NDA 21773

**WRITTEN REQUEST – AMENDMENT # 8**

AstraZeneca AB
C/O AstraZeneca Pharmaceuticals LP
Attention: Jeffy G. John, MBA
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. John:

Please refer to your correspondence dated July 3, 2020, requesting changes to FDA's March 29, 2006, Written Request for pediatric studies for exenatide.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 29, 2006, and as amended on September 8, 2006, April 18, 2007, March 18, 2008, October 27, 2010, September 16, 2014, August 16, 2018, and July 16, 2020, remain the same. (Text added is **bolded** and underlined. Text deleted is ~~strikethrough~~.)

REVISED WRITTEN REQUEST, AMENDMENT #8

**BACKGROUND**

**A Written Request (WR) for pediatric studies of exenatide (Byetta, NDA 02177) was initially issued on March 29, 2006, and subsequently amended. FDA is now amending the WR to remove required studies for Byetta (short-acting exenatide) and include required studies for Bydureon (longer-acting exenatide). This was prompted because of enrollment issues associated with the original studies and FDA's current thinking regarding health benefits of exenatide in the pediatric population, including a determination that Bydureon may produce health benefits in the pediatric population.**

**TYPE OF STUDIES:**

**Study 1:** A short-term pharmacokinetics (PK), pharmacodynamics (PD), and tolerability study in children with type 2 diabetes.

**Study 2:** A ~~clinical~~ **phase 3, double-blind, placebo-controlled, randomized, multicenter study to assess** safety and efficacy ~~study~~ of exenatide ~~as monotherapy and as an add on to metformin, a sulfonylurea, or a combination of metformin and sulfonylurea~~ **once weekly** in ~~children~~ **adolescents** with type 2 diabetes.

**INDICATION TO BE STUDIED (OBJECTIVE/RATIONALE):**

**Study 1:** To evaluate the PK, PD, and tolerability of single subcutaneous doses of 2.5 mcg and 5.0 mcg of exenatide in children with type 2 diabetes mellitus.

**Study 2:** To evaluate the safety and effectiveness of ~~twice daily subcutaneous administration of~~ exenatide ~~treatment at 5 mcg and 10 mc twice a day~~ **once weekly (EQW)** in ~~older children with type 2 diabetes who are treated with diet and exercise alone or diet and exercise plus metformin, a sulfonylurea, or a combination of metformin and sulfonylurea and adolescents~~ **pediatric patients 10 years of age and older with type 2 diabetes**.

**STUDY DESIGN:**

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board shall monitor the safety in Study 2 and impose appropriate, pre-specified rescue criteria.

**Study 1:** A randomized, patient-blinded, dose-rising, placebo-controlled, crossover PK/PD study. Within 4 weeks following the screening visit, eligible participants will be randomly assigned to their treatment sequences, in which they will receive a single dose of study medication per study day in a dose-rising fashion on 3 separate days within a 5-week period.

The three treatments will be placebo, exenatide 2.5 mcg, and exenatide 5 mcg, each administered as a single subcutaneous injection 15 minutes prior to breakfast, according to the assigned treatment sequence. Patients are admitted to the study site in the morning on Day 1, Day 2, and Day 3 to receive Dose 1, Dose 2, and Dose 3 of the study drug, respectively. PK endpoints will be measured prior to and over the 8-hour period following study medication administration. PD endpoints will be measured prior to and over the 6-hour period following study medication administration. For patients with HbA1c between 6% and 6.5%, exenatide will be administered only if their morning fasting glucose level is higher than 100 mg/dL, and the patients will be monitored more closely to avoid hypoglycemia if they have been treated with a sulfonylurea.

Patients will remain on the unit until each day's study procedures are completed and will be discharged approximately 8 hours following their dose of study medication on each day, provided that no additional observation is deemed necessary by the investigator.

