CTC North

A 28-week, multi-center randomized, double-blind, placebo-controlled study to evaluate the potential of Dapagliflozin plus Exenatide in combination with high-dose intensive insulin therapy compared to Placebo in obese insulin- resistant patients with Type 2 Diabetes mellitus

(Proof-of-concept study)

Clinical Study Report Synopsis

EudraCT-No.	2016-003738-25
Protocol-No.	Sponsor: ESR-16-12160 / UKE-DapEx-001 / CRO: CTC171344
Version / Date	1.0 / 09-DEC-2020
Study Phase	Phase III
Study Start and Completion Date	Study Start: 16 February 2018 Early Study Termination: 21 June 2019
Sponsor	University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg, Germany
Coordinating Investigator	Prof. Dr. med. Jens Aberle, MD Section Endocrinology/Diabetology University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg, Germany E-Mail: aberle@uke.de Phone: 0049 40 7410-54412

2 SYNOPSIS

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
Study Title	A 28-week, multi-center randomized, double-blind, placebo-controlled study to evaluate the potential of Dapagliflozin plus Exenatide in combination with high-dose intensive insulin therapy compared to Placebo in obese insulin- resistant patients with Type 2 Diabetes mellitus (Proof-of-concept study)	
Coordinating Investigator	PD Dr. med. Jens Aberle, MD	
Study centers	This multicenter study was conducted at 4 sites.	
Publication (reference)	NA	
Protocol No.	ESR-16-12160 / UKE-DapEx-001 (Sponsor), CTC171344 (CRO)	
EudraCT-No.	2016-003738-25	
Study Period	Date of first subject enrolled: Q1 2018 Date of last subject completed: Q2 2019	
Phase of development	Phase III	
Primary Objective	The primary objective was to compare the absolute change from baseline in HbA1c (hemoglobin A1c) at week 28 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy.	
Secondary Objectives	The secondary objectives were: To compare the absolute change from baseline in HbA1c at week 14 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy. To compare the change from baseline in total body weight at week 14 and 28 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy. To compare the change from baseline in BMI at week 14 and 28 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy. To compare the change in fasting plasma glucose (FPG) at week 14 and 28 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy.	

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
	To compare the change in total daily insulin dose (TDID) at week 14 and 28 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy. To compare the effects between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy.	
Safety Objective	The safety objective was to evaluate the safety of Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy.	
Methodology	A 28-week, multi-center, randomized, double-blind, placebo-controlled trial to study a potential synergistic effect of Dapagliflozin plus Exenatide once-weekly in combination with high-dose intensive insulin therapy compared to Placebo in obese insulin-resistant patients with Type 2 Diabetes mellitus (T2DM) and inadequate glycemic control (HbA1c ≥ 8.0% and ≤ 11.0%) (proof-of-concept study). Patients were randomly allocated to either one of the treatment arms indicated below in a double-blind manner : • Dapagliflozin (10mg orally once daily) plus Exenatide (2mg subcutaneous once-weekly injection) as add-on to high-dose intensive insulin therapy • Placebo (film-coated tablet once daily) plus Placebo (subcutaneous once-weekly injection) as add-on to high-dose intensive insulin therapy • Placebo (film-coated tablet once daily) plus Exenatide (2mg subcutaneous once-weekly injection) as add-on to high dose intensive insulin therapy.	
Subject population	Obese patients (BMI ≥ 30 kg/m2) with T2DM and inadequate glycemic control receiving a stable basal/bolus insulin regimen (BBIT) with a mean daily insulin dose of at least 80 U within the last 3 months prior to enrolment were randomized to 1 of the 3 treatment groups.	
Number of patients	Planned: 60 Screened: 14 Randomized: 13 Dosed: 13 Completed: 5 Discontinued: 8	

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
Indication	Type 2 Diabetes mellitus	
Main criteria for inclusion	For inclusion in the study patients had to fulfill the following criteria: 1. Informed Consent had to be obtained prior to any study procedures. 2. Patient had to be able to read, understand and sign the Informed Consent. 3. HbA1c ≥ 8.0% and ≤ 11.0% based on laboratory results 4. Currently treated with a stable TDID ≥ 80 U at least 3 months prior to enrolment 5. Patients who were receiving metformin had to be on a stable total daily dose ≥ 1500 mg or the maximum tolerated dose of metformin within 3 months prior to enrolment 6. BMI of ≥ 30 kg/m^2 at enrolment 7. Male or female and ≥18 and ≤75 years old at time of informed consent 8. For female patients: o Not breastfeeding. o Negative pregnancy test result (human chorionic gonadotropin, beta subunit [βhCG]) at Visit 0 (Screening) and Visit 1 (randomization) – not applicable to hysterectomized and post-menopausal females. o If of childbearing potential (including perimenopausal women who have had a menstrual period within 1 year), had to practice and be willing to continue to practice appropriate birth control (defined as a method which results in a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as implants, injectables, hormonal contraceptives [pills, vaginal rings, or patches], some intrauterine contraceptive devices [levonorgestrel-releasing or copper-T], tubal ligation or occlusion, or a vasectomized partner) during the entire duration of the study. As applicable, all methods had to be in effect prior to receiving the first dose of study medication.	

