Final Study Report

Synopsis

DAPA-DREAM

A Randomized, Double-Blind, Placebo-controlled, Single-center Phase 1 Inpatient Pilot Study to Explore the Safety and Efficacy of a Single-Dose of DAPAglifozin as Add-on to day and night closed-loop control using the DreaMed Substance Administration Device Software in Adolescent and Adult Subjects with Type 1 Diabetes mellitus

Study No:	ESR-15-11453
EudraCT number:	2016-002212-41
Sponsor and Principal Investigator	Prof. Dr. Thomas Danne Stiftung Hannoversche Kinderheilanstalt Kinder- und Jugendkrankenhaus AUF DER BULT Diabeteszentrum für Kinder und Jugendliche Janusz-Korczak-Allee 12 D-30173 Hannover, Germany
Report Responsibility:	Dr. Torben Biester Prof. Dr. Thomas Danne
Date:	18. Dezember 2020

Study Initiation	09. February 2017
First Patient Visit	22. February 2017
Last Patient Visit	19. December 2017
End of Study	July 2018 Data Transfer

This trial was conducted in compliance with ICH GCP (ICH Guideline, 06.12.2016 1996) applicable regulatory requirements, and in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2008).

Study Phase: Phase Phase 1

Indication: Type 1 Diabetes mellitus

Trial Objectives

Primary objective The purpose of the pilot study is to collect clinical data of a single-dose of 10mg dapagliflozin as add-on to night and day closed-loop control using the DreaMed Algorithm on the time within glucose range 70-180 mg/dl (3.9-10mmol/l) [%] for the ensuing 24 hours with two oral mixed-meals.

Secondary objectives

- To investigate the degree of insulin dose reduction during the DreaMed automated insulin delivery 24 hours after a single dose of 10mg dapagliflozin in patients with type 1 diabetes
- To investigate the effect on urinary glucose excretion
- To investigate if dapagliflozin influences postprandial insulin need
- To investigate if dapagliflozin is associated with elevated ß-hydroxybutyrate levels
- Extra samples will be taken potentially for additional analysis of the incretin axis (for example GIP) in case that elevated β-Hydroxyburate levels need to be elucidated further

Primary efficacy variable

Time within glucose range 70-180 mg/dl (3.9-10mmol/l) [%] during night and day closed-loop control using the DreaMed automated insulin delivery with two oral mixed-meals after oral administration of 10mg dapagliflozin

Secondary efficacy variables

- Percentage of glucose sensor readings below 70 mg/dl (3.9 mmol/l)
- Percentage of glucose sensor readings above 180mg/dl (10 mmol/l)
- Average and SD of glucose sensor readings

Exploratory endpoints

- Percentage of elevated ß-hydroxybutyrate-levels in blood
- Insulin need during the DreaMed automated insulin delivery

Safety Variables

- Hypoglycemic Events defined as BG < 70mg/dL
- DKA definded as β-Hydroxyburate ≥ 1,5 mmol/L and pH < 7,25

Medication

Name of active ingredient:

Dapagliflozin

Name of finished product:

FORXIGA

Dosage: Dapagliflozin (FORXIGA) 10 mg, oral administration,
Daily dose: 10 mg Dapagliflozin

Lot No/Batched: DAPA 10mg: P lot: 50626.27; Bulk lot: KF0352 / L010077

PTM: P lot: 50626.25; Bulk lot: 189096 / L010235

Study Duration Duration of study participation for one patient:
Minimum: 12 days
Maximum: 72 days
Overall duration of the study: 1 year

Design: Monocenter, randomized, double blind, Placebo-controlled, cross-over

Population: Diabetes mellitus Type 1 male and female patients, aged 12-21 years (both inclusive). 15 adults, 15 adolescents/children treated with CSII for at least 3 months.