**Study 2:**
~~A 28-week, randomized, double-blind, placebo-controlled, safety and efficacy study of the effect of exenatide on glucose control (HbA1c) in adolescent patients with type 2 diabetes treated with diet and exercise alone or diet and exercise plus metformin, a sulfonylurea or a combination of metformin and a sulfonylurea. Patients will be randomized to exenatide 5 mcg twice a day, exenatide 10 mcg twice a day, or placebo injection twice a day in addition to their baseline treatment. The study drug will be administered by subcutaneous injection before the morning and evening meals for a total of 28 weeks. Randomization will be stratified by the patient's use of antidiabetic drugs at baseline (diet and exercise alone versus previous antidiabetic drugs) and baseline HbA1c (< 8% versus ≥ 8%). The diet and exercise program should be standardized and documented for all treatment arms in Study 2. Documentation must be adequate to permit review and assessment of adherence to diet and exercise. Lack of implementation of this part of the program will constitute failure to adhere to good scientific principles. Population PK approach should be used to characterize the plasma exposure; a sparse sampling strategy is acceptable.~~

**A Phase 3, double-blind (controlled assessment period), placebo-controlled, randomized, parallel, multicenter study to assess the safety and efficacy of EQW as monotherapy and adjunctive therapy to oral antidiabetic agents and insulin.** ~~At least 40% and not more than 60% of the randomized patients must be females. Patients will be randomly assigned in a 5:2 ratio to receive either EQW 2 mg for 52 weeks or placebo for 24 weeks followed by EQW 2 mg for 28 weeks.~~ **The study includes a 24-week controlled period followed by a 28-week open-label extension in which all patients will receive EQW. All patients will participate in a lifestyle intervention program encompassing diet and physical activity modifications.** ~~At Visit 2 (Week 0), patients will complete baseline safety, efficacy, PD, and PK assessments. During the controlled assessment period, patients will return to the study site at 4- or 6-week intervals for safety, efficacy, PD, and PK assessments. On weeks with no scheduled study site visits, patients may opt to return to the study site to have the injection procedure monitored or provided by study site personnel. During the 28-week extension period, all patients will return to the study site at Weeks 28, 40 and 52 for safety, efficacy, PD, and PK assessments and will complete study termination procedures at Visit 11 (Week 62/Study Termination) the 10-week follow up visit.~~

**AGE GROUP IN WHICH STUDIES WILL BE PERFORMED ~~(Studies 1 and 2)~~:**

Male and female patients with type 2 diabetes mellitus ages 10 to 17 years, inclusive. ~~The number of subjects between 16 and 17 years must be limited to 10% of patients in each treatment arm.~~

**NUMBER OF PATIENTS TO BE STUDIED:**

**Study 1:** Twelve patients will be enrolled to obtain approximately nine or more completers.

**Study 2:** ~~A sufficient number of~~ **At least** ~~Approximately~~ 77 patients will be ~~randomized~~ **randomly assigned** to ~~provide data from~~ **the EQW and placebo groups in a 5:2 ratio to obtain** ~~approximately~~ **at least** ~~150 completers (50 per treatment arm)~~ **70 patients completing the 24-week controlled study period. At least 40% and not more than 60% of the randomized patients must be females.**

**ENTRY CRITERIA:**

**Study 1:**

A. Main inclusion criteria

- Males and females with an established diagnosis of type 2 diabetes mellitus and who are treated with diet and exercise alone or with a stable dose of metformin, a sulfonylurea, or a combination of metformin plus a sulfonylurea
- HbA1c 6.0% to 11.0%

B. Main exclusion criteria

- Known hypersensitivity to exenatide or any of the components of study medication
- Patients taking the sulfonylurea chlorpropramide
- If female, is sexually active and not actively practicing birth control per protocol; protocol will specify the use of two methods of birth control throughout the study
- A female who is pregnant or lactating

**Study 2:**

A. **Main** Inclusion Criteria

- ~~Males and females with an established diagnosis of type 2 diabetes and who are treated with (a) diet and exercise alone or (b) diet and exercise plus a stable dose of metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea for at least 3 months; or (c) a stable dose of metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea for at least 3 months without diet and exercise~~
  - **Is ~~a child or an adolescent of~~ 10 to < 18 years old, at ~~Visit 1~~ Screening**
  - **Has been diagnosed with type 2 diabetes mellitus per American Diabetes Association diagnostic criteria**

- **HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/sulfonylurea (SU), and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at ~~Visit 1~~ Screening**
- **Has a** C-peptide of > 0.6 ng/mL **at ~~Visit 1~~ Screening**

