the selected endpoints and aspects of the study design that may impact the ability of the phase 3 trials to support approval and product labeling for the 2-day split dosing and 1-day morning split dosing regimens.

**Endpoints: Overall Cleansing Success**

Based on the information provided in the meeting background package, the primary endpoints used in the phase 3 trials, both powered to demonstrate non-inferiority, are as follows:

- Overall bowel cleansing success rate of NER1006 using the HCS, wherein success corresponds to Grades A and B, and failure corresponds to Grades C and D.
- The “Excellent plus Good” cleansing rate in the colon ascendens of NER1006 using the segmental cleansing scoring system of the HCS, wherein the ordinal score of 4 corresponds to Excellent cleansing and score of 3 corresponds to Good cleansing.

- While the definition of an overall bowel cleaning success (i.e., Grades A and B on the Harefield Cleansing Scale [HCS]) is generally similar to the definition of successful bowel cleanse used for the approval of Moviprep, the criteria to define success are different than what was used to support approval for Suprep. If the efficacy of the active comparators was demonstrated using different scales other than the HSC, you will need to justify the use of the HCS to establish non-inferiority, as communicated in the end-of-phase 2 (EOP2) meeting minutes, dated May 6, 2014.

- It is not clear from the background package whether achieving success also required no interference with the exam or complete visualization of the mucosa in cases where small amounts of feces or fluid remained. This requirement was part of the responder definition (i.e., successful bowel cleanse) for both Moviprep and Suprep. Complete visualization of the mucosa is an important aspect of a successful bowel preparation, especially since Grade B (defined by 1 or more segments scored 2, where 2 is described as brown liquid/removable semi-sold stools) is included in the definition of success.

- In addition to the overall cleansing success, defined as Grades A and B on the HCS, we will evaluate the proportion of subjects who achieved Grade A (empty and clean or clear liquid) with complete visualization of the mucosa for NER1006 vs. the

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comparator product. In order to support the prespecified efficacy analysis, NER1006 will need to demonstrate persuasive results that indicate that NER1006 is not worse than the comparator, given the differences in the scales that were used to support the approvals of the comparators vs. the scale used in your trials.

- A key consideration regarding the persuasiveness of the data to support non-inferiority is whether the scoring was performed during advancement or withdrawal of the scope. As communicated in the Advice Letter, dated September 15, 2014, we expressed concerns that any bowel cleaning that occurred during advancement of the scope would not be captured in the primary efficacy data since the proposed scoring was to be performed during withdrawal of the scope. Any cleaning during advancement of the scope would result in a bias toward noninferiority; therefore, assessment of bowel cleansing after irrigation with the scope is not acceptable to support a successful bowel cleansing endpoint. Furthermore, the Moviprep label states that grading of the colon cleanse occurred twice (during introduction and withdrawal of the colonoscope) and the poorer of the two assessments was used in the primary efficacy analysis. As stated previously, it may be difficult to establish noninferiority between NER1006 and the comparator if the scoring method used in the phase 3 trials differs from the scoring used in the trials that supported product labeling for the comparator. To assess the amount of cleansing required, we would also expect to see documentation of the amount of irrigation (e.g., volume of water) required to reach the cecum reported in the NDA submission. In the NDA submission, also include the training manual that describes how the colonoscopy procedure and scoring were standardized across the study sites.

Endpoints: “Excellent plus Good cleansing in the colon ascendens”
- The endpoint of “Excellent plus Good cleansing rate in the colon ascendens” is unlikely to support product labeling since it is important to visualize the mucosa along the entire colon during colonoscopy, as communicated in the EOP2 meeting minutes, dated May 6, 2014. While the data may support individual subjects who met the criteria for success on both overall cleansing and excellent plus good in the ascending colon, the comparator products are not indicated for cleansing in the ascending colon; therefore, demonstrating non-inferiority to a product(s) that is not approved for this specific indication would not be sufficient. However, we would consider this endpoint further if superiority were demonstrated over the comparator.

Administration of the Comparator
- The split-dose regimen of Moviprep during the MORA study is not consistent with the administration instructions in the Moviprep label. In the background package, page 59/200, the description of the Moviprep 2-day split-dosing regimen states that “intake of the complete preparation and mandatory additional clear fluid must be completed at least 1 hour prior to colonoscopy. Additional clear fluids could be drunk ad libitum, however all fluid consumption had to have ceased at least 1 hour before the colonoscopy procedure.” In contrast, the current label for Moviprep
recommends that the preparation and fluid intake be completed at least 2 hours before the colonoscopy. To demonstrate noninferiority, the administration of the comparator should be consistent with the approved labeling. Completion of the preparation 1 hour before the colonoscopy instead of 2 hours, as labeled, may bias the trial results toward noninferiority.

- We note that the type of meal and time interval between the last meal and the initiation of the bowel preparation were different between the NER1006 and Moviprep arms. During the NDA review, we will consider the potential impact of those differences in diet on the observed efficacy outcomes of the trial.