Sample Size: 45 screened to achieve n = 30 completed patients

Method of assigning subjects to investigational products

Subjects were randomized to either start (at Visit 2) with the investigational product dapagliflozin followed by placebo at Visit 4 or the other way round. The two treatment sequences were:

- Sequence 1: Dapagliflozin followed by placebo
- Sequence 2: Placebo followed by dapagliflozin

Statistical Methods

To investigate the effect of dapagliflozin on the stability of the DreaMed system the primary efficacy variable 'relative time of glucose measurements in range 70-180 mg/dl' was tested via a non-inferiority setting (non-inferiority margin of 10%). The primary efficacy variable was determined per patient per phase as percentage so the differences between the phases dapagliflozin versus placebo were tested with a one-sided paired t-test.
The hypotheses for this non-inferiority setting were:
H0: The mean difference in relative time in glucose range from placebo phase to dapagliflozin phase is at most 10 %.
H1: The mean difference in relative time in glucose range from placebo phase to dapagliflozin phase is greater than 10 %.

Investigational Site:

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Administrative information:

First EC vote: 06-Dec-2016 (incl Am#01)
First BfArM approval: 14-Sep 2016

Amendments

Substantial Am#01: Double dose of dapagliflozin: Dapagliflozin dose was increased from 1x10mg to 2x10mg over a period of 2 days (10mg/day) due to short term efficacy of Dapagliflozin.
EC Vote: 06-Dec-2016
BfArM approval: 30-Nov-2016

Substantial Am#02 Informed Consent Form (ICF) on visit 1: The written consent can occur on visit 1 since patients and parents (where applicable) were already informed about the study before screening visit.
EC Vote: 15-Feb-2017
BfArM approval: 13-Apr-2017

Methodology:

This study was a randomized, double-blind, placebo-controlled, single-center, Phase 1 study with a cross-over design. Two doses of 10 mg dapagliflozin (1 x 10 mg before bedtime and 1 x 10 mg in the morning) were tested as add-on therapy to a CE marked sensor based insulin pump therapy using the DreaMed system in a closed-loop setting. 30 patients aged 12 to 20 years (15 adults, 15 adolescents) with type 1 diabetes completed the study after informed written consent and review of all inclusion/exclusion criteria.

The trial consisted of six visits: a screening visit (Visit 1), two dosing visits (Visit 2 and Visit 4), two telephone calls (Visit 3 and Visit 5) and a follow-up visit (Visit 6).
Before the screening visit took place, patients were provided with oral and written information about the trial and the procedures involved. On enrolment in the trial, the patient's demographic data and medical history were obtained and the patient underwent a physical examination.
Screening took place 2-21 days prior to the 1st dosing visit and the follow-up visit 5-21 days after the end of the 2nd dosing visit. The dosing visits were separated by a wash-out period (5-30 days between the end of the 1st dosing visit and begin of 2nd dosing visit). Each phone visit took place 3-5 days after the end of the respective dosing visit. The planned total duration of the trial was 12-72 days per subject. Each subject was randomised to a treatment sequence consisting of two treatment periods in which the subjects received dapagliflozin and placebo on two separate dosing visits. The overall trial design and visit schedule are outlined in the trial diagram (Figure 1).

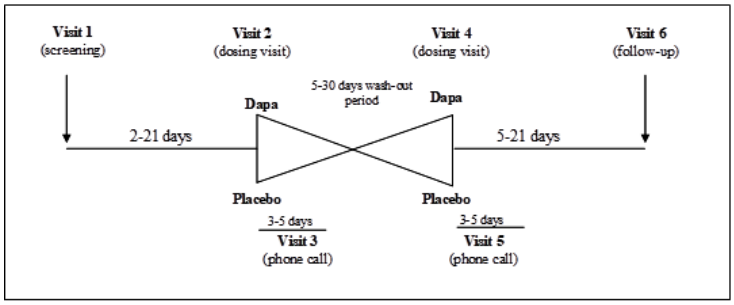

Figure 1: Overall study design

Results:

Efficacy

It could be seen that the relative time of glucose sensor readings in range of 70-180 mg/dl was higher when patients received dapagliflozin instead of placebo. 32% of the glucose levels were in normal range of 70-180 mg/dl during dapagliflozin treatment in sequence 1 and 2, respectively, but only 19.3 % in sequence 1 and 21.3 % in sequence 2 during placebo treatment. The estimated mean change of glucose sensor readings in range of 70-180 mg/dl amounted to 61.8 % (54.8 % in sequence 1 and 65 % in sequence 2).

