17 August 2017
EMA/588971/2017

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Onglyza

International non-proprietary name: Saxagliptin

Procedure no.: EMA/H/C/1039/P46/042

Marketing authorisation holder (MAH): AstraZeneca AB

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 3 May 2017, the MAH submitted completed paediatric studies for Onglyza, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Short critical expert overviews have also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the results of two studies. These studies are part of the agreed PIP. The study reports are included in this submission. In the context of the PIP, another study **CV181375** is still planned (Table 1).

Table 1 Tabular listing of clinical studies with saxagliptin in pediatric patients less than 18 years of age

Type of study/ Study identifier	Primary objective of the study	Study design and types of control	Test product; Dosage regimen; Route of administration	Number of patients	Healthy subjects or diagnosis of patients	Duration of treatment
Completed studies:						
Phase 3, efficacy, safety, tolerability, and PK/ CV181058	To assess the safety and tolerability of saxagliptin monotherapy in pediatric patients with T2DM aged 10 to <18 years when administered for up to 16 weeks of short-term therapy and 36 weeks of long-term therapy	Multicenter, randomized, double-blind, placebo-controlled	Saxagliptin 2.5 mg or 5 mg or placebo tablet administered orally once daily[a] during both the double-blind treatment period and the long-term extension period	136 patients planned; 8 patients randomized	Patients aged between 10 to <18 years (inclusive) with T2DM who are not receiving pharmacologic treatment for diabetes	Up to 52 weeks
Phase 3, efficacy, safety, tolerability/ CV181147	To assess the safety and tolerability of saxagliptin as an add-on to metformin therapy in pediatric patients with T2DM aged 10 to <18 years when administered for up to 16 weeks of short-term therapy and 36 weeks of long-term therapy	Multicenter, randomized, double-blind, placebo-controlled	Saxagliptin 2.5 mg or 5 mg or placebo tablet administered orally once daily[a] in addition to metformin IR or XR at a dose of 1000 mg to 2000 mg once daily during the double-blind treatment and long-term extension periods	236 patients planned; 6 patients randomized	Patients aged between 10 to <18 years (inclusive) with T2DM who are receiving a stable dose of metformin of 1000 mg to 2000 mg	Up to 52 weeks
Planned Study:						
Phase 3 safety, efficacy/ CV181375	To determine if there will be a greater mean reduction from baseline in HbA1c achieved after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg compared to placebo in pediatric patients with T2DM with HbA1c levels of 6.5% to 10.5% on diet and exercise and metformin (IR or XR), insulin, or metformin (IR or XR) plus insulin	Multicenter, randomized, double-blind, placebo-controlled	Saxagliptin 2.5 mg, dapagliflozin 5 mg, or placebo tablet administered orally once daily[a] up to 26 weeks in the short-term treatment period and up to 26 weeks in the long-term treatment period. At Week 12 in the short-term treatment period, patients may have their dose of dapagliflozin increased to 10 mg or their dose of saxagliptin increased to 5 mg	243 patients planned (81 patients in each treatment group)	Patients aged between 10 to <18 years (inclusive) with T2DM who have been treated with diet and exercise and a stable dose of metformin (IR or XR) for a minimum of 8 weeks, or a stable baseline dose of insulin for a minimum of 8 weeks, or a stable combination of metformin (IR or XR) and insulin for a minimum of 8 weeks.	Up to 52 weeks

HbA1c glycosylated hemoglobin; IR immediate-release; PK pharmacokinetics; T2DM type 2 diabetes mellitus; XR extended-release.
[a] Patients randomized to saxagliptin received a dose of 2.5 mg (if weighing 30 kg to ≤50 kg) or 5 mg (if weighing >50 kg).

2.2. Information on the pharmaceutical formulation used in the studies

Saxagliptin (BMS-477118) was supplied by Bristol-Myers Squibb (BMS) as plain, yellow, biconvex, round, film-coated tablets containing 2.5 mg or 5 mg of saxagliptin as the free base.