B. **Main Exclusion Criteria**

- ~~Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator~~
- **Has type 1 diabetes, e.g., positive antibody titers** ~~to~~ (glutamic acid decarboxylase (GAD65) ~~antibodies~~ **or islet cell antigen (ICA512)) at ~~Visit 1~~ screening**
- **Has a personal or family history of elevated calcitonin, calcitonin > 100 ng/L, medullary thyroid carcinoma, or ~~anti-islet cell antibodies~~ multiple endocrine neoplasia-2**
- ~~Use of an alpha-glucosidase inhibitor, a meglitinide, or pramlintide for more than 1 week during the 3 months prior to screening~~
- ~~Use of insulin for more than 10 weeks during the 3 months prior to screening~~
- ~~Prior use of exenatide~~
- Renal disease or serum creatinine >1.**5**~~6~~ mg/dL (males) or >1.4 mg/dL (females)
- Hepatic dysfunction (>3 times upper limit of normal for aspartate aminotransferase and alanine aminotransferase)
- ~~Known hypersensitivity to exenatide or any of the components of study medication~~
- ~~A female who is sexually active and not willing to use two methods of birth control throughout the study~~
- **Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any glucagon-like peptide-1 (GLP-1) receptor agonist (eg, liraglutide [Victoza®])**
- Is pregnant ~~or lactating~~
- ~~Participated in another investigational study within the past 2 months~~

**STUDY ENDPOINTS:**

**Study 1:**

A. Pharmacokinetic endpoints including:

- Area under concentration curve ($AUC_{0-□□}$ and $AUC_{0-8h}$)
- Peak plasma concentration ($C_{max}$)
- Time to peak concentration ($T_{max}$)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent elimination rate constant (k)

- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

B. Pharmacodynamic endpoints:

- Plasma glucose: absolute and incremental $AUC_{0\text{-}3h}$, absolute and incremental $AUC_{0\text{-}6h}$, $C_{ave(0\text{-}6h)}$, $C_{max}$, and $T_{max}$
- Serum insulin: absolute and incremental $AUC_{0\text{-}3h}$, absolute and incremental $AUC_{0\text{-}6h}$, $C_{ave(0\text{-}6h)}$, $C_{max}$, and $T_{max}$

C. Safety endpoints:

- Incidence and frequency of adverse events, including hypoglycemia
- Changes in vital signs, ECGs, and laboratory values

**Study 2:**

- The primary endpoint will be change in HbA1c from study baseline to Week **24**

- Secondary endpoints will ~~include~~ **be used to compare** the ~~incidence~~ **effects of EQW following 24 weeks of treatment with those achieved by placebo in children** and ~~frequency of hypoglycemia, percentage~~ **adolescents with type 2 diabetes mellitus on the following:**
  - **Fasting plasma glucose concentration**
  - **Proportion** of patients achieving ~~an~~ HbA1c ~~of < 7%, change of~~ goals
  - Body weight, and ~~fasting plasma glucose~~ ~~Tanner pubertal stage~~
  - **Blood pressure** and ~~serum~~ **lipids**
- ~~Secondary endpoint: change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostatic model assessment (HOMA) in children and adolescents with type 2 diabetes who are not taking insulin~~
- Safety evaluation will include reporting of adverse events, anti-exenatide antibodies, vital signs, ~~electrocardiograms~~ **physical exam, Tanner staging,** and laboratory measurements
- **Pharmacokinetic evaluation will include reporting of subject-level PK ($C_{ss,avg}$), and the relationship between demographic covariates (including, but not limited to: eGFR, age, sex, ideal body weight, and actual body weight) and $C_{ss,avg}$. Subject-level PK will be derived from a population PK model.**
- ~~PK endpoints for example, CL/F, V/F, $C_{max}$ and AUC derived from the population PK model using the combined data from Study 1 and Study 2 should be reported. The effect of demographic covariates (eg, age, gender, body weight) on exenatide PK should be analyzed.~~

- ~~To assess the PK of EQW in children and adolescents with type 2 diabetes mellitus~~
- **Pharmacodynamic evaluation will include exposure-response analysis of HbA1c versus steady-state average drug exposure**

**DRUG INFORMATION:**

**Study 1**

- **Dosage form:** Pre-filled pens are available to deliver exenatide at doses of either 5 mcg or 10 mcg. Each pre-filled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).
- **Route of administration:** Subcutaneous Injection
- **Formulation:** Same as marketed

Byetta (exenatide in sodium acetate buffer) 0.25 mg/mL sterile, preserved solution is administered by subcutaneous injection twice daily. A multiple-use, pen-cartridge device is used to deliver the study medication.