1-day Morning Split Dosing Regimen
- We will need to review the data for the 1-day morning split dose to determine whether the safety and efficacy data support approval of product labeling for this regimen. As communicated in the EOP2 meeting minutes, dated May 6, 2014, split dosing of bowel preparations has emerged as an important factor in bowel cleansing efficacy and patient tolerability. Accordingly, the American College of Gastroenterology and the US Multi-Society Task Force on Colorectal Cancer recommend the 2-day split-dose regimen as the preferred method of administration,3 and this has also been reflected in recently approved bowel cleansing products.4

- The 1-day morning split dose regimen was evaluated in one trial (i.e., MORA). In general, a single phase 3 trial may support product labeling, but the results of a single trial would need to be both clinically meaningful and highly statistically persuasive. Since there is no clear precedent for morning-only dosing from a regulatory standpoint, upon review of the data, replication of the efficacy and safety findings may be required to support product labeling of the 1-day morning split dose regimen. For additional information on circumstances where reliance on a single adequate and well controlled trial might be acceptable to establish effectiveness, refer to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. The adequacy of this single trial may be impacted by the administration schedule of the comparator. See our concern above under “Administration of the Comparator.”

Statistical Analysis of Primary Endpoints
- The multiplicity procedure you currently propose based on the Hochberg does not control the overall type I error rate. If you plan to test the key secondary endpoint when only winning on one of the two alternative endpoints, you should consider another multiplicity procedure that allows you to test the key secondary endpoint without the need to win on both alternative endpoints if the blind has not been broken.

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**Question 3:** Does the Agency agree that although superiority was demonstrated in the Per Protocol Set, as superiority was not demonstrated in the modified Full Analysis Set for the DAYB study, a day-before, 1-day split dosing regimen cannot be supported for NER1006 in adults?

**FDA Response to Question 3:** Yes, we agree that the per-protocol data from the day-before, 1-day split dosing regimen cannot be used to support the efficacy of NER1006 in adults. The comparator used in the DAYB study is not approved in the United States and we would not consider the data unless superiority was demonstrated in the mITT population.

**Question 4:** Does the Agency agree that the data generated during the clinical development support the proposed indication “for cleansing of the colon in preparation for colonoscopy in adults”?

**FDA Response to Question 4:** We cannot agree at this time. The wording of the indication statement ultimately will be a review issue; however, the design of the clinical program in general appears to be sufficient to allow for review of the data intended to support the proposed indication. The indication will reflect the study population and study design of the phase 3 trials that are submitted to support product labeling.

**Question 5:** Does the Agency agree on the adequacy of the clinical studies to support the efficacy and safety of NER1006 and that data are adequate across the NER1006 clinical program to support a NDA for NER1006?

**FDA Response to Question 5:** See our response to Question 2 for comments on the adequacy of the clinical trials related to efficacy. We cannot comment on the adequacy of the safety data at this time until after review of the data provided in the NDA; however, the safety profile of NER1006 will need to be similar or improved over the comparator product(s) to support approval. In general, the number of subjects exposed to NER1006 and the safety monitoring appear to be reasonable, given that biochemistry and hematology data are available in an adequate number of subjects after completion of the trials (i.e., 1 week post-colonoscopy) to assess renal function and electrolyte abnormalities.

**Question 6:** Does the Agency agree with the proposal to use only data from the Phase III NOCT and MORA studies, and not include the DAYB study, in the integration of efficacy?

**FDA Response to Question 6:** Yes, we agree that the efficacy data from the DAYB study should not be included to support efficacy. The DAYB study should not be included in the Integrated Summary of Efficacy (ISE). In general, analyses included in the ISE are for exploratory purposes. The data provided in the ISE are not relied upon to support product labeling; therefore, you should submit separate study reports with datasets for each phase.
We remind you that the efficacy data should not be pooled across treatment arms in the analyses presented in the individual study reports and corresponding datasets. It would not be acceptable to combine the NER1006 treatment arm data to show non-inferiority to the comparator arm.

**Question 7:** Does the Agency agree that the primary data supporting the efficacy and safety of NER1006 in the Integrated Summary of Efficacy and Integrated Summary of Safety, for inclusion in a NDA, will be based upon integrated data from the Phase III studies, with Phase I and II study data being supportive?

**FDA Response to Question 7:** Yes, it is acceptable to rely upon phase 3 studies for inclusion into the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), with phase 1 and 2 study data being supportive.

**Question 8:** Does the Agency agree with the proposed strategy for pooling of safety data from the three Phase III clinical studies into three different pools for NER1006?

**FDA Response to Question 8:** The pooling of safety data from three phase 3 trials (i.e., NOCT, MORA, and DAYB) into the three proposed pools is reasonable for inclusion into the Integrated Summary of Safety (ISS); however, pooling of safety data in the individual study reports would be considered as an exploratory analysis. In the individual study reports, you must present safety analyses that do not pool data. The safety data obtained from the DAYB study are insufficient to support product labeling since the comparator product is not approved in the United States.

