



NDA 218828

COMPLETE RESPONSE

Zealand Pharma US, Inc.
Attention: Christopher DeFusco, PhD
Head of US Regulatory Affairs
50 Milk Street, 16th Floor
Boston, MA 02109

Dear Dr. DeFusco:

Please refer to your new drug application (NDA) (b) (4) for
glepaglutide injection proposed for the treatment of short bowel syndrome (SBS).

We recognize that short bowel syndrome with associated intestinal failure is a serious disease with an unmet medical need and limited available treatments. In situations such as this, we recognize the need to incorporate regulatory flexibility, while still ensuring that substantial evidence of effectiveness is demonstrated. We have completed our review of this application, as amended. Based upon our review of your submitted data, we are unable to conclude that there is substantial evidence of effectiveness (SEE), nor that the benefits outweigh the known and anticipated risks. As such, we have determined that we cannot approve application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICS:

As was conveyed in the Filing Communication – Filing Review Issues Identified Letter dated (b) (4) the Mid Cycle Communication Letter dated (b) (4), and subsequently in the Discipline Review Letter dated (b) (4), our review identified deficiencies with the ability of the submitted data to demonstrate substantial evidence of effectiveness and adequately characterize the safety of the dosage proposed for the treatment of SBS. We have completed our review of NDA 218828 and have determined that the data submitted in the NDA are inadequate to support demonstration of efficacy and safety of glepaglutide for the treatment of adult patients with short bowel syndrome.

Efficacy:

1. The results of EASE-1, your single phase 3 trial, are not sufficiently persuasive and robust to support establishing SEE. Although the results of EASE-1

demonstrated a statistically significant difference from placebo on the primary efficacy endpoint for the twice weekly (TW) dosage, there are numerous uncertainties that limit the interpretability and/or persuasiveness of the results.

- A. In EASE-1, nearly half of the subjects in each treatment arm had ≥ 1 PS adjustments that deviated from the protocol-specified algorithm. Per study protocol, the final PS volume reached (i.e., by Week 20 to Week 24 of EASE-1) is based on cumulative adjustments in the PS volume performed at all visits over time during the trial. Therefore, these observed inconsistencies in weaning raise concerns that the observed changes in PS volume may have been impacted by factors other than the drug's efficacy and may not accurately represent PS volume requirements of the subject.
- B. Incomplete or missing documentations of urinary output in the 48 hours prior to study visits were observed in up to 12% of subjects in EASE-1 and 68% of subjects in EASE-2. Additionally, up to 20% of subjects in EASE-2 had no documentation for urinary volume at ≥ 5 visits. The protocol-specified algorithm for weaning PS was based primarily upon the urinary output in the 48 hours prior to the visit. These observations raise further concerns about the reliability of the PS adjustment/reduction and the final PS volume used for primary and secondary efficacy endpoint assessments.
- C. You communicated on (b) (4), just prior to study completion, that the study's eDiary was not properly configured to distinguish between parenteral support (PS) volume values of 0 and those that were missing, and proposed to retrospectively modify/revise the missing weekly PS volumes based on "notes-to-file." Although results of sensitivity analyses conducted by FDA with and without the "notes-to-file" data appeared to be consistent with the primary analysis, uncertainty remains regarding the accuracy and reliability of the PS volume data, especially when viewed together with other trial conduct issues described in this letter.
- D. The qualitative data from exit interviews with (b) (4) of (b) (4) subjects from EASE-1 were inadequate to support the interpretation of the meaningfulness of the PS volume-related endpoint results. Given the small sample size of exit interviews, there was uncertainty whether the interviewed subjects were representative of the larger clinical trial population.
- E. The quantitative analyses conducted were inadequate to determine clinically meaningful within-patient change in PS volume. Your anchor-based analyses were conducted using the Patient Global Impression of Change (PGIC), supplemented with empirical cumulative distribution function curves, to assess the clinically meaningful change in PS volume-related endpoints of EASE-1. However, the PGIC is prone to recall error and captures a broad concept, as previously communicated in the Type B End-of-Phase 2 Meeting

Minutes dated (b) (4), and Advice/Information Request Letter dated (b) (4). Specifically, your analyses based on the PGIC scale queries subjects' overall status since the start of the study (a recall period of 24 weeks, which may be too long for subjects to accurately estimate change) and is not specific to SBS symptoms and/or impacts, both of which compromise the utility of the PGIC as the sole anchor to conduct anchor-based analyses.

