# CLINICAL PHARMACOLOGY MEMO

| | |
|---|---|
| **NDA Number** | 201280 |
| **Submission Date** | 12/20/2022 |
| **Submission Type** | Efficacy Supplement (Supplement number: 027) |
| **Generic name** | Linagliptin |
| **Brand name** | Tradjenta® |
| **Applicant** | Boehringer Ingelheim Pharmaceuticals Inc. |
| **Dosage form** | Film-coated tablets (5 mg) |
| **Mechanism of action** | Dipeptidyl peptidase-4 (DPP-4) inhibitor |
| **Indications** | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) |
| **Dosing Regimen** | The recommended dose of Tradjenta® is 5 mg once daily which can be taken with or without food |
| **OCP Division** | Division of Cardiometabolic and Endocrine Pharmacology (DCEP) |
| **OND Division** | Division of Diabetes, Lipid Disorders, and Obesity (DDLO) |
| **Primary Reviewer** | Harisudhan Thanukrishnan, Ph.D., Xiaolei Pan, Ph.D. |
| **Secondary Reviewer** | Edwin Chow, Ph.D., Justin Earp, Ph.D. |

**Summary of pediatric studies:**

The supplemental NDA (sNDA) submission is an efficacy supplement with data from the pediatric study (DINAMO) that had a written request. In addition to DINAMO, Applicant (Boehringer Ingelheim Pharmaceuticals, Inc.) has conducted pediatric PMR studies for linagliptin, as listed below.

| Trial | Phase | Study Design | Randomized subjects | Treatment duration | Doses of study drug | Study population |
|---|---|---|---|---|---|---|
| 1218.56 (PMR 1766-1) | 2b | Double-blind, randomized, placebo- controlled parallel group | 39 | 12 weeks | Linagliptin: 1 mg,5 mg daily | 10 to 17 years with T2DM |
| 1218.91 (DINAMO) (PMR 3300-1) | 3 | Double-blind, randomized, placebo- controlled, parall group plus double- blind active treatment safety extension period | 157 | 26 weeks plus safety extension up to 52 weeks | Empagliflozin: 10 mg, 25 mg daily<br><br>Linagliptin: 5 mg daily | 10 to 17 years with T2DM |

The Applicant is not seeking a pediatric indication for linagliptin, as efficacy was not demonstrated in the 10-17 years old pediatric subjects with T2DM.

Dose selection based on Study 1218.56:

The PK/PD study 1218.56 was previously reviewed by the OCP (Reference ID: 4036957, dated 05 Jan 2017) and determined to satisfy the clinical pharmacology pediatric PMR (1766-1) of NDA 201280. This

study was a randomized, double-blind, placebo-controlled, parallel group, dose-finding study of linagliptin (1 or 5 mg orally once daily) over 12 weeks in children and adolescents, with T2D. OCP concluded that the results of the pediatric pharmacokinetic (PK) evaluation demonstrated lack of clinically meaningful differences in linagliptin pharmacokinetics/pharmacodynamics between pediatric patients (10 to 17 years inclusive) and adults, thereby, supported carrying over the adult doses for evaluation in pediatric Phase 3 DINAMO study.

Pivotal study 1218.91 (DINAMO):

DINAMO was a randomized, placebo-controlled, double-blind, and parallel group trial with 3 treatment arms (placebo, 5 mg linagliptin, 10 mg empagliflozin) lasting 26 weeks. The trial included a double-blind active treatment safety extension period up to 52 weeks: patients on placebo were re-randomized at Week 26 to receive either linagliptin or empagliflozin (10 mg or 25 mg). A total of 158 patients were randomized and 157 patients were treated (placebo: 53 patients, linagliptin 5 mg: 52 patients, empagliflozin pooled: 52 patients).

Most of the treated patients (94.3%) had background antidiabetic treatment at baseline (metformin and/or insulin), and the baseline HbA1c was 8.03%. At the Week 26, the treatment effect of linagliptin 5 mg compared with placebo was not statistically significant (adjusted mean change from baseline at Week 26 in HbA1c −0.34%; 95% CI: −0.99% to 0.30%; p = 0.2935) and hence the treatment was not considered to have met the primary endpoint for efficacy.

Pharmacokinetic samples to confirm the systemic exposure to linagliptin was obtained at 2 time points, pre-dose and 1.5 h post-dose at Week 26 and Week 52. The samples were analyzed using a validated LC-MS/MS method. The results for linagliptin plasma concentrations showed similar values for weeks 26 and 52 indicating the steady state and the descriptive comparisons did not indicate the influence of any covariates like age, gender, body weight, renal function, or the dose of metformin. A substantial overlap in the steady state linagliptin values was reported for pediatric and adult patients with T2D.