2.3. Clinical aspects

2.3.1. Introduction

ONGLYZA (saxagliptin) is a highly potent, selective, reversible, and competitive dipeptidyl peptidase-4 inhibitor indicated in adult patients aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control. The approved formulation in European Union (EU) is a film-coated tablet containing 2.5 mg or 5.0 mg saxagliptin. The recommended dose of ONGLYZA in adults is 5 mg taken once daily. To date, the safety and efficacy of saxagliptin 2.5 mg film-coated tablets in children aged birth to <18 years has not been established.

The MAH submitted final reports for:

- Study CV181058: A Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Saxagliptin (BMS-477118) as Monotherapy in Pediatric Patients with Type 2 Diabetes
- Study CV181147: A Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination with Metformin IR or Metformin XR in Pediatric Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Alone

AstraZeneca procedures, internal quality control measures and audit programs provide reassurance that the clinical study program was carried out in accordance with good clinical practice, as documented by the International Conference on Harmonisation and the FDA.

2.3.2. Regulatory history of the Paediatric Investigational Plan for saxagliptin

The original PIP for saxagliptin was approved by EMA/Paediatric Committee (PDCO) in September 2009 (EMA decision number P/176/2009) and included 2 clinical studies (Study CV181058 and Study CV181147). Subsequent PIP modifications numbered 01 through 04 for these studies were approved by EMA/PDCO in February 2010 (EMA decision number P/16/2010), March 2011 (EMA decision number P/69/2011), April 2011 (EMA decision number P/97/2011), and March 2013 (EMA decision number P/0061/2013), respectively. PIP modification number 05 (M05), submitted to the EMA/PDCO in May 2015 proposed a new study (Study CV181374) that was based on the Committee of Medical Products for Human Use Qualification Advice (EMEA/H/SAB/0531/1/QA/2014) received in December 2014. The intent was to fulfil EMA PIP requirements by replacing the 2 original paediatric studies (Study CV181058 and Study CV181147) with Study CV181374. On the basis of the review of the rationale submitted by the Applicant for modifying the agreed PIP, the EMA/PDCO considered that the proposed changes in PIP M05 could not be accepted (EMA/368095/2015), and the Applicant withdrew its application in August 2015.

PIP modification number 06 (M06), submitted to the EMA/PDCO in November 2015 proposed a new study (Study CV181375) to replace Studies CV181058 and CV181147. The design of Study CV181375 was to evaluate the efficacy and safety of once daily dapagliflozin 5 mg, dapagliflozin 10 mg, saxagliptin 2.5 mg, and saxagliptin 5 mg for 24 weeks of double-blinded add-on treatment, followed by a 28-week site and patient-blinded treatment extension for safety assessment in paediatric patients with T2DM aged 10 to <18 years with glycosylated haemoglobin (HbA1c) of 6.5% to 10.5% who are

on a diet and exercise regimen and receiving metformin (IR or XR), insulin, or metformin IR or XR plus insulin. The EMA/PDCO approved PIP M06 in January 2016.

After discussions with the US Food and Drug Administration (FDA) and PDCO, a more recent PIP modification (PIP M07) was submitted to EMA/PDCO in November 2016 with the intention to replace the previously approved PIP M04 (version dated 26 March 2013, EMA decision number P/0061/2013). In PIP M07, the design of Study CV181375 was updated to a 26-week, multicenter, randomized, placebo-controlled, double-blind, parallel group study with a 26-week safety extension period to evaluate the safety and efficacy of dapagliflozin 5 mg and 10 mg, and saxagliptin 2.5 mg and 5 mg in paediatric patients with T2DM who are between 10 and <18 years of age with HbA1c of 6.5% to 10.5% who are on a diet and exercise regimen and receiving metformin (IR or XR), insulin, or metformin IR or XR plus insulin. The primary objective of the study was modified to determine if there will be a greater mean reduction from baseline in HbA1c achieved after 26 weeks of oral double-blind add-on therapy compared to placebo when low dose dapagliflozin (5mg) or saxagliptin (2.5 mg) is administered with titration to a higher dose permitted for patients who do not achieve the glycaemic target of HbA1c <7% at 12 weeks. On 17 March 2017, EMA/PDCO approved PIP M07 for saxagliptin. The date of completion of the paediatric investigation plan is by December 2020.