- F. Up to 23% of subjects in the TW dosage group lost significant (>10%) body weight during EASE-1 and EASE-2, raising concerns regarding the clinical benefit of the observed reduction in PS volume achieved at the end of EASE-1. Sensitivity analyses conducted removing the subjects from EASE-1 and EASE-2 who lost >10% of body weight at any study visit demonstrated that the differences between the TW dosage group and the placebo group were no longer statistically significant for the key secondary endpoints of at least 20% reduction in actual weekly PS volume and reduction in days on PS \geq 1 day/week. The results for these two key efficacy endpoints were driven by subjects who experienced a body weight loss >10%. As the goal of treatment is to reduce reliance upon PS to maintain nutritional status, significant weight loss raises concerns regarding whether the reduction in PS was appropriate and consistent with clinically meaningful benefit.
- G. Inconsistency in efficacy results (dose-response) was observed between EASE-1 and EASE-2. In EASE-1, the 10 mg TW dosage performed better than the 10 mg once weekly (OW) dosage regimen. However, the descriptive efficacy results of a subset of patients in EASE-2 who received active treatment for the first time in EASE-2 showed no clear dose response after 24 weeks of treatment (a similar duration as EASE-1). Although EASE-2 was intended to provide additional supportive clinical efficacy and safety data to support the results of EASE-1, these descriptive results raise concerns regarding the strength of the evidence from EASE-1 (and selected 10 mg TW dosage) to serve as a single, robust AWC trial.
- H. Uncertainty remains regarding the proposed to-be-marketed (TBM) dosage. The dosages selected for evaluation in your phase 3 study (10 mg OW and TW) were not evaluated in your phase 2 studies wherein you evaluated 0.1 mg, 1 mg, and 10 mg daily regimen for 3 weeks, using different endpoints than those evaluated in EASE-1. Although an apparent dose-response relationship was observed in EASE-1, exposure response analyses suggested a lack of relationship between observed glepaglutide exposure and the primary efficacy endpoint. Taken together with the discrepant efficacy results observed between EASE-1 and EASE-2, uncertainty remains regarding the appropriateness of the selected TBM dosage.

2. The results of EASE-2 and EASE-3 do not provide confirmatory evidence to support EASE-1 results. Studies EASE-2 and EASE-3 are continuations of EASE-1; these studies provide additional safety data but were not designed to provide an independent source of evidence of effectiveness. Additionally, the descriptive efficacy results in EASE-2 from the subset of subjects who were previously unexposed to glepaglutide in EASE-1 did not confirm the dose response observed in EASE-1. Further, EASE-3 (which evaluated only the OW dosage that differs from the TBM dosage) had no concurrent control and no objective criteria for weaning PS volume; thus, it does not provide interpretable evidence to support a continued benefit from long-term exposure to glepaglutide.
3. The results from the two metabolic studies ZP1848-15073 and EASE-4 did not provide adequate mechanistic or confirmatory evidence to support EASE-1 results for the following reasons:
 - A. Study ZP1848-15073 used wet weight of ostomy output/diarrhea and urinary output as pharmacodynamic (PD) markers of change in absorptive capacity. The results showed inconsistent dose response between the three evaluated doses (0.1 mg, 1 mg, 10 mg daily) and their effects on wet weight ostomy output/diarrhea and urinary output (reported as urine weight). Additionally, the data on several electrolytes collected did not demonstrate a clear and dose-dependent improvement in absorption (i.e., magnesium, calcium, potassium).
 - B. Study EASE-4 did not meet its primary endpoint of change from baseline to Week 24 in absorption of wet weight/fluids (assessed by 48-hour metabolic balance studies). Additional limitations of the study include a small sample size (n=10), lack of a concurrent control arm, and the studied dosage (10 mg OW) that differs from the TBM dosing regimen.