**Question 9:** Does the Agency agree with the proposed safety parameters for the evaluation of data in the Integrated Summary of Safety, including the intent to summarize the data in the three defined safety pools, in a NDA for NER1006?

**FDA Response to Question 9:** In general, the proposed safety parameters appear reasonable for inclusion into the Integrated Summary of Safety (ISS). In addition, as communicated in the EOP2 meeting minutes, dated May 6, 2014, the type and amount of intravenous fluids given during the colonoscopy should also be described, along with the use or interruption of concomitant medications during the procedure. We would also expect to see the results of the laboratory analyses to assess electrolytes and renal function at 48-72 hours after the colonoscopy, 1 week post-colonoscopy follow-up, and any abnormal laboratory values that were followed until resolution. See our response to Questions 6 and 8 for comments on the pooling of data.

**Question 1:** Does the Agency agree with Norgine’s proposal to evaluate safety for the proposed subgroups in the Integrated Summary of Safety for NER1006?
FDA Response to Question 10: The evaluation of safety for the proposed subgroups in the Integrated Summary of Safety (ISS) appears reasonable. You should also perform these subgroup analyses for inclusion in the individual study reports for both of the phase 3 trials (i.e., MORA and NOCT). See our response to Question 8.

**Question 2:** Does the Agency agree with the proposal to present the results of the two alternative primary endpoints for each individual study for efficacy of NER1006 in support of a NDA for NER1006?

FDA Response to Question 11: See our response to Question 2.

**Question 3:** Does the Agency agree with the proposal to combine key secondary endpoint data from 1) the NOCT and MORA studies for 2-day split dosing, and 2) the pooled 2-day and 1-day split dosing for the MORA study combined with the 2-day split dosing for the NOCT study?

FDA Response to Question 12: No, we cannot agree to your proposed plan to pool efficacy data to support approval of secondary endpoints. Combining the data from the key secondary endpoints may be reasonable for the Integrated Summary of Efficacy (ISE); however, the study reports for each of the phase 3 trials should include direct comparisons between treatment arms for the key secondary endpoints in each trial. Since the comparators used in these studies were different products, the comparison based on pooled data may not be meaningful to assess efficacy of the secondary endpoints.

**Question 4:** Does the Agency agree with the proposed strategy for the assessment and statistical analysis of key secondary endpoints for efficacy of NER1006 in support of a NDA for NER1006?

FDA Response to Question 13: See our response to Question 12.

**Question 5:** Does the Agency agree with the proposed strategy for the assessment and supportive statistical analysis of BBPS outcomes in support of a NDA for NER1006?

FDA Response to Question 14: The proposed strategy for the assessment and supportive statistical analysis of the Boston Bowel Preparation Scale (BBPS) appears acceptable for exploratory purposes. See also our response to Question 12.

**Question 6:** Does the Agency agree with the proposed subgroups for exploratory evaluation within the Integrated Summary of Efficacy, in support of a NDA for NER1006?

FDA Response to Question 15: Yes, this approach seems to be reasonable for the proposed subgroups for exploratory evaluation in the Integrated Summary of Efficacy (ISE). Subgroup analyses should also be performed for efficacy and presented in the individual
study reports for the phase 3 trials. The individual study reports and corresponding datasets should not include pooled or combined data across treatment arms. See our response to Question 6.

**Question 16:** Does the Agency agree with the proposed Statistical Analysis Plans as a proposal for the Integrated Summaries of Safety and Efficacy for NER1006?

**FDA Response to Question 16:** In general, the data provided in the ISS and ISE are not relied upon to support product labeling. These analyses will be considered as exploratory. See our responses to Questions 6, 8, and 12.

**Question 17:** Does the Agency agree that the proposed plans provide appropriate data integration and analysis to support a NDA for NER1006?

**FDA Response to Question 17:** See our response to question 16.

2.3. Regulatory

**Question 18:** Does the Agency agree that, based on the inclusion of new clinical investigations, and a complete nonclinical package with study reports, the approval of the proposed 505(b)(1) NDA for NER1006, as a novel combination of known actives, will meet the requirements for 3 year exclusivity?

**FDA Response to Question 18:** We cannot agree at this time. FDA does not make exclusivity determinations pursuant to Sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described in 21 CFR 314.50(j), you should include in the NDA a description of the exclusivity to which you believe you are entitled. We will consider your assertions regarding exclusivity after approval of the application.

**Question 7:** Does the Agency agree with the proposed organization of the eCTD NDA?

**FDA Response to Question 19:** From a technical standpoint (i.e., not content related), the proposed format for the planned NDA is acceptable. We have the additional comments below.

- 1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.

- Study Tagging Files are only required in m4 and m5 (not m2 and m3). Attributes are required in m2 and m3.
• For Drug Substance of the same (e.g., Ascorbic Acid and Sodium Ascorbate) with different manufacturer, it is acceptable to provide a single 2.3.S and 3.2.S section for “Ascorbic Acid” and a single 2.3.S and 3.2.S section for “Sodium Ascorbate” using “ALL” as the manufacturer’s attribute and use leaf titles to differentiate between manufacturers. Additionally, indicating the substance at the beginning of leaf title helps sorting abilities when sorting by substance (e.g., Ascorbic Acid-General Information- and Ascorbic Acid-General Information-).

