A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus

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DINAMOTM (main study)The objective of this study is to assess the efficacy and safety of anempagliflozin dosing regimen and one dose of linagliptin versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON55783

Source
ToetsingOnline

Brief title
DINAMO

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Diabetes mellitus type 2

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim en Eli Lilly

Intervention

Keyword: children, empagliflozin, linagliptin, type 2 diabetes mellitus

Outcome measures

Primary outcome

DINAMOTM

The primary efficacy endpoint will be the change in HbA1c (%) from baseline to

the end of 26 weeks.

DINAMOTM Mono

The primary efficacy endpoint will be the occurrence of treatment failure up to

or at Week 26 as a binary endpoint, defined as meeting at least one of the

following criteria:

* Use of rescue medication at any time up to Week 26

* Increase from baseline in HbA1c by 0.5% at Week 26

* Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with

baseline HbA1c < 7.0%.

See protocol section 5.1.1

Secondary outcome

The secondary endpoints to assess efficacy are listed below:

DINAMOTM

* Change in FPG (mg/dL) from baseline to the end of 26 weeks

* Change in body weight (kg) from baseline to the end of 26 weeks

* Change in SBP (mmHg) from baseline to the end of 26 weeks

* Change in DBP (mmHg) from baseline to the end of 26 weeks

* Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks

* Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks

DINAMOTM Mono

* Time to treatment failure

* Change in HbA1c (%) from baseline to the end of 26 weeks

* Change in FPG (mg/dL) from baseline to the end of 26 weeks

* Change in body weight (kg) from baseline to the end of 26 weeks

* Change in SBP (mmHg) from baseline to the end of 26 weeks

* Change in DBP (mmHg) from baseline to the end of 26 weeks

* Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks

* Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks

Study description

Background summary

T2DM in children and adolescents (youth-onset T2DM) has also become an increasingly important public health concern throughout the world with unique

characteristics and demographics in many countries. Youth-onset T2DM occurs most often during the second decade of life and coincides with the peak of physiologic pubertal insulin resistance. Diabetes is causing elevated glucose levels which are harmful to the body. There is a medical need for new antidiabetic drugs for children and adolescents for whom lifestyle change is not sufficient and as add-on to metformin and/or insulin therapy. See protocol section 1.1

Study objective

DINAMOTM (main study)
The objective of this study is to assess the efficacy and safety of anempagliflozin dosing regimen and one dose of linagliptin versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus treated with metformin and/or insulin or who are not tolerating metformin.

DINAMOTM Mono (ancillary study)
The objective of this study is to explore the effect of an empagliflozin dosing regimen and one dose of linagliptin as Monotherapy in children and adolescents with type 2 diabetes mellitus.

In addition, the trial will assess the long term safety of empagliflozin and linagliptin after 52 weeks of treatment. See protocol section 2.1 & 2.2

Study design

A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin (10mg and possibly 25 mg at week 14 when not achieving HbA1c target < 7%) and linagliptin (5mg) over 26 weeks, with a double-blind active treatment) empagliflozin (10 mg and 25 mg) and linagliptin (5mg)) safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus

See protocol section 3.1 & 3.2

Intervention

All subjects will receive placebo matching linagliptin (5 mg) or empagliflozin (10 mg or 25 mg) during the run-in period.

After randomization:
* The placebo group receives once daily during 26 weeks a placebo and after 26 weeks linagliptin (5mg) of empagliflozin (10mf of 25mg).
* The Linagliptin group receives once daily Linagliptin (5 mg).
* The Empagliflozin group receives once daily Empagliflozin (10mg) and at week 14, when not achieving HbA1c target < 7%, Empagliflozin 10 mg or 25 mg.

See protocol section 4.1 & 4.1.4

Study burden and risks

blood sampling: 9 times
number of clinic visits: 11
number of phone visits: 5
diaries: self-Blood Glucose Monitoring and self-blood Ketone Monitoring
emotional discomfort: determine Tanner staging (a scale of pubertal development in children) - 3 times unless at visit 2 or 5 stage 5 has been determined, then it's resp. once or twice.

The currently known side effects are stated in the Dutch package insert of Linagliptin and Empagliflozin which both will be provided to the subject. There may be other risks of Linagliptin or Empagliflozin that are currently unknown.

The trial is double-blinded, so subject nor investigator knows who gets the active treatment or placebo. Because for all subjects there's a likelihood for a therapeutic effect, this trial could benefit all subjects. 2 out of 3 subjects will be treated with Linagliptin or Empagliflozin up to 52 weeks. 1 out of 3 patients will receive a placebo during the first 26 weeks (and the standard treatment; diet and exercise, metformin, insulin) and then treated up to 52 weeks with Linagliptin or Empagliflozin. The treatment with Linagliptin or Empagliflozin might have positive glycaemic effects, since in adults it has already demonstrated favourable HbA1c and fasting plasma glucose changes.

