Responses to FDA questions dated 11 July 2023 to Dasiglucagon clinsite.xpt file for
Study ZP4207-17103, Study ZP4207-17106, and Study ZP4207-17109
Dasiglucagon injection 4.0 mg/mL

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Clinical

Question

We are in receipt of the clinsite.xpt file for Study ZP4207-17103, Study ZP4207-17106, and Study ZP4207-17109 submitted in Module 5 of your June 30, 2023 submission to NDA 217724. We are unable to complete quality control (QC) for load of clinsite data to CDER's Clinical Investigator Site Selection Tool due to the following reasons:

A. Study ZP4207-17103 is a two-part study, in which Part 1 is a crossover study with two periods. We request you provide data in a revised clinsite file to differentiate two parts of the study as well as the two periods of Part 1. We recommend you provide the data for STUDYID "ZP4207-17103 Part 1" and STUDYID "ZP4207-17103 Part 2"; in STUDYID "ZP4207-17103 Part 1", we recommend you provide the period information (i.e., Period 1 and Period 2) with using variable COHORT in the revised clinsite file.

B. For Study ZP4207-17106, it appears that data of TRTEFFR (Treatment Efficacy Result) is mean AVAL (Analysis Value) in the associated ADEFF.xpt file for PARAM of "CGM Percent Time in Hypoglycemia <70 mg/dL (%)" at all timepoints including Baseline. We request you provide the efficacy data (TRTEFFR) for ENDPOINT of "Change from baseline in CGM time in hypoglycemia < 70 mg/dL (%)" for each treatment arm at each site in the revised clinsite file.

C. Study ZP4207-17109 is a two-period study. We request you provide data in the revised clinsite file to differentiate two treatment periods of the study. We recommend you provide the data for STUDYID "ZP4207-17109 Period 1" and STUDYID "ZP4207-17109 Period 2". We also request you provide the efficacy data (TRTEFFR) for ENDPOINT of "Change from baseline in hypoglycemia event rate" for each treatment arm at each site in the revised clinsite file.

We request you reconfirm, or where necessary, revise, all data provided in a revised clinsite.xpt file, and provide the revised clinsite.xpt file and associated define file with all the data corrected.

Response to Question A

We have revised the clinsite data for 17103 trial considering the trial design comprising 2 parts, a crossover (2 periods, 48 hours each), double-blind, placebo-controlled Part 1, and an open-label, single-arm Part 2 of 21 days. In order to comply with the Study data technical conformance guide Version 5.4 **(Section 7.1 eCTD Specifications)** and align with submitted trial data packages, we are keeping STUDYID as "ZP4207-17103". Instead, as proposed in the information request question, we are providing the period information in the COHORT variable. Two crossover periods in Part 1 can be differentiated with the Planned Treatment Arm information provided in ARM variable. ARM value "Run-In" has been included to differentiate the records captured during the Run-In period.

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COHORT's populated and the description for ZP4207-17103 Trial:

COHORT	Description of COHORT
Part 1	Comprising 2 parts, a crossover (2 periods, 48 hours each), double-blind, placebo-controlled Part 1
Part 2	Open-label, single-arm Part 2 of 21 days

The data in the clinsite dataset has been updated based on STUDYID, SITEID, ARM and COHORT.

Summary statistics for primary efficacy endpoint, TRTEFFR (Treatment Efficacy Result) and TRTEFFS (Treatment Efficacy Result STD) also has been rederived considering the COHORT variable.

Primary Efficacy Endpoint for ZP4207-17103 Trial:

The primary efficacy endpoint of this study is the weighted Mean IV glucose infusion rate (GIR) in the last 12 hours of each treatment period during Part 1 (Day 1 to 4) (dasiglucagon or placebo administration).

No primary or secondary efficacy endpoints assess the GIR during Part 2, hence ENDPOINT, ENDPTYPE, TRTEFFR, and TRTEFFS is left blank for Part 2.

Define.xml and Bioresearch Monitoring (BIMO) Data Reviewer's Guide (bdrg.pdf) has been updated in order to reflect the updates done.

Response to Question B

As proposed in the information request, we have populated ENDPOINT with "Change from baseline in CGM time in hypoglycemia < 70 mg/dL (%)" and revised TRTEFFR (Treatment Efficacy Result) instead of the 4th key secondary efficacy endpoint "CGM Percent Time in Hypoglycemia <70 mg/dL (%) ". Updated TRTEFFS (Treatment Efficacy Result STD) variable also accordingly.

Define.xml and Bioresearch Monitoring (BIMO) Data Reviewer's Guide (bdrg.pdf) has been updated in order to reflect the updates done.

Response to Question C

We have revised the clinsite data for 17109 trial considering the trial design comprising 2 periods. In order to comply with the Study data technical conformance guide Version 5.4 **(Section 7.1 eCTD Specifications)** and algin with submitted trial data packages, we are keeping STUDYID as "ZP4207-17109". Instead, as proposed in the information request question, we are providing the period information in the COHORT variable.

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COHORT's populated and the description for ZP4207-17109 Trial:

COHORT	Description of COHORT
Period 1	Treatment Period 1
Period 2	Treatment Period 2

The data in the clinsite dataset has been updated based on STUDYID, SITEID, ARM and COHORT.

As proposed in the information request, we have populated ENDPOINT with "Change from baseline in hypoglycemia event rate" instead of the primary efficacy endpoint "Hypoglycemia event rate, defined as average weekly number of hypoglycemic events (PG <70 mg/dL or 3.9 mmol/L)". We have revised TRTEFFR (Treatment Efficacy Result) during Weeks 2-4, as detected by SMPG for Treatment Period 1. For Treatment Period 2, we have derived "Change from baseline in hypoglycemia event rate" as TRTEFFR (Treatment Efficacy Result) instead of the 2nd secondary efficacy endpoint "Hypoglycemia event rate during Weeks 6-8". TRTEFFS (Treatment Efficacy Result STD) variable was also updated accordingly.

Summary statistics for efficacy endpoint, TRTEFFR (Treatment Efficacy Result) and TRTEFFS (Treatment Efficacy Result STD) also has been rederived considering the COHORT variable.

Define.xml and Bioresearch Monitoring (BIMO) Data Reviewer's Guide (bdrg.pdf) has been updated in order to reflect the updates done.