• Ensure that your approach to submit module 2 summaries, fits the DTD and the “http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/...pdf

• Providing Table of Contents in m5.1 is not necessary in the eCTD structure. The reviewer’s aid submitted in the cover letter section should also entail m5 section.

• Ensure that all “Appendices” under the study tagging file (STF) are properly file tagged.

**Question 8:** Does the Agency agree with Norgine’s proposal to address the Fixed Dose Combination Rule in accordance to 21CFR 300.50 by providing Pharmaceutical Development and clinical study data?

**FDA Response to Question 20:** In general, your approach seems reasonable; however, we will need to review the data to determine whether the Fixed Dose Combination Rule has been addressed. To address the Fixed Dose Combination Rule under 21 CFR 300.5, you should submit evidence (e.g., pharmacodynamic or clinical efficacy data, or both) to demonstrate that each component of NER1006 makes a contribution to adequate bowel preparation. Since the diet contributes to the quality of the preparation, you should also address how variations in diet strategies contribute to the bowel preparation to support that the fixed dose combination rule has been met.

We note that various combinations of active components, the amount of liquid intake, as well as dosing regimen were studied in the OUT and OPT studies. To facilitate the review, we request that you provide a short summary of the effect of each variation (e.g., effect of ascorbate dose, effect of liquid intake, etc). In addition, the effect of different dosing regimens on pharmacodynamic (PD) or clinical endpoint(s) should also be presented by total osmolarity of each dose and total dose.

**Question 9:** Does the Agency agree that the data to support applicability of the Fixed Combination Rule can be summarized and submitted in Module 2 of the proposed NDA?
**FDA Response to Question 21:** Yes, we agree.

**Question 10:** Is the proposed format and output of the Clinical Study Reports and Integrated Summary of Safety/Integrated Summary of Efficacy for NER1006 to be included in Module 5 acceptable to the Agency in support of a NDA submission?

**FDA Response to Question 22:** Providing the Clinical Study Report in full eCTD format with each component included as a separate PDF is acceptable. In the background package, the details of the components of Module 5.3.4.1 and 5.3.4.2 are listed; however, specific information was not provided for the proposed contents of Module 5.3.5, which will contain the phase 3 trials (i.e., NOCT and MORA). Module 5.3.5 should also include all of the related information (e.g., synopsis, protocol, list and description of investigators, protocol deviations, etc) for the NOCT and MORA studies.

Based on the information provided on the eCTD structure in the background package, only datasets were included in Module 5 (M5). In the meeting request, dated 11/20/2015, it appears that only SDTM data will be submitted for each individual trial and ADAM for ISS and ISE. Provide the SDTM version for the submission. In addition to SDTM and ADAM data, a CRF, define file, and SAS programs for ADAM and primary and key secondary endpoints are required for the NDA submission.

**Additional FDA Comments**

**Clinical**

1) Given that the patient reported outcome (PRO) instrument, “BOCLIR,” is not considered adequately qualified as per current FDA Guidance.

**Clinical Pharmacology**

2) Based on your background information, it is unclear if you have measured metabolites of PEG3350, including but not limited to, ethylene glycol (EG) and diethylene glycol (DEG), while apparently you measured other analytes including PEG3350, ascorbate, sulfate, and oxalic acid in plasma, urine, and feces. We recommend you measure the additional metabolites of PEG3350, including but not limited to, diethylene glycol and ethylene glycol in previously collected specimens of plasma and urine.

3) The systemic exposure to potentially toxic metabolite(s) of EG and DEG, such as glycolic acid, should be studied. Per literature information, the important metabolites of EG, DEG are glycolic acid, glyoxylic acid, glycoaldehyde, oxalic acid, 2-hydroxyethoxyacetic acid (HEAA), and diglycolic acid. You may study a subset of...

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Reference ID: 3878563
metabolites with justification.

4) We recommend that you provide the summary of bioanalytical assay methods and the bioanalytical assay validation results for each component in Module 2.7.1, with hyperlinks to the bioanalytical assay validation reports and bioanalytical assay reports in Module 5.3.1.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 4, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

4.0 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.

5.0 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.