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
	o Had to practice appropriate birth control as stated above for 10 weeks after the last dose of study medication. 9. Patients who were receiving the following medications had to be on a stable treatment regimen for a minimum of 2 months prior to Visit 0 (Screening): o Antihypertensive agents o Thyroid replacement therapy o Antidepressant agents	
Test product, dose and mode of administration, batch no.	**Dapagliflozin and matching Placebo:** Dapagliflozin 10mg tablets or Placebo matching Dapagliflozin was administered orally once daily for the 28-week double-blind treatment period. **Exenatide once-weekly and matching Placebo:** Exenatide vials 2mg/vial powder for injection or Placebo matching Exenatide was administered subcutaneously once-weekly for the 28-week double-blind treatment period. Dapagliflozin: AAC1984/L003017 Dapagliflozin Placebo: 149606/L003305 Exenatide: FT4600 Exenatide Placebo: HB4600	
Duration of treatment	Study duration was at least 33 weeks, including a 2-week pre-study Screening period, a 28-week double-blind treatment period and a 3-week safety follow-up period. Treatment period visits 0 (Visit 1), 1 (Visit 2), 8 (Visit 3), 14 (Visit 4) and 28 (Visit 5) weeks after randomization were chosen considering the multiphasic release of Exenatide over approximately 10 weeks with two concentration peaks that could be observed at around week 2 and week 6-7. The initial peak with therapeutic concentrations at week 2 occurs due to release of surface-bound Exenatide, Steady state is reached by week 7 primarily due to microsphere release of the drug that degrade slowly in the body allowing for once-weekly dosing [(1)].	
Reference product, dose and mode of administration, batch no.	NA	

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
Criteria for evaluation Efficacy and Safety	The trial involved obese subjects with inadequate glycemic control (HbA1c ≥ 8.0%) despite high-dose intensive insulin therapy. A treat-to-target approach was used to evaluate the efficacy and safety between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy. Insulin titration was performed in each arm during the entire treatment period (28 weeks) in addition to the blinded study regimen in order to achieve a target FPG of 100-120 mg/dL (5.6-6.7 mmol/L). Assessment of glycemic parameters based on FPG confirmed by laboratory measurements was performed and/or 6-point SMBG (Self-Monitoring of Blood Glucose) on 3 days in the week prior to the study visit was evaluated at each study visit to determine if criteria for insulin titration were met. Insulin titration was executed as judged by the investigator during the entire treatment period seeking a target FPG of 100-120 mg/dL. Insulin titration was evaluated by the investigator during each visit and during weekly patient contacts via telephone, fax or E-mail to review glucose values.	
Planned Statistical methods	**Sample size / Precision** The sample size of 20 patients per group was chosen based on feasibility considerations. Wilding *et al.* reported results on high dose insulin therapy plus different doses of Dapagliflozin in a very similar patient cohort [(2)]. They reported a difference of -0.57% (95% CI [-0.72%, -0.42%]) for the comparison of insulin plus 10 mg Dapagliflozin vs. insulin plus placebo. Assuming the same variability for differences between treatment groups, i.e. a standard deviation of 0.75%, the three pairwise treatment differences could be estimated with a precision of +/ 0.48% at a confidence level of 95%. **Analysis of the primary and secondary endpoints** The analysis of the primary endpoint was performed according to the intention-to-treat (ITT) principle and was therefore based on the full analysis set (FAS). The FAS included all randomized patients, and patients were analyzed as belonging to their randomized arm, regardless of whether they refused therapy, or whether other protocol deviations were known. Patients were randomized as late as possible to achieve a high compliance.	

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
	The effects of Dapagliflozin plus Exenatide, Exenatide monotherapy and placebo as add-on to high-dose intensive insulin therapy with respect to the primary endpoint absolute change in HbA1c at 28 weeks after randomization were estimated within a linear regression model. The analysis included fixed effects for treatment, study center, HbA1c at randomization, visit (14 and 28 weeks) and treatment-by-visit interaction, as well as a random patient effect. The treatment effects of Dapagliflozin plus Exenatide and Exenatide monotherapy vs. Placebo at week 28, the predicted mean change in HbA1c from baseline to week 28 per treatment and the predicted pairwise mean differences in change in HbA1c from baseline to week 28 between the three treatments were calculated with two-sided 95% confidence intervals. The secondary endpoints body weight (at week 14 and 28), BMI (at week 14 and 28), FPG (at week 14 and 28) and TDID (at week 14 and 28) were analyzed analogously using linear regression. The effect of treatment on the secondary endpoint 'HbA1c of ≤ 7%' at 28 weeks compared to baseline was analyzed using a logistic regression model.	
Safety Results	Overall, the clinical trial was performed without major safety issues in 13 patients. The study medication was well tolerated and no deaths were reported. In this trial, 2 SAEs were reported in 2 patients (15.4%). Both SAEs were considered to be "unrelated" to the IMP. These SAEs belonged to the treatment group Dapagliflozin (plus Exenatide. No action was taken with study treatment due to these events. 11 patients (84.6%) experienced a total of 22 AEs. Out of the 22 reported AEs, 9 of them (in 4 patients) occurred during treatment with Dapagliflozin plus Exenatide. 4 AEs were reported in 3 patients in the treatment group with Placebo plus Placebo and remaining 9 AEs were reported in 4 patients in the treatment group with Placebo plus Exenatide.	