Safety:

4. The size of your safety database is limited to inform the benefit-risk assessment to support the approval of the TBM dosing regimen of glepaglutide, a new molecular entity (NME) intended for chronic administration. We acknowledge that your 120-day safety update report included additional safety information available for the TBM dosage, providing a total of (b) (4) subjects who received the TBM dosage for at least 1 year in your safety database. However, we generally recommend a safety database that includes at least ~100 subjects treated with the TBM dosage for at least 1 year, to inform the safety profile of a new drug intended for chronic use.
5. Multiple safety concerns, including potential drug-induced liver injury, cancers (gastric neuroendocrine carcinoma, basal cell carcinoma of skin and basosquamous carcinoma of skin), and gastric polyps were identified within this limited safety database. Several of these are unique adverse events of special

interest (AESI) that were not previously reported in the other drug approved in this class.

6. FDA inspection of one clinical investigator site ((b) (4)) identified several concerning observations, including numerous unreported adverse events in 6 out of 9 enrolled subjects. This included two unreported serious adverse events (hospitalization due to acute kidney injury, hospitalization due to hypomagnesemia) and an unreported AESI of increased liver enzymes. Given that this site enrolled a relatively large representation of the study population (approximately 9%), as well as the types and frequency of the adverse events observed but were omitted from this site's safety data, these inspection findings raise significant concerns regarding the reliability of the data to inform the benefit-risk assessment of glepaglutide.

Information needed to resolve the deficiencies:

To resolve the above-noted deficiencies, we recommend you conduct a second adequate and well-controlled trial before resubmitting your application. We recommend that you leverage the existing data to inform the design of the new study to confirm the efficacy of the TBM dosage of glepaglutide and generate additional controlled safety data to support chronic administration. The study design of the proposed trial should address uncertainties listed in this letter. We encourage you to meet with the Division prior to trial initiation to reach agreement on key study design elements.

We recommend that you conduct a double-blinded, placebo-controlled trial including a treatment period of at least 52 weeks. While the primary efficacy assessment may be conducted at Week 24, given the limitations of and the uncertainties raised by your EASE-1 and EASE-2 study results, we recommend that you extend the controlled period to at least 52 weeks to better characterize the safety profile of glepaglutide and assess the durability of response in the intended population. Specifically, controlled data beyond 24 weeks are necessary to demonstrate that the early reduction in PS volume (as assessed at Week 24) can be maintained over time, with concurrent maintenance of body weight/nutritional status.

To aid in the interpretation of PS volume related endpoint results, a range of within-patient score change thresholds that patients consider clinically meaningful should be established through anchor-based methods using appropriate anchor measures, supplemented with empirical cumulative distribution function (eCDF) curves using data pooled across treatment arms. Additional data (e.g., from exit interviews, proportion of patients achieving full enteral autonomy, etc.) may also be needed to ascertain clinically meaningful improvement, given the challenges with conducting anchor-based analyses that you encountered during the conduct of EASE-1.

We look forward to engaging with you as you consider the study design for a future trial of glepaglutide in patients with SBS and advise you to continue to benefit from the frequent interactions with FDA available to you.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

We reserve comment on the proposed labeling until the application is otherwise adequate.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Due to the unfavorable risk-benefit determination, the Office of New Drugs and the Office of Surveillance and Epidemiology are unable to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure the benefits of the drug outweigh the risks, and if necessary, what the required elements will be.

FACILITY INSPECTIONS

Following a CGMP inspection of (b) (4) listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your application. Therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a pre-approval inspection/pre-licensing inspection (PAI/PLI) of the facility. Satisfactory outcomes of both the PAI/PLI and the CGMP surveillance inspections will be needed prior to an approval of the application.

PROPRIETARY NAME

Please refer to correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact

(b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (4)

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