### 6.0 **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.

<table>
<thead>
<tr>
<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Example: Published literature</td>
<td>Nonclinical toxicology</td>
</tr>
<tr>
<td>2. Example: NDA XXXXXX “TRADENAME”</td>
<td>Previous finding of effectiveness for indication X</td>
</tr>
<tr>
<td>3. Example: NDA YYYYY “TRADENAME”</td>
<td>Previous finding of safety for Carcinogenicity, labeling section XXX</td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
</tbody>
</table>

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.
7.0 **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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item⁶</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
[m5]
  [datasets]
    [bimo]
      [site-level]
```

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.

⁶ Please see the OSI Pre-ND/BLA Request document for a full description of requested data files.
References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

For general help with eCTD submissions: ESUB@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN K STRONGIN
01/27/2016
IND 120089

MEETING MINUTES

Norgine Limited
Attention: Abhijit Pangu, RAC
Senior Regulatory Affairs Manager
50 Division Street, Suite #206
Somerville, NJ 08876 USA

Dear Mr. Pangu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NER1006 Powder for Oral Solution.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2014. The purpose of the meeting was to discuss the Agency’s feedback on Norgine’s clinical program.

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) 402-4276.

Sincerely,

{See appended electronic signature page}

Kelly Richards, MSN, RN
Captain, USPHS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: April 16, 2014, 9:00 a.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 120089
Product Name: NER1006 Powder for Oral Solution
Indication: Bowel clearance that requires a clean bowel
Sponsor/Applicant Name: Norgine Limited

Meeting Chair: Robert Fiorentino, M.D., MPH
Meeting Recorder: Kelly Richards, RN, MSN

FDA ATTENDEES
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Robert Fiorentino, M.D., MPH, Medical Team Leader, DGIEP
Preeti Venkataraman, M.D., Clinical Reviewer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, Ph.D, Pharmacologist, DGIEP
Kevin Bugin, MS, RAC, Senior Regulatory Health Project Manager, DGIEP
Kelly Richards, RN, MSN, Regulatory Health Project Manager, DGIEP
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Hamid Shafiei, Ph.D., Quality Reviewer, Office of New Drugs Quality Assessment (ONDQA)
Freda Cooner, Ph.D., Statistical Team Lead, Office of Biostatistics, (OB) Division of Biostatistics III (DBIII)
Nneka Onwudiwe, Pharm.D., PhD, MBA, Regulatory Reviewer, Office of Prescription Drug Promotion (OPDP)
Meeta Patel, Pharm.D., Regulatory Reviewer, OPDP

Reference ID: 3501946
1.0 BACKGROUND

The Sponsor submitted IND 120089 for NER1006 to FDA on 18 December 2013 and became effective on 18 January 2014. Based on availability of the Phase II results, Norgine requests an End of Phase 2 meeting to discuss and obtain agreement on the following items:

1) The adequacy of the CMC documentation to support the Phase III clinical trial program.
2) The adequacy of the nonclinical data to support the safety of NER1006.
3) The adequacy of the completed Phase II clinical trial to provide evidence of dose selection for the Phase III clinical trial program.
4) The adequacy of clinical safety data from Phase I/II to support a Phase III clinical trial program.
5) The adequacy of the proposed Phase III clinical trial program to generate evidence of efficacy and safety of NER1006 for the proposed indication.

To this effect, the Sponsor submitted a meeting request to the Division of Gastroenterology and Inborn Errors Products on February 15, 2014. The meeting was granted and occurred on April 16, 2014.

2.0 DISCUSSION

**Question 1:** Does the Agency agree that the available stability data on the NER1006 investigational product expected to be available at the projected time of Phase III study start
should be sufficient to support the use of the new flavor formulations in the planned Phase III clinical study program?

**FDA Response to Question 1:**
Yes, we agree that six months of stability data for the new flavor formulation at the time of initiating Phase 3 trials will be acceptable.

**Question 2**
*Does the Agency agree that the proposed CMC data are adequate to support the conduct of the Phase III clinical trial program?*

**FDA Response to Question 2:**
The CMC information you have provided in the briefing package generally support the use of your proposed formulation in the Phase 3 trial. However, your product will need to be formulated with PEG that contains a sufficiently low content to ensure that the daily dose of these two impurities does not exceed 8 mg/day. In addition, you will need to include specification limits for the impurities identified in our response to question 4.

**Question 3**
*Does the Agency agree with the proposed manufacturing strategy and that an increase in scale of the manufacturing process and potential changes to manufacturing line are acceptable to implement after completion of Phase III, and prior to NDA submission?*

**FDA Response to Question 3:**
Your proposal to scale up the manufacture of your product for commercialization, after completion of your Phase 3 trial will be acceptable if the manufacturing scale of the Phase 3 batches is no less than [redacted] of commercial scale and both processes use comparable manufacturing equipment.

**Question 4**
*Does the Agency agree that the available nonclinical safety information is sufficient to support NER1006 for the Phase III clinical studies and the NDA?*

**FDA Response to Question 4:**
We have identified the following issues that need to be addressed prior to phase 3:

- The proposed specification for [redacted] (NMT [redacted]) and [redacted] (NMT [redacted]) in NER1006 formulation Pouch b [redacted] is above the ICH qualification threshold (ICHQ3A) of 0.05% and is not acceptable.
- You need to provide toxicological qualification of [redacted] in the drug product to support the specification of NMT [redacted].