If one compares this with the burden and risks associated with participation, the trial conduct is justified. Patients safety will be monitored closely by the investigator and her/his team and by blood- and urine analysis and by self-Blood Glucose Monitoring and self-blood Ketone Monitoring
See protocol section 2.3

Contacts

Public
Boehringer Ingelheim

Comeniusstraat 6
Alkmaar 1817MS
NL
Scientific
Boehringer Ingelheim

Comeniusstraat 6

Alkmaar 1817MS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Patients aged 10 to 17 years (inclusive) at the time of randomisation (Visit 2)
2. Male and female patients
3. Women of childbearing potential (WOCBP)1 must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is
provided in the patient's legal representative information sheet as well as in Section 4.2.2.3.
4. Signed and dated written informed consent provided by the patient's parent(s) (or legal guardian) and patient's assent in accordance with ICH-GCP and local legislation prior to admission to the trial (informed assent will be sought according to the patient's age, level of maturity, competence and capacity)
5. Documented diagnosis of T2DM for at least 8 weeks at Visit 1A
6. Insufficient glycaemic control as measured by the central laboratory at Visit 1A:
a. DINAMOTM: HbA1c >= 6.5% and <= 10.5%
b. DINAMOTM Mono: HbA1c >= 6.5% and <= 9.0%
7. a. DINAMOTM: Patients treated with
- diet and exercise plus metformin at least 1000 mg/day (or up to a maximal tolerated dose) at a stable dose for 8 weeks prior to Visit 2 or not tolerating metformin (defined as patients who were on metformin treatment for at least 1 week and had to discontinue metformin due to metformin-related side effects as

assessed by the investigator)
AND/OR
- diet and exercise plus stable basal or MDI insulin therapy, defined as a weekly average variation of the basal insulin dose <= 0.1 IU/kg over 8 weeks prior to Visit 2

b. DINAMOTM Mono: Drug-naïve patients or patients not on active treatment (including discontinuation of metformin for at least 12 weeks prior to Visit 2)
8. BMI >= 85th percentile for age and sex according to WHO references at Visit 1B
9. Non-fasting serum C-peptide levels >= 0.6 ng/ml as measured by the central laboratory at Visit 1A
10. Negative for both islet cell antigen auto-antibodies (IA-2) and glutamic acid decarboxylase (GAD) auto-antibodies as measured by the central laboratory at Visit 1A
11. Compliance with trial medication intake must be between 75% and 125% during the open-label placebo run-in period

Exclusion criteria

1. Any history of acute metabolic decompensation such as diabetic ketoacidosis within 8 weeks prior to Visit 1A and up to randomisation (mild to moderate polyuria at the time of randomisation is acceptable)
2. Diagnosis of monogenic diabetes (e.g. MODY)
3. History of pancreatitis
4. Diagnosis of metabolic bone disease
5. Gastrointestinal disorders that might interfere with study drug absorption according to investigator assessment
6. Secondary obesity as part of a syndrome (e.g. Prader-Willi syndrome)
7. Any antidiabetic medication (with the exception of metformin and/or insulin background therapy for DINAMOTM) within 8 weeks prior to Visit 1A and until Visit 2
8. Treatment with weight reduction medications (including anti-obesity drugs) within 3 months prior to Visit 1A and until Visit 2
9. History of weight-loss surgery or current aggressive diet regimen (according to investigator assessment) at Visit 1A and until Visit 2
10. Treatment with systemic corticosteroids for > 1 week within 4 weeks prior to Visit 1A and up to Visit 2. Inhaled or topical use of corticosteroids (e.g. for asthma/chronic obstructive pulmonary disease) is acceptable.
11. Change in dose of thyroid hormones within 6 weeks prior to Visit 1A or planned change or initiation of such therapy before Visit 2
12. Known hypersensitivity or allergy to the investigational products or their excipients
13. Impaired renal function defined as estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73m² (according to Zappitelli formula) as measured by the central laboratory at Visit 1A

14. Indication of liver disease defined by serum level of either alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase above 3 fold upper limit of normal (ULN) at Visit 1A as
measured by the central laboratory at Visit 1A
15. History of belonephobia (needle phobia)
16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to Visit 1A, except appropriately treated basal cell carcinoma of the skin or in situcarcinoma of uterine cervix
17. Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells (e.g. malaria, babesiosis, haemolytic anaemia)
18. Any other acute or chronic medical or psychiatric condition or laboratory abnormality that, based on investigator's judgement, would jeopardize patient safety during trial participation or would affect the study outcome
19. Medical contraindications to metformin according to the local label (for patient on metformin background therapy)
20. Patient not able or cannot be supported by his/her parent(s) or legal guardian to understand and comply with study requirements based on investigator's judgement
21. Previous randomisation in this trial
22. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other
investigational treatment(s)
23. Chronic alcohol or drug abuse within 3 months prior to Visit 1A or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial
24. Female patients who are pregnant, nursing, or who plan to become pregnant in the trial

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2018
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Jardiance
Generic name:	empagliflozin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Trajenta
Generic name:	linagliptin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-03-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-07-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	24-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2021

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000669-21-NL
ClinicalTrials.gov	NCT03429543
CCMO	NL64235.100.18