2.3.3. Study CV181058

Study CV181058 was designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of saxagliptin as monotherapy (2.5 mg or 5 mg according to body weight) during a 16-week double-blind treatment period in paediatric patients 10 to <18 years of age with T2DM. Approximately 136 patients (68 patients per treatment group) were planned to be randomized in a 1:1 ratio to receive saxagliptin or placebo during the double-blind treatment period. The study was initiated in June 2011. Eight patients were randomized and treated in the study (4 patients were randomized to saxagliptin and 4 patients were randomized to placebo) over a period of approximately 34 months. In March 2014, the independent Data Monitoring Committee (DMC) recommended that the Sponsor discontinue enrolment due to slow recruitment. The DMC considered that the continued slow accrual was preventing the study from achieving its objective, thereby exposing participants to the unnecessary risk of participating in a clinical trial. The DMC acknowledged the difficulty in conducting studies in the paediatric population with diabetes as well as the efforts that the Sponsor had taken to increase enrolment. The DMC noted that review of the safety data showed no safety concerns; thus, treatment of patients already randomized in the study could continue. Six patients (3 patients in each treatment group) completed the 16-week double-blind treatment period and 5 patients (3 patients in the saxagliptin group and 2 patients in the placebo group) completed the 36-week long-term extension period.

Benefits

A total of 12 patients with T2DM entered the 2-week lead-in period of the study and received placebo. Eight patients were subsequently randomized and treated in the 16-week double-blind treatment period. These 8 patients included 4 males and 4 females of Caucasian (n=4), black (n=3), or Asian (n=1) ethnicity who ranged in age from 11 to 16 years and had body mass index values from 28.2 to 55.2 kg/m2. The primary efficacy analysis in the study was the comparison of saxagliptin and placebo on the change in HbA1c from baseline to Week 16 in double-blind treatment period. Data was collected on the 8 patients randomized in the study and is provided as line listings in the clinical study report.

Given the small number of patients enrolled in Study CV181058, no definitive conclusions could be made regarding any potential benefit of saxagliptin in paediatric patients with T2DM.

Risks

Adverse events (AEs) by Medical Dictionary for Regulatory Activities Version 19.0 preferred term reported by more than 1 patient during treatment in the double-blind and long-term extension treatment periods included oropharyngeal pain all with the reported term “sore throat” (2 patients on saxagliptin, 1 patient on placebo), headache (1 patient on saxagliptin, 1 patient on placebo), and cough (1 patient on saxagliptin, 1 patient on placebo). There were no events of hypoglycaemia. All AEs reported in the study were assessed by the investigator as mild or moderate in intensity, and none necessitated action with regards to blinded study drug. There were no deaths or discontinuations due to AEs. One serious adverse event (SAE) of moderate non treatment-related pneumonia was reported in a patient who received placebo at Week 8 during the double-blind treatment period. The SAE of pneumonia resolved within 2 days and the patient continued treatment in the study.

Laboratory parameters that met pre-defined criteria for marked abnormalities (MAs) were infrequent among the patients treated in this study. One MA in serum sodium was reported as an AE of mild non-treatment-related hypernatremia (result=154 mmol/L; upper limit of normal=147 mmol/L) and occurred at Week 52 in a patient receiving saxagliptin. The patient was asymptomatic and declined follow-up testing. No other laboratory MAs were assessed by the investigator as AEs.