**Study 2**

- **Dosage form: Pre-filled syringes/vials or dual chamber pens to deliver exenatide at 2 mg once weekly.**
- ~~Once-weekly 2 mg dosage forms (provided as a 4-week supply):~~
  - ~~Pre-filled syringes containing diluent for suspension of EQW powder provided in vials~~
  - ~~Dual chamber pens containing 2.0 mg powder and solvent for prolonged release suspension~~
- **Route of administration: Subcutaneous injection**
- **Formulation: Same as marketed**

**EQW is an extended release formulation of exenatide and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactide-co-glycolide.** ~~For use in the pre-filled syringes, the EQW microspheres and matching placebo will be supplied in vials containing the white to off white dry powder (40 mg of EQW microspheres). For use in the dual chamber pen, the exenatide microspheres or matching placebo and the diluent for suspension will be supplied in a pre-filled single use injection pen. Diluent for suspension will be supplied in pre-filled syringes. Each syringe will contain 0.75 mL.~~ **The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided.**

~~EQW (Bydureon; exenatide suspension) is administered by subcutaneous injection once weekly. The dual chamber pen is intended to be used by all study participants recruited from August 2018 onwards.~~

**REGIMEN:**

**Study 1:** Following an overnight fast, a single subcutaneous injection of study medication will be administered 15 minutes prior to breakfast, according to the patient's assigned treatment sequence. Each patient will receive a single subcutaneous injection of placebo, exenatide 2.5 mcg, and exenatide 5 mcg on three separate days.

**Study 2:**
~~There will be three arms corresponding to placebo, exenatide 5 mcg twice a day, and exenatide 10 mcg twice a day before the morning and evening meals. Patients randomized to the 10 mcg twice a day arm will be started on 5 mcg twice a day for the first 4 weeks to minimize nausea, then the drug will be administered at its full dosage of 10 mcg twice a day for the subsequent 24 weeks.~~
**During the 24-week controlled assessment period, patients will be randomized to treatment with exenatide 2 mg once weekly or placebo. During the subsequent 28-week, open-label extension, all patients will receive exenatide 2 mg once weekly. Study drug will be administered by subcutaneous injection with injection sites rotated to avoid frequent use of the same site.**
~~Preparation of study medication will be demonstrated to caregivers and patients by a medically qualified person when the first dose is administered.~~

**DRUG-SPECIFIC SAFETY CONCERNS:**

- The incidence, frequency, and severity of gastrointestinal adverse events (reported rates in adults: nausea in 44%, vomiting in 13%, diarrhea in 13%, and dyspepsia in 6% of exenatide- treated patients).

- The titers of anti-exenatide antibodies and their impact on efficacy.

- The incidence, frequency, and severity of clinically significant hypoglycemia. The addition of exenatide to a sulfonylurea increases the risk of hypoglycemia.

- The incidence, frequency, and severity of hyperglycemia-diabetic ketoacidosis.

**STATISTICAL INFORMATION, INCLUDING POWER OF STUDY AND STATISTICAL ASSESSMENT:**

**Study 1:** A sample size based on 9 completed patients is expected to provide

sufficient information to evaluate the PK, PD, and general tolerability of exenatide in adolescent patients with type 2 diabetes mellitus.

**Study 2: Patients will be randomly assigned in a 5:2 ratio to receive either EQW 2 mg for 52 weeks or placebo for 24 weeks followed by EQW 2 mg for 28 weeks.** ~~The analysis of~~ The primary efficacy **analysis** will ~~use an ANCOVA model with HbA1c change from baseline at Week 28 or last prior visit as the dependent variable, treatment and randomization stratification factors as independent variables, and baseline HbA1c as covariate. The primary analysis population will be the intent to treat (ITT) population which includes~~ **compare treatment groups with respect to change in HbA1c from baseline to Week 24 by using the mixed model repeated measures approach in the evaluable study population (ie**, all randomized patients who ~~have a baseline HbA1c and~~ **receive** at least ~~one~~ **1 dose of randomized study medication and have at least 1 baseline and** post- ~~randomization HbA1c. The sample size of 50 per~~ **baseline HbA1c). The model will include change in HbA1c as the dependent variable and** treatment group**, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects. Assuming a 10% drop-out rate, approximately 70 patients** will ~~provide 84%~~ **complete the 24-week controlled treatment period. The study will have an overall** power ~~to detect a 0.6%~~ **of 74% to reject the null hypothesis of no** difference between **the 2** treatment groups **assuming a true treatment difference of -0.7% between EQW and placebo** in ~~HbA1c~~ change from baseline ~~with~~ **HbA1c**.