- [redacted] is weakly genotoxic and showed positive results in 2-year carcinogenicity studies in male rats and mice (NTP). The specification of [redacted] in the drug product (Pouch b) has to be set per the draft ICH M7 Guidance [Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic
Risk, February 2013] at a level sufficient such that daily exposure to PEG 3350 from the drug product does not exceed 1400mg per day.

- You need to provide the levels of the following impurities if present in the drug substance/drug product: [ These impurities have been associated with PEG 3350. In addition, you also need to qualify the levels of these impurities if they exceed the acceptable limits. [ICH Q3A and ICH Q3B(R2)]

**Question 5**

*Does the Agency agree that adequate evidence of efficacy and safety, and justification for the recommended formulation and dosage regimen (OPT007) have been provided in support of initiation of the Phase III studies?*

**FDA Response to Question 5:**

Because it does not appear that you evaluated a clinically meaningful endpoint in your phase 2 trial, we cannot assess whether preliminary evidence of efficacy was achieved. In addition, it is difficult to assess whether preliminary evidence of safety was established as subject-level safety data were not submitted in your phase 2 study report.

**Discussion:**

*The Sponsor clarified that they evaluated bowel cleansing with the HCS in part B of their phase 2 study. They will submit the data to the IND.*

**Question 6**

6a) *Does the Agency agree that Norgine’s strategy for the conduct and the design of the Phase III clinical study program (i.e. with studies #1 and #2 as described above, using a trisulfate-based bowel preparation and MOVIPREP® as the respective comparator products) will generate data that could support the two dosing regimens, split-dosing (evening/morning) and morning-only dosing?*

**FDA Response to Question 6a:**

Because you have provided only protocol synopses, we cannot provide definitive comments regarding all study design elements. However, we do not agree with your proposed co-primary endpoint model using both an overall success rate and mean change in the HCS for ascending colon. You have not defined what constitutes a successful bowel cleansing based on the HCS within the synopses. Given that the efficacy of the active comparators in your proposed non-inferiority trials was demonstrated using different scales, you will need to justify the use of HCS to establish non-inferiority.

In addition, we cannot accept a mean change in a numerical scale to define successful bowel cleansing as you have not provided adequate justification for what would be a clinically meaningful difference between mean HCS scores. We recommend that you redefine your primary endpoint to be a clinical response based on a prespecified definition of successful bowel cleansing (e.g., proportion of subjects with an “excellent” bowel cleansing).
Adequate visualization is critical for early detection of lesions, and the current practice guidelines recommend the split-dose regimen due to improved quality of preparation, patient compliance, and increased adenoma and polyp detection rates.\(^1\) Split dosing of bowel preparations has emerged as an important factor in bowel cleansing efficacy and patient tolerability.\(^2\) Accordingly, the American College of Gastroenterology guidelines for colorectal cancer screening (2008) recommend that bowel preparations be given in split doses. We typically recommend the split-dose regimen as the preferred method of administration for colorectal cancer screening and this has been reflected in recently approved bowel cleansing products. There is no clear precedent for morning-only dosing from a regulatory standpoint. In addition, we are not aware of randomized controlled trials evaluating a morning-only dosing regimen as an adequate bowel preparation.

6b) Does the Agency agree that data from the Phase III non-US study(ies)/sites can be submitted in support of an NDA for NER1006?

FDA Response to Question 6b:
Data from non-US studies may be submitted for review. The sponsor is reminded that they must ensure that the study complies with the requirements in 21 CFR 312.120 in order to use the study as support for application for marketing approval.

Discussion:
The Agency emphasized the importance of targeting the achievement of an excellent score. The Agency is concerned that the definitions of the various sub scores are not currently precisely defined well enough to be reproducible among endoscopists. The Sponsor stated that they would have central and local reads. The Agency stated that the definition of the scores still needed to be more clearly delineated. The Sponsor presented that scoring would only occur during withdrawal of the scope from the cecum. The Agency expressed concern that any cleaning that occurred during advancing the scope to the right colon would not be captured in the primary efficacy data since the current plan is only to do scoring during withdrawal. This needs to be addressed in the protocol plan because cleaning during advancement of the scope would result in bias towards non-inferiority.

The Sponsor presented published data that reportedly showed that morning only regimens are non-inferior to split-dose. They will submit those publications for Agency review. The Agency asked if the phase 2 results established the time interval necessary for patients to complete the cleansing and leave their home to travel to endoscopy. This will be important information for planning the phase 3 trial, labeling, and assessing whether the time interval is in fact akin to “day before dosing”.

Question 7

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**Does the Agency agree that the proposed clinical development plan for NER1006 will provide sufficient evidence of safety in the intended population to support an NDA for NER1006 in the two dosage regimens, split-dosing (evening/morning) and morning only dosing?**

**FDA Response to Question 7:**
We cannot agree given our previous concerns regarding your clinical development program. It appears that the duration of the exposure to the study drug will be sufficient to allow for an assessment of the safety of your drug product in phase 3. However, whether or not your data will provide evidence of safety in the intended population will need to be reviewed at the time of the NDA submission.