2.3.4. Study CV181147

Study CV181147 was designed to evaluate the efficacy and safety of saxagliptin as an add-on therapy to metformin during a 16-week double-blind treatment period in paediatric patients 10 to <18 years of age with T2DM who have inadequate glycaemic control on metformin alone. Approximately 236 patients (118 patients per treatment group) were planned to be randomized in a 1:1 ratio to receive saxagliptin (2.5 mg or 5 mg according to body weight) or placebo taken once daily in combination with metformin 1000 mg to 2000 mg formulated as immediate release (IR) or extended release (XR) tablets. The study was initiated in May 2012. Six patients were randomized and treated in the study (4 patients were randomized to saxagliptin and 2 patients were randomized to placebo) over a period of approximately 23 months. In March 2014, the independent Data Monitoring Committee (DMC) recommended that the Sponsor discontinue enrolment due to slow recruitment. The DMC considered that the continued slow accrual was preventing the study from achieving its objective, thereby exposing participants to the unnecessary risk of participating in a clinical trial. The DMC acknowledged the difficulty in conducting studies in the paediatric population with diabetes as well as the efforts that the Sponsor had taken to increase enrolment. The DMC noted that review of the safety data showed no safety concerns; thus, treatment of patients already randomized in the study could continue. Six patients (4 patients in the saxagliptin group and 2 patients in the placebo group) completed the 16-week double-blind treatment period and 2 patients (1 patient in each treatment group) completed the 36-week long-term extension period.

Benefits

In Study **CV181147**, a total of 7 patients entered the 2-week lead-in period of the study and received placebo. Six patients were subsequently randomized and treated in the 16-week double-blind

treatment period. These 6 patients were all female (100%) and mostly Caucasian (66.7%), with ages ranging from 11 to 17 years and body mass index values ranging from 23.7 kg/m2 to 37.4 kg/m2.

The primary efficacy analysis in the study was the comparison of saxagliptin and placebo, as add-on therapy to metformin IR or metformin XR on the change in HbA1c from baseline to Week 16 in the double-blind treatment period. Data was collected on the 6 patients randomized in the study and is provided as line listings in the clinical study report. Given the small number of patients enrolled in Study CV181147, no definitive conclusions could be made regarding any potential benefit of saxagliptin as add-on therapy to metformin IR or metformin XR in paediatric patients with T2DM.

Risks

The adverse event (AE) by Medical Dictionary for Regulatory Activities Version 19 preferred term reported by more than 1 patient in the study was headache (2 patients on saxagliptin). There were no events of hypoglycaemia. All AEs reported in the study were assessed by the investigator as mild or moderate in intensity, and none necessitated action with regards to blinded study drug. There were no deaths, serious adverse events, or discontinuations due to AEs.

Laboratory parameters that met pre-defined criteria for marked abnormalities (MAs) were infrequent among the 6 treated patients, and none of these MAs were assessed by the investigator as AEs.

No new safety risks were identified in Study CV181058 or CV181147. Given the small dataset in these studies, it was not possible to draw any conclusions about the potential risks associated with the administration of saxagliptin compared with placebo in paediatric patients with T2DM.

2.3.5. Discussion on clinical aspects

Due to the small number of patients enrolled in Study CV181058 and CV181147, it was not possible to make a benefit/risk assessment of saxagliptin compared with placebo in paediatric patients with T2DM.

Saxagliptin was well tolerated by the paediatric patients with T2DM in these studies, when administered as monotherapy or as add-on to metformin once daily at doses up to 5 mg. Given the small number of patients in the study, no definitive conclusions could be made about the efficacy and safety of saxagliptin as monotherapy in a broader paediatric population. The safety and efficacy profile for saxagliptin in the EU remains unaltered. The saxagliptin tablet label will not be updated with paediatric use information in the EU.

3. Rapporteur's overall conclusion and recommendation

The data that were presented from Study CV181058 and Study CV181147 are extremely limited as both studies were prematurely aborted due to particularly slow recruitment. Efficacy cannot be evaluated; no new safety issues have emerged. It is agreed with the MAH that these data do not warrant an amendment in the product information.

☒ Fulfilled:

No regulatory action required.