**A sensitivity analysis will be performed, which assumes the data are missing not at random. The estimate of treatment effect as compared to the estimate of the primary analysis will be disadvantaged by assuming that EQW withdrawals follow a trajectory based on the completers in the placebo arm. Additionally, the primary mixed model repeated measures analysis and the sensitivity analysis mentioned above will also be performed for the treatment policy estimand. Data collected after treatment discontinuation and rescue will be included in these models.**

## TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the studies that meet the terms of the Written Request dated March 29, 2006, and as amended on September 8, 2006, April 18, 2007, March 18, 2008, October 27, 2010, September 16, 2014, **August 16, 2018, ~~and~~ July 16, 2020, October 15, 2020** must be submitted to the Agency on or before ~~January 31,~~ **February 7, 2021**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

    1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
    2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
    3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that exenatide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within

210 days of submission of your study report(s).
These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 29, 2006, and as amended on September 8, 2006, April 18, 2007, March 18, 2008, October 27, 2010, September 16, 2014, August 16, 2018, and July 16, 2020, must be submitted to the Agency on or before February 7, 2021, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

  (3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that exenatide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
  - the action taken (i.e., approval, complete response); or
  - the exclusivity determination (i.e., granted or denied).

  FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

trial and submission of trial results. Additional information on these requirements and the submission of this information can be found on the Clinical Trials website.[2]

If you have any questions, call Arati B. Kamath, Ph.D., Regulatory Project Manager, at (301) 796-3159.

Sincerely,

*{See appended electronic signature page}*

Ellis Unger, M.D.
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

[2] www.ClinicalTrials.gov

**PROPOSED CHANGES IN WRITTEN REQUEST AMENDMENT 8 FOR PEDIATRIC STUDIES**

## BACKGROUND

A Written Request (WR) for pediatric studies of exenatide (Byetta, NDA 021773) was initially issued on March 29, 2006, and subsequently amended. FDA is now amending the WR to remove required studies for Byetta (short-acting exenatide) and include required studies for Bydureon (longer-acting exenatide). This was prompted because of enrollment issues associated with the original studies and FDA's current thinking regarding health benefits of exenatide in the pediatric population, including a determination that Bydureon may produce health benefits in the pediatric population.

## TYPE OF STUDIES:

**Study 1:** A short-term pharmacokinetics (PK), pharmacodynamics (PD), and tolerability study in children with type 2 diabetes.

**Study 2:** A phase 3, double-blind, placebo-controlled, randomized, multicenter study to assess safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes.

## INDICATION TO BE STUDIED (OBJECTIVE/RATIONALE):

**Study 1:** To evaluate the PK, PD, and tolerability of single subcutaneous doses of 2.5 mcg and 5.0 mcg of exenatide in children with type 2 diabetes mellitus.

**Study 2:** To evaluate the safety and effectiveness of exenatide once weekly (EQW) in pediatric patients 10 years of age and older with type 2 diabetes.

## STUDY DESIGN:

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board shall monitor the safety in Study 2 and impose appropriate, pre-specified rescue criteria.

**Study 1:** A randomized, patient-blinded, dose-rising, placebo-controlled, crossover PK/PD study. Within 4 weeks following the screening visit, eligible participants will be randomly assigned to their treatment sequences, in which they will receive a single dose of study medication per study day in a dose-rising fashion on 3 separate days within a 5-week period. The three treatments will be placebo, exenatide 2.5 mcg, and exenatide 5 mcg, each administered as a single subcutaneous injection 15 minutes prior to breakfast, according to the assigned treatment sequence. Patients are admitted to the study site in the morning on Day 1, Day 2, and Day 3 to receive Dose 1, Dose 2, and Dose 3 of the study drug, respectively. PK endpoints will be measured prior to and over the 8-hour period following study medication administration. PD endpoints will be measured prior to and over the 6-hour period following study medication administration. For patients with HbA1c between 6% and 6.5%, exenatide will be administered only if their morning fasting glucose level is higher than 100 mg/dL, and the patients will be

monitored more closely to avoid hypoglycemia if they have been treated with a sulfonylurea. Patients will remain on the unit until each day's study procedures are completed and will be discharged approximately 8 hours following their dose of study medication on each day, provided that no additional observation is deemed necessary by the investigator.