**Question 8**

8a) Does the Agency agree that Norgine’s strategy for the conduct and the design of the Phase III Clinical Study #3 (i.e. as described above, using a sodium picosulfate + magnesium citrate-based product as the comparator product) will generate data that, taken together with Studies #1 and #2, could support the addition of a day before-only dosing regimen to the product labelling?

**FDA Response to Question 8a:**
We cannot agree given our previous concerns regarding the planned study designs in your clinical development program (see 7). We typically recommend the split-dose regimen as the preferred method of administration for colorectal cancer screening. However, the day-before-only dosing approach may be acceptable as an alternative dosing method for patients whom the split-dosing is inappropriate.

One of the concerns regarding preparations administered entirely the day before colonoscopy is the impaired visualization of the colon due to residual fecal matter. In patients who take the last purgative dose 8 to 12 hours before colonoscopy, small bowel effluent can reaccumulate in the cecum and ascending colon, making visualization of mucosal detail difficult.3 On pages 179-180 of the Final Synopsis of the DAYB study (Study #3), you indicate that on the day of colonoscopy, Group 2 should take the first sachet of SP+MC product at 08:00, and the second sachet be administered 6 to 8 hours later. This dosing is not consistent with the day-before dosing regimen of PREPOPIK. These patients will also be instructed to intake only clears after the first 08:00 dose of SP+MC, which raises concern regarding food compliance with this regimen. There is a significant amount of time that fecal effluent may accumulate prior to colonoscopy in Group 2. In addition, patients in Group 1 of this study will be receiving NER1006 at 18:00H and a second dose 1-2 hours later. As there is a difference in timing of 10 hours of drug product administration in the two groups, it may be difficult to rely on Group 2 as an adequate comparator. Please clarify your proposed timing and administration of the SP+MC treatment in Group 2.

**Discussion:**
The Sponsor clarified that their pico-sulfate based bowel regimen is not the same as Prepopik because it has different composition and dosing schedule. The Agency stated that

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3 [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2886377/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2886377/)
this comparator could not be used to establish non-inferiority because it is not approved in the United States. In order for this comparator to support approval in the United States, superiority must be established, and the Sponsor would have to provide evidence that NER1006 has comparable effectiveness to FDA approved bowel regimens.

8b) Does the Agency agree that the full clinical development program for NER1006 (Studies #1, #2 and #3) should generate sufficient evidence of safety in the intended population to support an NDA for NER1006 in the three dosage regimens, split-dosing (evening/morning), morning-only dosing and day before-only dosing?

FDA Response to Question 8b:
We cannot agree given our previous concerns regarding your clinical development program (see 7).

**Question 9**
Does the Agency agree with the proposed statistical design and testing strategy?

FDA Response to Question 9:
No, we do not agree. Co-primary endpoints, by definition, should both demonstrate statistically significant treatment benefit in order to declare a successful trial. Moreover, your currently proposed gate-keeping scheme with the Hochberg method at each step for the multiplicity adjustment is inadequate. It is unclear when using a non-separable method, such as Hochberg, how much alpha or whether any alpha can be carried over to the next step if at least one of the comparisons at that step fail to show statistical significance. Hence, it is questionable whether the study-wise Type I error rate can be controlled under 5% using your proposed multiplicity adjustment scheme. Finally, you should provide detailed justification for your proposed non-inferiority margin using historical data on the primary efficacy endpoint(s). For more details on the study design and non-inferiority margin of a non-inferiority study, please refer to the draft FDA guidance entitled, “Guidance for Industry: Non-Inferiority Clinical Trials,” located at the following web address:

From a clinical standpoint, your proposed non-inferiority margin should not be larger than the differences in effect sizes observed in recent trials (i.e., to avoid “biocreep”).

**Discussion:**
The Sponsor clarified that they wanted to design the study such that success can be declared when ascending colon meets the pre-specified criteria but the overall assessment does not show non-inferiority. The Agency stated that this scenario was highly unlikely to support approval since it important to visualize the mucosa along the entire colon during endoscopy. For this reason we cannot agree to your proposed testing strategy.

**Question 10**
Does the Agency agree that the change from \( \text{(b)(4)} \) to one pouch for the first dose formulation is acceptable and that it is appropriate in Phase III studies for the patients to be responsible for the preparation of the solutions for self-administration at home?

**FDA Response to Question 10:**
As long as patients are adequately educated regarding administration of the drug product, it appears acceptable for adult patients to prepare and self-administer the formulations at home. The method of administration would be reflected in the labeling.

**Question 11**
Does the Agency agree that data from subjects who are undergoing screening, surveillance or diagnostic colonoscopies in the Phase III studies will support a label indication of ‘use prior to any clinical procedure requiring a clean bowel, e.g. colonoscopy, \( \text{(b)(4)} \)?

**FDA Response to Question 11:**
No, we do not agree. The effectiveness of bowel preparation that is necessary for a