The one-sided paired t-test showed that dapagliflozin as an add-on to night and day closed-loop control using the DreaMed Algorithm led to significant benefits in glycemic control and increased the time within glucose range 70-180 mg/dl (3.9-10 mmol/l) for the ensuing 24 hours with two oral mixed-meals. On the profiles plot a line is drawn for each patient from left to right connecting the relative time of glucose sensor readings in range during treatment with dapagliflozin and placebo, regardless of the periods in which they occurred. On the agreement plot the relative time of glucose sensor readings in range receiving dapagliflozin treatment is plotted against the relative time of glucose sensor readings in range receiving placebo treatment for each patient, respectively. The plot reveals that only two patients had higher relative time of glucose sensor readings in range of 70-180 mg/dl under treatment with placebo than with dapagliflozin.

The 24 h urine collection ranged between nearly 1 l and 4.9 l at the first dosing visit and between 1 l and 4.5 l at the second dosing visit and it could be seen that the amount of collected urine was higher when patients received dapagliflozin than placebo. The estimated mean change of the amount of collected urine amounted to 27.2 % (42.9 % in sequence 1 and 25 % in sequence 2**Fehler! Verweisquelle konnte nicht gefunden werden.**).

The one-sided paired t-test showed that dapagliflozin increased the volume of 24 h urine collection significantly. The profile plot and the agreement plot show that the amount of collected urine in the 24 h period was only higher in six patients under placebo treatment than under dapagliflozin.

The urinary glucose concentration ranged between 555 mg/dl and 5830 mg/dl at the first dosing visit and between 1266 mg/dl and 6220 mg/dl at the second dosing visit. The concentration of glucose was higher when patients received dapagliflozin than placebo. The estimated mean change of the urinary glucose concentration amounted to 156.1 % (135.5 % in sequence 1 and 182.7 % in sequence 2.

The one-sided paired t-test showed that patients had significantly higher urinary glucose concentration when treated with dapagliflozin than with placebo. No patient showed higher urinary glucose concentration associated with the placebo treatment than with dapagliflozin, as seen on the plots.The location of the points on the agreement plot with respect to the

diagonal line reveals the strength and direction of the difference. The tighter the clustering is along the same direction as the line, the stronger the positive correlation of the two measurements for each subject.

The urinary glucose content ranged between 19,325 mg/24h and 238,422 mg/24h at the first dosing visit and between 15,000 mg/24h and 215,212 mg/24h at the second dosing visit. The urinary glucose content was higher when patients received dapagliflozin instead of placebo. The estimated mean change of the urinary glucose content was 212.2 % (191.3 % in sequence 1 and 244.6 % in sequence 2).

The one-sided paired t-test showed that the urinary glucose content was significantly higher when patients received dapagliflozin instead of placebo. The profiles plot and the agreement plot reveal that only one patient had negligible higher urinary glucose content when treated with placebo than with dapagliflozin. The agreement plot shows a positive correlation of the measurements for the subjects.

Safety

A total of 19 adverse events occurred in 15 patients (48.4 %). The most often documented AE were “Nasopharyngitis” (31.6 %) and “Headache” (15.8 %) followed by “Gastroenteritis” (10.5%). All other events occurred with a frequency of less than 6%. None of the adverse events was serious and almost half of the events occurred when dapagliflozin was administered 47.4 %. 73.7 % of the events were judged as “mild” and 26.3 % as moderate. Most adverse events were completely resolved (89.5 %), 10.5 % remained ongoing and had to be followed. In 3 out of 19 cases (15.8%) first symptoms of the adverse event occurred when no study medication was administered. Furthermore 10.5 % of the events were “possibly” and 84.2 % “unlikely” related to the study medication. No action was necessary in all cases concerning the treatment of the adverse event. Finally, no event occurred due to technical problems or incompatibility reaction.