**Study 2:**

A Phase 3, double-blind (controlled assessment period), placebo-controlled, randomized, parallel, multicenter study to assess the safety and efficacy of EQW as monotherapy and adjunctive therapy to oral antidiabetic agents and insulin. The study includes a 24-week controlled period followed by a 28-week open-label extension in which all patients will receive EQW. All patients will participate in a lifestyle intervention program encompassing diet and physical activity modifications.

**AGE GROUP IN WHICH STUDIES WILL BE PERFORMED:**

Male and female patients with type 2 diabetes mellitus ages 10 to 17 years, inclusive.

**NUMBER OF PATIENTS TO BE STUDIED:**

**Study 1:** Twelve patients will be enrolled to obtain approximately nine or more completers.

**Study 2:** At least 77 patients will be randomly assigned to the EQW and placebo groups in a 5:2 ratio to obtain at least 70 patients completing the 24-week controlled study period. At least 40% and not more than 60% of the randomized patients must be females.

**ENTRY CRITERIA:**

**Study 1:**

A. Main inclusion criteria

- Males and females with an established diagnosis of type 2 diabetes mellitus and who are treated with diet and exercise alone or with a stable dose of metformin, a sulfonylurea, or a combination of metformin plus a sulfonylurea
- HbA1c 6.0% to 11.0%

B. Main exclusion criteria

- Known hypersensitivity to exenatide or any of the components of study medication
- Patients taking the sulfonylurea chlorpropramide
- If female, is sexually active and not actively practicing birth control per protocol; protocol will specify the use of two methods of birth control throughout the study
- A female who is pregnant or lactating

**Study 2:**

A. Main Inclusion Criteria

- Is 10 to < 18 years old, at Screening

- Has been diagnosed with type 2 diabetes mellitus per American Diabetes Association diagnostic criteria
- HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/sulfonylurea (SU) , and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at Screening
- Has a C-peptide of > 0.6 ng/mL at Screening

B. Main Exclusion Criteria

- Has type 1 diabetes, e.g., positive antibody titers (glutamic acid decarboxylase (GAD65) or islet cell antigen (ICA512)) at screening
- Has a personal or family history of elevated calcitonin, calcitonin > 100 ng/L, medullary thyroid carcinoma, or multiple endocrine neoplasia-2
- Renal disease or serum creatinine >1.5 mg/dL (males) or >1.4 mg/dL (females)
- Hepatic dysfunction (>3 times upper limit of normal for aspartate aminotransferase and alanine aminotransferase)
- Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any glucagon-like peptide-1 (GLP-1) receptor agonist (eg, liraglutide [Victoza®])
- Is pregnant

**STUDY ENDPOINTS:**

**Study 1:**

A. Pharmacokinetic endpoints including:

- Area under concentration curve ($AUC_{0-\infty}$ and $AUC_{0-8h}$)
- Peak plasma concentration ($C_{max}$)
- Time to peak concentration ($T_{max}$)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent elimination rate constant (k)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

B. Pharmacodynamic endpoints:

- Plasma glucose: absolute and incremental $AUC_{0-3h}$, absolute and incremental $AUC_{0-6h}$, $C_{ave(0-6h),}$ $C_{max}$, and $T_{max}$
- Serum insulin: absolute and incremental $AUC_{0-3h}$, absolute and incremental $AUC_{0-6h}$, $C_{ave(0-6h),}$ $C_{max}$, and $T_{max}$

C. Safety endpoints:

- Incidence and frequency of adverse events, including hypoglycemia
- Changes in vital signs, ECGs, and laboratory values

**Study 2:**

- The primary endpoint will be change in HbA1c from study baseline to Week 24
- Secondary endpoints will be used to compare the effects of EQW following 24 weeks of treatment with those achieved by placebo in children and adolescents with type 2 diabetes

mellitus on the following:
- Fasting plasma glucose concentration
- Proportion of patients achieving HbA1c goals
- Body weight, and
- Blood pressure and lipids

- Safety evaluation will include reporting of adverse events, anti-exenatide antibodies, vital signs, physical exam, Tanner staging, and laboratory measurements

- Pharmacokinetic evaluation will include reporting of subject-level PK ($C_{ss,avg}$), and the relationship between demographic covariates (including, but not limited to: eGFR, age, sex, ideal body weight, and actual body weight) and $C_{ss,avg}$. Subject-level PK will be derived from a population PK model.