**Question 12**
Does the Agency agree with Norgine’s approach to evaluation of NER1006 in renal and cardiac impaired subjects?

**FDA Response to Question 12:**
Patients with mild renal and cardiac insufficiency will be included in the study. As patients with moderate renal and cardiac impairment will require bowel cleansing for colon cancer screening as well, it is unclear if excluding these patients is appropriate. Please justify your rationale for excluding these patients.

**Question 13**
*Does the Agency agree that a special study in patients with hepatic impairment is not needed?*

FDA Response to Question 13:
Yes, we agree.

**Question 14**
*Does the Agency agree that a TQT study is not required?*

FDA Response to Question 14:
Yes, we agree.

**Question 15**
*Does the Agency agree that the validated BOCLIR PRO instrument is adequate?*

FDA Response to Question 15:
Because BOCLIR is not considered adequately validated as per current FDA Guidance, In addition, the Office of Prescription Drug Promotion (OPDP) has provided the following comments:

Therapeutic compliance or drug regimen compliance is the extent to which the patient's medication-taking behavior, in terms of actual history of drug administration, corresponds to the prescribed regimen—both quantity and timing of dose(s). This term is often used interchangeably with adherence, however, compliance and persistence are both a function of adherence.

There’s no true gold standard and each method has its strengths and weaknesses. There are several methods for assessing compliance: pill count, the easiest to perform, however this method has limited accuracy because it assumes that the patient has ingested the medication; patient-recall assessment/patient interview is also easy to perform, however, it’s also a crude method with limited accuracy; assessment of medication refill history, does not provide information on actual drug administration; electronic monitoring, only provides information on timing and dosing interval between administration; pharmacological assessment of body fluid or tissue to detect active drug or metabolite, however, may not be ideal for drugs with a short half-life; and direct observation of the patient receiving the medication.
The accuracy of the compliance method should be determined by its validity (sensitivity and specificity) and the reference standard used to test the method in question. In addition, the assessment of patient compliance should take into account factors affecting therapeutic compliance such as demographic factors, side effects, duration of treatment, route of administration, efficacy, etc.

**Question 16**
*Does the Agency agree that, except for the proposed Phase III safety and efficacy studies, no additional clinical studies are needed to support an NDA for the proposed adult indication?*

**FDA Response to Question 16:**
Since two or more drugs are combined in a single dosage form, the Combination Rule needs to be addressed under 21 CFR 300.50. To address the Combination Rule, the Applicant should submit evidence (e.g., pharmacodynamic (PD) or clinical efficacy data, or both) to demonstrate that individual components of NER1600 would be inferior to the combination in providing adequate bowel preparation.

**Additional Comments to Sponsor:**

1) In your phase 2 study, subjects’ electrolytes were assessed during the screening period, the day before the colonoscopy, and on the day of colonoscopy. There was no follow-up after the completion of the study, so it is unclear if any patients experienced subsequent dehydration or electrolyte abnormalities. As osmotic bowel preparations are known to cause fluid shifts, electrolyte derangements, and dehydration, follow-up should extend beyond the day of colonoscopy to assess renal function and electrolytes in your phase 3 trials. At a minimum, we recommend laboratory testing before colonoscopy, on the day of colonoscopy, within 48-72 hours of colonoscopy, and at 1 week post-colonoscopy. Patients should have orthostatic blood pressure measurements before and on the day of colonoscopy, as well as adequate discharge instructions regarding fluid intake. Because concomitant medications (e.g., sedation medications used for the procedure, diuretics) and drug product use (e.g., volume actually consumed by subjects, reason(s) for not consuming the entire volume) may provide useful information in the assessment of safety and efficacy of your product, we encourage you to capture and record concomitant medications and details of product use within the clinical trials. The type and amount of intravenous fluids given during the colonoscopy should also be captured, as well as use (or interruption) of antihypertensives (ACEi/ARB’s, diuretics, etc.)

**Discussion:**
*At the meeting, the Sponsor proposed submitting responses to questions 15 and 16 via Sponsor-submitted minutes. The Agency points out that in order to provide official responses, we would require questions to be proposed in formal correspondence.*
As stated in the meeting, there were additional comments that were not included in the preliminary meeting comments correspondence. These comments are listed below:

**Additional Clinical Pharmacology Comment:**
The systemic exposure to the active components of your proposed product, including PEG-3350, sulfate and ascorbate, should be characterized.

### 4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.


### 5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
6.0 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 CDER/CBER Position on Use of SI Units for Lab Tests.

7.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.
8.0    ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion identified during the meeting. However, the Sponsor, while acknowledging understanding that FDA’s meeting minutes are considered the official record of the meeting, intends to submit their responses to part of Question 9 and to the entirety of Questions 15 and 16 that were not discussed due to time constraints. These responses will be submitted to the IND as Sponsor Meeting Minutes.

9.0    ATTACHMENTS AND HANDOUTS

The Sponsor provided OPT Protocol Appendix E The Harefield Cleansing Scale© as a handout during the meeting.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KELLY D RICHARDS
05/06/2014