Summary

This study was a randomized, double-blind, placebo-controlled, single-center, Phase 1 study with a cross-over design. Two doses of 10 mg dapagliflozin (1 x 10 mg before bedtime and 1 x 10 mg in the morning) were tested as add-on therapy to a CE marked sensor based insulin pump therapy using the DreaMed system in a closed-loop setting. The trial consisted of six visits: a screening visit, two dosing visits, two telephone calls and a follow-up visit.

A total number of 34 patients were screened, however 3 patients violated an inclusion or exclusion criterion and were not randomized. The remaining 31 patients were randomized and treated with the study medication. One patient who terminated the study prematurely due to investigator’s decision was replaced.

It could be seen that the relative time of glucose sensor readings in range of 70-180 mg/dl was higher when patients received dapagliflozin instead of placebo. 32% of the glucose levels were in normal range of 70-180 mg/dl during dapagliflozin treatment in sequence 1 and 2, respectively, but only 19.3 % in sequence 1 and 21.3 % in sequence 2 during placebo treatment. The estimated mean change of glucose sensor readings in range of 70-180 mg/dl amounted to 61.8 % (54.8 % in sequence 1 and 65 % in sequence 2). The one-sided paired t-test showed that dapagliflozin as an add-on to night and day closed-loop control using the DreaMed Algorithm led to significant benefits in glycemic control and increased the time within glucose range 70-180 mg/dl (3.9-10 mmol/l) for the ensuing 24 hours with two oral mixed-meals ($p < 0.0001$). Only two patients had higher relative time of glucose sensor readings in range of 70-180 mg/dl under treatment with placebo than with dapagliflozin.

The 24 h urine collection ranged between nearly 1 l and 4.9 l at the first dosing visit and between 1 l and 4.5 l at the second dosing visit and it could be seen that the amount of collected urine was higher when patients received dapagliflozin than placebo. The estimated mean change of the amount of collected urine amounted to 27.2 % (42.9 % in sequence 1 and 25 % in sequence 2). The one-sided paired t-test showed that dapagliflozin increased the volume of 24 h urine collection significantly ($p < 0.0001$). The amount of collected urine in the 24 h period was only higher in six patients under placebo treatment than under dapagliflozin.

The urinary glucose concentration ranged between 555 mg/dl and 5830 mg/dl at the first dosing visit and between 1266 mg/dl and 6220 mg/dl at the second dosing visit. The concentration of glucose was higher when patients received dapagliflozin than placebo. The estimated mean change of the urinary glucose concentration amounted to 156.1 % (135.5 % in sequence 1 and 182.7 % in sequence 2). The one-sided paired t-test showed that patients had significantly higher urinary glucose concentration when treated with dapagliflozin than with placebo ($p < 0.0001$). No patient showed higher urinary glucose concentration associated with the placebo treatment than with dapagliflozin.

The urinary glucose content ranged between 19,325 mg/24h and 238,422 mg/24h at the first dosing visit and between 15,000 mg/24h and 215,212 mg/24h at the second dosing visit. The urinary glucose content was higher when patients received dapagliflozin instead of placebo. The estimated mean change of the urinary glucose content was 212.2 % (191.3 % in sequence 1 and 244.6 % in sequence 2).

The one-sided paired t-test showed that the urinary glucose content was significantly higher when patients received dapagliflozin instead of placebo ($p < 0.0001$). Only one patient had negligible higher urinary glucose content when treated with placebo than with dapagliflozin. A positive correlation of the measurements for the subjects could be seen.

Glucose sensor readings in range of 70-180 mg/dl showed lower blood glucose levels during dapagliflozin treatment than during treatment with placebo, regardless of the sequence (mean

of 124.6 mg/dl and 126.1 mg/dl during dapagliflozin treatment versus 137.3 mg/dl and 134.6 mg/dl during treatment with placebo for sequence 1 and 2, respectively). The estimated mean change amounted to -14.1 % (-15.1 % in sequence 1 and -14.1 % in sequence 2). An ANOVA with the factors “treatment”, “sequence”, “period” (i.e. dosing visit) and “subject within sequence” showed that the glucose sensor readings mainly depended on “treatment”. Furthermore, it could be seen that the insulin dose used in 24 hours calculated per kg bodyweight was much lower when patients received dapagliflozin instead of placebo. The estimated mean change amounted to -21.0 % (-17.7 % in sequence 1 and -21.8 % in sequence 2). The used insulin dose significantly depended on “treatment” and “sequence” (ANOVA). Further on the median ß-hydroxybutyrate was only elevated during dapagliflozin treatment in patients of sequence 2. The percentage of elevated ß-hydroxybutyrate significantly depended on “treatment” (ANOVA). Estimated differences in ß-hydroxybutyrate between dapagliflozin and placebo were 0.12 mmol/l (0.12 mmol/l in sequence 1 and 0.11 mmol/l in sequence 2). The mean ß-hydroxybutyrate level showed higher values when patients were treated with dapagliflozin instead of placebo. The percentage of elevated ß-hydroxybutyrate significantly depended on “treatment” and the insulin need on “treatment” and “sequence” (ANOVA). Regarding the point estimates for mean changes in insulin need between dapagliflozin and placebo, a mean change of -0.1 % (-0.1 % in both sequences, respectively) could be seen for patients who received two meals per visit.

Written informed consent was given by all patients or legal guardians at information or screening visits. The patients fulfilled all inclusion criteria and did not violate any exclusion criterion. The median age of the patients amounted to 17 years, with a range from 12 to 20 years. 16 patients were pubertal (51.6 %) and 15 (48.4%) adolescents. More than half of the patients were female (61.3 %). All patients were non-hispanic or latino and white. Median height was 1.69 m and median weight at screening 66 kg, which led to a median BMI of 22.6 kg/m^2 (23.1 kg/m^2 for patients of sequence 1 and 21.4 kg/m^2 for patients of sequence 2). Furthermore, the median systolic blood pressure amounted to 128 mmHg, the diastolic to 61 mmHg. The median pulse was 76 bpm and the median temperature 36.9 ^oC. No significant abnormalities occurred in the urine with respect to urine specific weight, pH, leukocytes, nitrite, protein, glucose, ketone, urobilinogen, erythrocytes and hemoglobin. The result of the drug test “Kombitest 10” was negative for all patients. Blood samples were taken for all patients during screening visit. 45.2 % of the patients were diagnosed with Type 1 diabetes in their first 5 years of life. The HbA1c measurement was performed in all patients during screening visit. More than half of them showed an A1c value between 7.5 and 9 (54.8 %). Finally, all patients received training for the glucose sensor system. For 9.7 % of the patient’s alarm setting was performed during the run-in phase.

All inclusion and exclusion criteria for the dosing visits were fulfilled and hence all patients were randomized. Additionally, none of the female patients was pregnant. Blood samples were collected within the time window of +/- 5 minutes according to protocol in 98.7 % of the cases. The mean capillary glucose level was lower in patients who received dapagliflozin compared to placebo before first and second administration of ensure and after second administration of ensure, respectively. Whereas the mean β-hydroxyburyrate was higher in patients treated with dapagliflozin than patients treated with placebo for each point in time, respectively. The analysis of blood samples showed that the average concentration of active GLP-1, total GLP-1 and GIP were lower during the first dosing visit than the second dosing visit (median of 1.9 pmol/l and 2.0 pmol/l for GLP-1 active, 21.6 pg/ml and 22.7 pg/ml for GLP-1 total and 350.4 pg/ml and 368.9 pg/ml for GIP during first and second dosing visit, respectively irrespective of the sequence. The average concentration of glucagon showed a higher level during the first dosing visit than the second dosing visit (median of 47.5 pmol/l and 46.2 pmol/l, respectively irrespective of the sequence. The average concentration of iso-insulin revealed a lower level when patients were treated with dapagliflozin than placebo. Study medication was given to all patients who did not discontinue prematurely.