- Pharmacodynamic evaluation will include exposure-response analysis of HbA1c versus steady-state average drug exposure.

**DRUG INFORMATION:**

**Study 1**
- **Dosage form:** Pre-filled pens are available to deliver exenatide at doses of either 5 mcg or 10 mcg. Each pre-filled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).
- **Route of administration:** Subcutaneous Injection
- **Formulation:** Same as marketed

Byetta (exenatide in sodium acetate buffer) 0.25 mg/mL sterile, preserved solution is administered by subcutaneous injection twice daily. A multiple-use, pen-cartridge device is used to deliver the study medication.

**Study 2**
- **Dosage form:** Pre-filled syringes/vials or dual chanber pens to deliver exenatide at 2 mg once weekly.
- **Route of administration:** Subcutaneous injection
- **Formulation:** Same as marketed

EQW is an extended release formulation of exenatide and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactide-co-glycolide. The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided.

**REGIMEN:**

**Study 1:** Following an overnight fast, a single subcutaneous injection of study medication will be administered 15 minutes prior to breakfast, according to the patient's assigned treatment sequence. Each patient will receive a single subcutaneous injection of placebo, exenatide 2.5 mcg, and exenatide 5 mcg on three separate days.

**Study 2:** During the 24-week controlled assessment period, patients will be randomized to treatment with exenatide 2 mg once weekly or placebo. During the subsequent 28-week, open-label extension, all patients will receive exenatide 2 mg once weekly. Study drug will be administered by subcutaneous injection with injection sites rotated to avoid frequent use of the same site.

**DRUG-SPECIFIC SAFETY CONCERNS:**

- The incidence, frequency, and severity of gastrointestinal adverse events (reported rates in adults: nausea in 44%, vomiting in 13%, diarrhea in 13%, and dyspepsia in 6% of exenatide- treated patients).

- The titers of anti-exenatide antibodies and their impact on efficacy.

- The incidence, frequency, and severity of clinically significant hypoglycemia. The addition of exenatide to a sulfonylurea increases the risk of hypoglycemia.

- The incidence, frequency, and severity of hyperglycemia-diabetic ketoacidosis.

**STATISTICAL INFORMATION, INCLUDING POWER OF STUDY AND STATISTICAL ASSESSMENT:**

**Study 1:** A sample size based on 9 completed patients is expected to provide sufficient information to evaluate the PK, PD, and general tolerability of exenatide in adolescent patients with type 2 diabetes mellitus.

**Study 2:** Patients will be randomly assigned in a 5:2 ratio to receive either EQW 2 mg for 52 weeks or placebo for 24 weeks followed by EQW 2 mg for 28 weeks. The primary efficacy analysis will compare treatment groups with respect to change in HbA1c from baseline to Week 24 by using the mixed model repeated measures approach in the evaluable study population (ie, all randomized patients who receive at least 1 dose of randomized study medication and have at least 1 baseline and post-baseline HbA1c). The model will include change in HbA1c as the dependent variable and treatment group, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects. Assuming a 10% drop-out rate, approximately 70 patients will complete the 24-week controlled treatment period. The study will have an overall power of 74% to reject the null hypothesis of no difference between the 2 treatment groups assuming a true treatment difference of -0.7% between EQW and placebo in change from baseline HbA1C.

A sensitivity analysis will be performed, which assumes the data are missing not at random. The estimate of treatment effect as compared to the estimate of the primary analysis will be disadvantaged by assuming that EQW withdrawals follow a trajectory based on the completers in the placebo arm. Additionally, the primary mixed model repeated measures analysis and the sensitivity analysis mentioned above will also be performed for the treatment policy estimand. Data collected after treatment discontinuation and rescue will be included in these models.

## TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the studies that meet the terms of the Written Request dated March 29, 2006, and as amended on September 8, 2006, April 18, 2007, March 18, 2008, October 27, 2010, September 16, 2014, August 16, 2018, July 16, 2020, and October 15, 2020, must be submitted to the Agency on or before **February 7, 2021**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

    1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
    2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
    3) you have not marketed the formulation within one year after the Agency publishes such notice,

    the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that exenatide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted

in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
  - the action taken (i.e., approval, complete response); or
  - the exclusivity determination (i.e., granted or denied).

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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**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.**

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/s/

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