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
Safety Results (continued)	For most of the AEs from the three treatment groups the 'relationship between event and Dapagliflozin' or the 'relationship between event and Exenatide' were assessed as "unrelated". Whereas, for 1 AE (constipation) the 'relationship between event and Dapagliflozin' and the 'relationship between event and Exenatide' was reported as "related". 2 AEs ('gastrointestinal infection' and 'diarrhea') were reported as "related" only to the 'event and Exenatide' in the treatment group Placebo plus Placebo. However, both of these AEs were reported as "unrelated" to the 'event and Dapagliflozin'. For 1 AE, (flatulence) the 'relationship between event and Dapagliflozin' and the 'relationship between event and Exenatide' was reported as "related" in the treatment group Placebo plus Exenatide. The remaining 2 AEs ('diarrhea' and 'nausea') were reported as "related" only to the 'event and Exenatide'. However, both of these AEs were reported as "unrelated" to the 'event and Dapagliflozin'. Due to an unrelated AE (atheroma) 1 clinically significant abnormality (condition after atheroma operation) was reported in 1 patient at Visit 6 belonging to the treatment group Dapagliflozin plus Exenatide. Another clinically significant abnormality (diabetic foot syndrome) was reported in 1 patient at Visit 0 and a further 2 clinically significant abnormalities (2x diabetic polyneuropathy) were reported at Visit 0 and Visit 1 in 1 patient belonging to the treatment group Placebo plus Placebo. Otherwise, in most of the patients, physical examinations were reported as normal at all Visits or the reported abnormal findings were evaluated as not clinically significant by investigator. There were no relevant clinically significant changes in safety laboratory, vital signs, ECG when comparing pre-study and post-study results. No safety concerns raised at any time during conduct of the clinical trial.	

Conclusion	The aim of this phase III, multi-center, randomized, double-blind, placebo-controlled clinical trial was to compare the absolute change from baseline in HbA1c at week 28 between Dapagliflozin plus Exenatide, Placebo or Exenatide monotherapy added to high-dose intensive insulin therapy. Due to the premature termination and enrollment of only 13 patients, no efficacy analysis was performed in this clinical trial. Although the inclusion and exclusion criteria were determined in close cooperation with the involved study centers who are experienced in conducting clinical studies the planned number of patients recruitment was not achieved. The possible reasons might be: o The daily insulin dose defined as the inclusion criterion might be too high o The patients who met the inclusion criterion of the daily insulin dose were currently or in the past mostly treated in combination with one of the new substances (especially GLP-1 analogues, please refer to exclusion criterion number 3.129 of Section 9.3.2), which was defined as an exclusion criterion (“Had been treated, was currently being treated, or was expected to require or undergo treatment with any of the following treatment excluded medications: any DPP-4 inhibitor within 3 months prior to Visit 0 (Screening), any GLP-1 analogue within 1 year prior to Visit 0 (Screening). The exclusion criterion number 3.129 of Section 9.3.2 should have been limited to a shorter period. As the efficacy analysis based on enrollment of 60 patients, due to poor recruitment and premature termination of this trial an analysis of the efficacy according to protocol was not possible. Hence, the primary and secondary objectives of the trial were not achieved. Overall, the safety evaluation revealed that the study medications were generally well tolerated in all 13 patients. The clinical trial was performed without major safety issues. The study medications were well tolerated and no deaths were reported. The reported 2 SAEs during the trial conduct were considered to be “unrelated” to the IMPs. The majority of the AEs occurred in all three treatment groups and the ‘relationship between event and Dapagliflozin’ or the ‘relationship between event and Exenatide’ were assessed as ”unrelated”. In total, the ‘relationship between event and Dapagliflozin’ was reported in 2 patients (15.4%), whereas the ‘relationship between event and Exenatide’ was reported in 7 patients (53.8%). Due to an unrelated AE (atheroma), 1 clinically significant abnormality was reported in 1 patient pertaining to the treatment group Dapagliflozin plus Exenatide.

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: Dapagliflozin and Exenatide	**Page:**	
	A clinically significant abnormality (diabetic foot syndrome) was reported in 1 patient and a further 2 clinically significant abnormalities (2x diabetic polyneuropathy) were reported in 1 patient from the treatment group Placebo plus Placebo. Otherwise, in most of the patients, physical examinations were reported as normal at all Visits or the reported abnormal findings were evaluated as not clinically significant by investigator. There were no relevant clinically significant changes in safety laboratory, vital signs, ECG when comparing pre-study and post-study results. No safety concerns raised at any time during conduct of the clinical trial. In conclusion, the primary and secondary objectives of this trial were not achieved due to the premature termination, poor recruitment and insufficient number of patients required for the efficacy analysis. The study medications were well tolerated and safe. However, further investigated with sufficient number of patients are needed to confirm this statement	
Date of Report	09-DEC-2020	