Clinical trial results:
A 24 Week Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years

Summary

EudraCT number	2015-005041-31
Trial protocol	GB HU RO
Global end of trial date	06 April 2020

Results information

Result version number	v3 (current)
This version publication date	13 February 2022
First version publication date	16 October 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D1690C00017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02725593
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Forskargatan 18, Sudertalje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca AB, +46 18872409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca AB, +46 18872409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000694-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2020
Global end of trial reached?	Yes
Global end of trial date	06 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study aimed to compare the mean change from baseline in glycated haemoglobin (HbA1c) achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in participants aged 10 to less than 25 years with type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	72
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	7

Adolescents (12-17 years)	46
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 42 study centres in 7 countries worldwide.

Pre-assignment

Screening details:

Participants reported to the clinical study site for screening within 12 to 8 weeks of 1st study drug administration. 168 participants were screened and 72 participants were randomized and included in the full analysis set.

Period 1

Period 1 title	Blinded treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10mg/ Dapagliflozin 10mg

Arm description:

Dapagliflozin (10 mg) tablet administered orally, once daily for the 24 week double-blinded treatment period. The participants then continued to receive Dapagliflozin (10 mg) once daily for a further 28 weeks in the open label long term-extension.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg administered orally once daily.

Arm title	Placebo/ Dapagliflozin 10mg

Arm description:

Matching placebo tablet administered orally, once daily for the 24 weeks double-blinded treatment period. The participants then received Dapagliflozin (10 mg), orally, once daily for a further 28 weeks in the open label long-term extension.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo administered orally once daily.

Number of subjects in period 1	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg
Started	39	33
Received treatment	39	33
Completed	34	27
Not completed	5	6
Consent withdrawn by subject	4	3
Withdrawal by Parent/Guardian	-	2
Lost to follow-up	1	1

Period 2

Period 2 title	Long term extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 10mg/ Dapagliflozin 10mg

Arm description:

Dapagliflozin (10 mg) tablet administered orally, once daily for the 24 week double-blinded treatment period. The participants then continued to receive Dapagliflozin (10 mg) once daily for a further 28 weeks in the open label long term-extension.

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg administered orally once daily.

Arm title	Placebo/ Dapagliflozin 10mg

Arm description:

Matching placebo tablet administered orally, once daily for the 24 weeks double-blinded treatment period. The participants then received Dapagliflozin (10 mg), orally, once daily for a further 28 weeks in the open label long-term extension.

Arm type	Placebo
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg administered orally once daily.

Number of subjects in period 2[1]	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg
Started	33	27
Completed	32	24
Not completed	1	3
Consent withdrawn by subject	1	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 1 participant who completed Period 1 did not enter the long-term extension.

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin 10mg/ Dapagliflozin 10mg
Reporting group description:	
Dapagliflozin (10 mg) tablet administered orally, once daily for the 24 week double-blinded treatment period. The participants then continued to receive Dapagliflozin (10 mg) once daily for a further 28 weeks in the open label long term-extension.	
Reporting group title	Placebo/ Dapagliflozin 10mg
Reporting group description:	
Matching placebo tablet administered orally, once daily for the 24 weeks double-blinded treatment period. The participants then received Dapagliflozin (10 mg), orally, once daily for a further 28 weeks in the open label long-term extension.	

Reporting group values	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg	Total
Number of subjects	39	33	72
Age Categorical Units: Participants			
≥10 and ≤15	16	14	30
>15 and <18	13	10	23
≥18 and <25	10	9	19
Age Continuous Units: Years			
arithmetic mean	16.1	16.2	
standard deviation	± 3.3	± 3.6	-
Sex: Female, Male Units: Participants			
Female	24	19	43
Male	15	14	29
Race/Ethnicity, Customized Units: Subjects			
White	28	16	44
Black or African American	8	10	18
Asian	0	1	1
Native Hawaiian or other Pacific Islander	1	0	1
American Indian or Alaska Native	2	3	5
Other	0	3	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	12	24
Not Hispanic or Latino	26	21	47
Unknown or Not Reported	1	0	1
Geographic Region Units: Subjects			
North America	16	16	32
Latin America	7	9	16
Europe	16	8	24
Asia/Pacific	0	0	0

End points

End points reporting groups

Reporting group title	Dapagliflozin 10mg/ Dapagliflozin 10mg
Reporting group description:	
Dapagliflozin (10 mg) tablet administered orally, once daily for the 24 week double-blinded treatment period. The participants then continued to receive Dapagliflozin (10 mg) once daily for a further 28 weeks in the open label long term-extension.	
Reporting group title	Placebo/ Dapagliflozin 10mg
Reporting group description:	
Matching placebo tablet administered orally, once daily for the 24 weeks double-blinded treatment period. The participants then received Dapagliflozin (10 mg), orally, once daily for a further 28 weeks in the open label long-term extension.	
Reporting group title	Dapagliflozin 10mg/ Dapagliflozin 10mg
Reporting group description:	
Dapagliflozin (10 mg) tablet administered orally, once daily for the 24 week double-blinded treatment period. The participants then continued to receive Dapagliflozin (10 mg) once daily for a further 28 weeks in the open label long term-extension.	
Reporting group title	Placebo/ Dapagliflozin 10mg
Reporting group description:	
Matching placebo tablet administered orally, once daily for the 24 weeks double-blinded treatment period. The participants then received Dapagliflozin (10 mg), orally, once daily for a further 28 weeks in the open label long-term extension.	