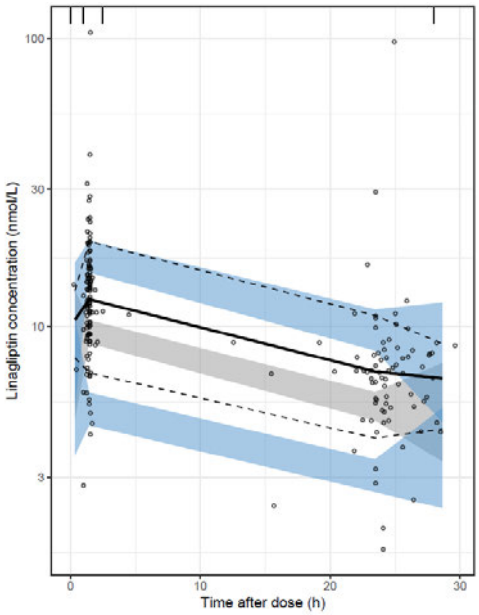
The efficacy was not demonstrated for linagliptin in DINAMO Study due to low sample size. The applicant further provided the Bayesian borrowing analyses in an effort to address the sample size concerns with the DINAMO study. For further details of the review of Bayesian borrowing analysis, please refer to the statistical review by Dr. Satyajit Ghosh. Bayesian prior distributions were derived from previously fitted pharmacokinetic and exposure-response models for linagliptin and empagliflozin based on available historical data in adult and pediatric patients with T2DM (Report c37380493-01). The adult/pediatric population PK and ER datasets were developed from the pooled data from a total of 9 studies (i.e., Trials 1218.2, 1218.3, 1218.5, 1218.6, 1218.10, 1218.16, 1218.20, 1218.36, 1218.56). Among these 9 studies, there is only 1 study that includes children and adolescents from 10 to 17 years of age with T2D, which contributed to 2.3% of total observations in the population PK model, and 1.7% of total observations in the ER model. Based on diagnostic plots and visual predictive check plots, this adult/pediatric model is acceptable for describing the pooled adult and pediatric data in these 9 studies. These models were used to simulate individual and placebo-corrected mean changes in HbA1c (%) at 26 weeks in a pediatric population with baseline characteristics matching the DINAMO population in relevant covariates. Based on population PK/PD simulation, the mean predicted change in HbA1c (%) was −0.64% and the standard error of the mean of was 0.02%. However, this model is not further refined by data from DINAMO study. Out-of-sample predictive check using this adult/pediatric

population PK model shows the model underpredicted the linagliptin concentrations in DINAMO study (**Figure *1***). This adult/pediatric ER model also over-predicts the HbA1c change from baseline (%) following 5 mg dose of linagliptin (**Figure *2***). Therefore, the Bayesian borrowing analysis results from this model should be interpreted with caution when considering the pediatric population.

This applicant is not seeking the pediatric indication for treatment of T2D for linagliptin.

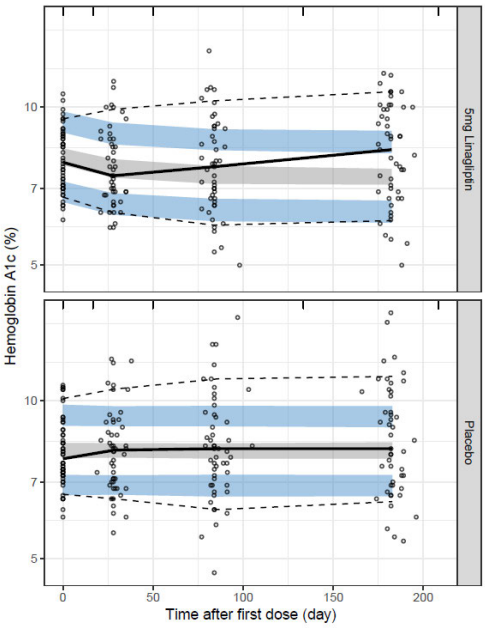
**Based on the results from DINAMO study in the current submission, the Applicant has fulfilled all requirements for PMR 3300-1. The results from the study in this submission are updated to the currently approved package insert.**

**Figure 1. Out-of-sample visual predictive check (VPC) for DINAMO linagliptin concentration versus time after dose using adult/pediatric population PK model from Report c37380493-01.**




Source: Study report c39218172-01, Figure 9, page 80.

**Figure 2. Out-of-sample visual predictive check (VPC) for Study 1218.91 HbA1c versus time after first dose adult/pediatric ER model from Report c37380493-01.**




Source: Study report c39218172-01, Figure 85, page 156.

---

**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/

---

HARISUDHAN THANUKRISHNAN
06/13/2023 03:48:00 PM

XIAOLEI N PAN
06/14/2023 09:18:09 AM

JUSTIN C EARP
06/14/2023 09:54:47 AM

EDWIN C CHOW
06/14/2023 09:59:07 AM