Patients received in median 404 ml ensure in sequence 1 and 393 ml respective 402 ml ensure in sequence 2 during first and second dosing visit, respectively, whereat one patient in sequence 1 did not receive a second intake of ensure. Besides 96.7 % of the 24 h urine probes were collected within the time window of +/- 5 minutes according to protocol. Urine sample was collected for all patients during dosing visits. 83.3 % of these urine probes were collected within the time window of +/- 5 minutes according to protocol. The median amount of insulin used in 24 h per kg bodyweight was much less in patients treated with dapagliflozin in comparison to placebo. The phone calls were carried out with all patients, but problems/questions were only documented in one case. In addition, physical examination of the skin revealed 19 significant abnormalities at screening and 14 significant abnormalities were observed at follow-up. Blood sample was collected for all patients at follow-up.

30 out of 31 patients finished the trial regularly and one patient terminated the study prematurely due to investigator’s decision. Furthermore, a total of 39 previous or current diseases were documented for 24 patients. 37 of these were still ongoing. Lipohypertrophy was the most commonly documented concomitant illness with a share of more than 30%, all other concomitant illnesses only occurred once or twice.

Besides all patients experienced hypoglycemia. Patients showed in median 11 hypoglycemic events (9 events in sequence 1 and 12 events in sequence 2). 281 out of 432 total hypoglycemic events were symptomatic. In only one case a self-treatment was not possible. But there was no need for treatment by another person due to impossible self-treatment. It was documented that patients did not experience unconsciousness in 99.5 % of hypoglycemic

events. The median blood sugar level before treatment amounted to 59 mg/dl and ranged from 20 mg/dl to 76 mg/dl. Furthermore, patients carried out an activity prior to hypoglycemia in 10 % of the cases.

All patients received at least one concomitant medication. Most patients received actual diabetes treatment at screening (96.9 %) in a median daily dose of 0.9 IU per kg bodyweight, ranging from 0.7 IU/kg to 1.5 IU/kg. Other indications than “diabetes mellitus” (51.6%) were “concomitant illness” and “adverse events” (16.1 %, respectively).

Finally, a total of 19 adverse events occurred in 15 patients (48.4 %). The most often documented AE were “Nasopharyngitis” (31.6 %) and “Headache” (15.8 %) followed by “Gastroenteritis” (10.5%). All other events occurred with a frequency of less than 6%. None of the adverse events was serious and almost half of the events occurred when dapagliflozin was administered (47.4 %). 73.7 % of the events were judged as “mild” and 26.3 % as moderate. Most adverse events were completely resolved (89.5 %), 10.5 % remained ongoing and had to be followed. In 3 out of 19 cases (15.8%) first symptoms of the adverse event occurred when no study medication was administered. Furthermore 10.5 % of the events were “possibly” and 84.2 % “unlikely” related to the study medication. No action was necessary in all cases concerning the treatment of the adverse event. In addition, no event occurred due to technical problems or incompatibility reaction.

Conclusion:

Insulin pump therapy reduces the risk of DKA and hypoglycemia, at least in pediatric populations [i]. As closed-loop approaches are currently a very promising approach to optimize insulin therapy and several different systems provide safe and effective insulin administration [ii,iii], possibly a combination of closed-loop insulin administration with adjunct SGLT-inhibitor therapy, as shown in this trial may constitute a novel approach to maximize TIR during insulin therapy. Regardless of insulin delivery method (injection or infusion), with proper DKA risk mitigation, such intensive insulin management with adjunctive SGLT therapy holds great potential in helping patients achieve meaningful clinical benefits HbA1c reductions. As a diabetes community we need work together to ensure that life changing closed loop systems can be safely made available to those who wish to use them whether this would be with or without adjunctive therapy in order to further optimize glycemic control.

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i Karges B, Schwandt A, Heidtmann al.. Association of Insulin Pump Therapy vs Insulin Injection Therapy With Severe Hypoglycemia, Ketoacidosis, and Glycemic Control Among Children, Adolescents, and Young Adults With Type 1 Diabetes. JAMA. 2017 Oct 10;318(14):1358-1366

ii Weisman A, et al. Effect of artificial pancreas systems on glycemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol. 2017 Jul;5(7):501-512

iii Bekiari E, Kitsios K, Thabit H, et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ. 2018 Apr 18;361:k1310

Author(s)

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