Primary: Adjusted change from baseline in glycated haemoglobin (HbA1c) at Week 24

End point title	Adjusted change from baseline in glycated haemoglobin (HbA1c) at Week 24
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	23		
Units: Percentage of HbA1c				
least squares mean (standard error)	-0.25 (± 0.30)	0.50 (± 0.34)		

Statistical analyses

Statistical analysis title	Dapagliflozin vs Placebo
Comparison groups	Dapagliflozin 10mg/ Dapagliflozin 10mg v Placebo/

	Dapagliflozin 10mg
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Mixed model repeated measures analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.45

Secondary: Adjusted change from baseline in fasting plasma glucose (FPG) at Week 24

End point title	Adjusted change from baseline in fasting plasma glucose (FPG) at Week 24
End point description:	
End point type	Secondary
End point timeframe: Baseline to Week 24	

End point values	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	23		
Units: mmol/L				
least squares mean (standard error)	-0.07 (± 0.53)	0.72 (± 0.61)		

Statistical analyses

Statistical analysis title	Dapagliflozin vs Placebo
Comparison groups	Dapagliflozin 10mg/ Dapagliflozin 10mg v Placebo/ Dapagliflozin 10mg

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Mixed model repeated measures analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	0.85
Variability estimate	Standard error of the mean
Dispersion value	0.81

Secondary: Percentage of participants who required glycemic rescue medication or permanently discontinued treatment due to lack of glycemic control

End point title	Percentage of participants who required glycemic rescue medication or permanently discontinued treatment due to lack of glycemic control

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	33		
Units: Percentage of participants				
number (not applicable)	5.1	9.1		

Statistical analyses

Statistical analysis title	Dapagliflozin vs Placebo
Comparison groups	Dapagliflozin 10mg/ Dapagliflozin 10mg v Placebo/ Dapagliflozin 10mg

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.655
Method	Fisher’s exact test
Parameter estimate	Mean difference (final values)
Point estimate	-3.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.11
upper limit	9.62

Secondary: Percentage of participants with baseline glycated haemoglobin (HbA1c) >= 7% who achieved HbA1c level < 7% at Week 24

End point title	Percentage of participants with baseline glycated haemoglobin (HbA1c) >= 7% who achieved HbA1c level < 7% at Week 24
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: Percentage of participants				
number (not applicable)	25.0	4.2		

Statistical analyses

Statistical analysis title	Dapagliflozin vs Placebo
Comparison groups	Dapagliflozin 10mg/ Dapagliflozin 10mg v Placebo/ Dapagliflozin 10mg
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	Fisher’s exact test
Parameter estimate	Mean difference (final values)
Point estimate	20.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	41.11

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to a maximum of 56 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1
Reporting groups	
Reporting group title	Dapagliflozin 10mg/ Dapagliflozin 10mg
Reporting group description: -	
Reporting group title	Placebo/ Dapagliflozin 10mg
Reporting group description: -	

Serious adverse events	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	3 / 33 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 39 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 39 (2.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 39 (2.56%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 39 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Dapagliflozin 10mg/ Dapagliflozin 10mg	Placebo/ Dapagliflozin 10mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 39 (61.54%)	19 / 33 (57.58%)	
Investigations			
Weight increased			
subjects affected / exposed	2 / 39 (5.13%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 39 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	5 / 39 (12.82%)	4 / 33 (12.12%)	
occurrences (all)	6	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 39 (5.13%)	2 / 33 (6.06%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	3 / 39 (7.69%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
Toothache			

subjects affected / exposed	1 / 39 (2.56%)	2 / 33 (6.06%)	
occurrences (all)	1	4	
Vomiting			
subjects affected / exposed	2 / 39 (5.13%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 39 (10.26%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
Cough			
subjects affected / exposed	2 / 39 (5.13%)	2 / 33 (6.06%)	
occurrences (all)	2	3	
Sinus congestion			
subjects affected / exposed	2 / 39 (5.13%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Microalbuminuria			
subjects affected / exposed	1 / 39 (2.56%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Pain in extremity			
subjects affected / exposed	2 / 39 (5.13%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	2 / 39 (5.13%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Fungal infection			

subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	5 / 39 (12.82%)	2 / 33 (6.06%)	
occurrences (all)	5	3	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Pharyngotonsillitis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	3 / 39 (7.69%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Dyslipidaemia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 39 (2.56%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Vitamin D deficiency			
subjects affected / exposed	5 / 39 (12.82%)	2 / 33 (6.06%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2016	The protocol was amended to incorporate new safety information related to DKA. Symptoms and predisposing factors for DKA were described for patients to be appropriately assessed and management of HbA1c values.
13 February 2017	The protocol was amended to reflect the end of Bristol Myers Squibb's role in the study. The duration of the screening period was extended, and details relating to the masking of spot urine glucose, the study weeks relating to lack of glycaemic control criteria for initiation of rescue medication, and the use of third-party vendors for lost to follow-up patients were clarified.
20 September 2017	The protocol was amended to increase the number of participants randomized in the study to ensure that at least 50 patients would complete the 24-week treatment period on study drug and the Week 24 assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported