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Efficacy and safety of using insulin glargine in patients with type 2 diabetes on non-insulin antidiabetic therapy failing to achieve control of blood sugar: the Toujeo-1 trial

Submission date
24/06/2019

Recruitment status
No longer recruiting

Registration date
25/06/2019

Overall study status
Completed

Last Edited
04/07/2024

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
People with type 2 diabetes usually start their diabetes treatment with life style modifications and oral antidiabetic drugs. However, type 2 diabetes is a progressive disease and therefore, in many cases also insulin supply is needed. An often used way to start with insulin therapy in type 2 diabetes is to add one shot of basal insulin per day to the oral antidiabetic drugs used. To take insulin goes hand in hand with hypoglycemia, an unwanted state of too low blood sugar with several symptoms, sometimes even including fainting and coma. Therefore, fear of hypoglycemia often prevents people with diabetes to achieve their blood sugar targets. On the other hand it is very important for patients with diabetes to reach their blood sugar targets to avoid late-stage complications like kidney disease, eye disorders and cardiovascular diseases. Several newer types of insulins have been developed, which reduce the risk for hypoglycemia compared to older types of insulin. The aim of this study is to find out, if starting insulin therapy with insulin glargine 300 units per milliliter, a newer basal insulin, allows more people with type 2 diabetes on oral antidiabetic drugs, who did not reach their target blood sugar levels, to achieve their blood sugar targets safely, i.e. with low risk for hypoglycaemia, in daily clinical practice.

Who can participate?
Adults at or over the age of 18 years with type 2 diabetes who use oral antidiabetic drugs and are treated by a German or Swiss physician.

What does the study involve?
Participants are elected by their treating physician to join this study, if the physician had already decided to start a basal insulin therapy with insulin glargine 300 units per milliliter independent of the participation in this study. Participants will be treated by their physician as usual and will visit their doctor in the usual time intervals (in Germany and Switzerland usually every three months for diabetes patients). The physician will document several parameters at the first visit, when the basal insulin is started, and at least 6 and 12 months thereafter. The study lasts one

year in total. The participants are asked to answer a diabetes treatment satisfaction questionnaire at the first visit and at the visit 12 months thereafter.

What are the possible benefits and risks of participating?
There will be no immediate direct benefit or risk to those taking part, because this is a non-interventional study which means that patients are treated as they would be without participation in this study. However, the results of this study will add to the knowledge of how insulin glargine 300 units per milliliter is used in daily clinical practice and how its use in combination with oral antidiabetic drugs can be improved.

Where is the study run from?
The Toujeo-1 study is being run by Sanofi-Aventis Deutschland GmbH and takes place in diabetologists' and general practioners', family physicians' and internists' practices all over Germany and Switzerland, where people with type 2 diabetes are treated.

When is the study starting and how long is it expected to run for?
July 2015 to December 2017

Who is funding the study?
Sanofi-Aventis Deutschland GmbH (Germany)

Who is the main contact?
Prof. Dr. Martin Pfohl, chief physician of Medical Clinic I, General Internal Medicine, Ev. Krankenhaus BETHESDA, Heerstr. 219, D-47053 Duisburg, Germany, email: medklinik1@bethesda.de

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
GLARGL07589

Study information

Scientific Title
A prospective observational study assessing the clinical benefit of Toujeo initiation after oral antidiabetic drug failure in insulin naïve patients with type 2 diabetes mellitus

Acronym
Toujeo-1

Study objectives
The aim of this non-interventional study (NIS) was to document the treatment effectiveness and safety after 6 and 12 months for patients with type 2 diabetes mellitus (T2DM) who started a basal Insulin supported oral therapy (BOT) with insulin glargine 300 U/mL used under real-life conditions in daily clinical practice.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 02/06/2015, Ethikkommission der Ärztekammer Nordrhein / Ethical committee of the state medical council of Northrhine (Tersteegenstr. 9, D-40474 Düsseldorf, Germany; +49-211-4302-2272; Ethik@aekno.de), ref: 2015162
2. Approved 18/01/2016, Commission cantonale d'éthique de la recherche sur l'etre humain / Cantonal ethical committee for the research in humans (Canton de Vaud, Av. de Chailly 23, 1012 Lausanne, Switzerland; +41-21-316 18 30; secretariat.CER@vd.ch), ref: 464/15

Study design

Non-interventional open-label multi-center multi-national single-arm prospective observational study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Type 2 diabetes mellitus in adult patients requiring basal insulin therapy.

Interventions
All data were collected three times during this study: at baseline, approximately 6 and approximately 12 months after starting insulin glargine 300 U/mL therapy. Baseline documentation had to start immediately after adding insulin glargine 300 U/mL to the existing OAD therapy. This had to occur after the physician had independently of the participation in this study decided to prescribe insulin glargine 300 U/mL and when thereafter the physician and the patient had decided the participation of the latter in this study. Next measurements were documented approximately 6 months thereafter and last measurements were documented approximately 12 months thereafter. Besides this, all fasting blood glucose (FBG) measurements available were collected on a monthly base asking for documentation of changes during the last four weeks each month. Also, dosing information was captured every month; i.e. actual dose and frequency of dose changes during the last four weeks. Data had to be generated during daily therapeutic routine of the physicians. Any change in the patient's antidiabetic therapy regimen was strictly left at the physician's discretion. No therapeutic decision of the physician should have been based upon participation in this study. Titration algorithm was also left at investigator's discretion. Participating physicians were distributed equally all over Germany and Switzerland to allow for a representative sample of German and Swiss patients with T2DM initiating basal insulin therapy as add-on to their oral antidiabetic treatment.
In order to allow for a valid statistical analysis even in smaller subgroups of patients (as distribution within the predefined subgroups may not be equal) it was originally planned to document and analyze about 3,500 patients in this NIS (3,000 patients from Germany and 250 from Austria and Switzerland, each). The planned number of participating sites was 790. However, the study could not be conducted in Austria due to restrictions in re-imbursement of basal insulin analogs. Therefore, numbers reduced to 3,250 planned patients in about 770 sites.

Intervention Type
Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)
Insulin glargine

Primary outcome measure
HbA1c response rate during month 1-6 and month 1-12 after start of insulin glargine 300 U/mL treatment, respectively; Response being defined as achieving at least one HbA1c value below the predefined individual target value within the respective observational period. Response rates were summarized with frequency distribution and, in addition, adjusted frequency distribution considering only patients with non-missing data. Exact 95% confidence intervals (CI) according to Clopper-Pearson were calculated.

Secondary outcome measures
1. Absolute change in HbA1c from baseline to 6 to 12 months
2. Absolute change in FBG from baseline to 6 to 12 months
3. Response rate 6 and 12 months after start of insulin glargine 300 U/mL treatment defined by
3.1 reaching two FBG values ≤110 mg/dL (≤6.1 mmol/L) or at least once the predefined individual HbA1c target value
3.2 reaching two FBG values ≤110 mg/dL (≤6.1 mmol/L)
3.3 reaching two FBG values ≤110 mg/dL (≤6.1 mmol/L) and at least once the predefined individual HbA1c target value
4. Time from start of insulin glargine 300 U/mL treatment to response for each of the response endpoints (see definitions above, including primary efficacy parameter) was analyzed using Kaplan-Meier methods. Reaching a response criterion for the first time was considered as event in these analyses. Response in FBG required at least two values ≤110 mg/dL (≤6.1 mmol/L) whereas start of response was defined at the first occurrence. Patients without response were censored at the date of last measurement of FBG or HbA1c, respectively. Median time to response and corresponding 95% CI were estimated using the Kaplan-Meier method. In addition, cumulative incidence curves were
produced.
5. Duration (persistence) of response for each of the response endpoints (see definitions above, including primary efficacy parameter) was analyzed using Kaplan-Meier methods.
Only patients with documented response and valid duration time (not missing, not negative) were included in these analyses. End of response was defined as one of the following (depending on endpoint definition):
5.1 the second FBG value >110 mg/dL (>6.1 mmol/L) after start of FBG response
5.2 the first HbA1c value above the predefined individual target
5.3 change to another form of insulin therapy or change of basal insulin
Patients without documented end of response were censored at the date of last measurement of FBG or HbA1c, respectively. Median duration of response and corresponding 95% CI were estimated using the Kaplan-Meier method. In addition,
Kaplan-Meier curves were produced.
6. Incidences and event rates per patient year were calculated for symptomatic, confirmed symptomatic, nocturnal, severe, and severe nocturnal hypoglycemia as reported in the electronic Case Report Form (eCRF). Confirmation of symptomatic hypoglycemia was defined as self-measured blood glucose (SMBG) measurement ≤70 mg/dL (≤3.9 mmol/L). Severe hypoglycemia was defined as necessity of the assistance of another person or a SMBG measurement of ≤56 mg/dL (≤3.1 mmol/L). Nocturnal hypoglycemia was defined as hypoglycemia occurring during the night (approximately 10pm-6am), while the patient was asleep (symptomatic or confirmed by SMBG measurement ≤70 mg/dL [≤3.9 mmol/L]). Severe

nocturnal hypoglycemia was defined as those nocturnal hypoglycemia fulfilling the definition of a severe hypoglycemia. 95% CIs for incidence rates were calculated according to Clopper-Pearson. Rates per patient year were calculated as cumulative number of hypoglycemic events for all patients divided by the cumulative duration of insulin glargine 300 U/mL therapy in years, whereas patients with missing treatment duration or missing number of hypoglycemic events were excluded. Details for calculation are provided in the Statistical Analysis Plan (SAP).
7. Absolute change in the 4-point blood glucose profile
8. Absolute change in body weight
9. Absolute change in daily insulin doses (number of units and number of units per kg body weight [BW]) and number of dose modifications per visits
10. Values and absolute changes for blood lipids (triglycerides, high-density Lipoprotein [HDL], low-density Lipoprotein [LDL] and total cholesterol)
11. Type of LLT overall and by LDL subgroups (<70 mg/dL, <100 mg/dL, 100-190 mg/dL, >190 mg /dL at respective visit). An intensification of LLT was defined as administration of an additional LLT drug compared to baseline, or a higher dosing of statin, i.e. change from moderate at one visit to intensive at a following visit.

Overall study start date
30/10/2014

Completion date
21/12/2017

Eligibility

Key inclusion criteria
1. Patients with type 2 diabetes (oral antidiabetic drugs).
2. Adults and Seniors: Age at least 18 years, no upper age limit.
3. HbA1c between 7.5% to 10.0%.
4. Ability and willingness to perform blood glucose self-monitoring.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
3250

Total final enrolment
1748

Key exclusion criteria

1. Type 1 diabetes.
2. Contraindications for a therapy with insulin glargine 300 U/mL.
3. Any kind of existing insulin therapy.
4. Patients with known cancer disease.
5. Pregnancy.
6. Drug or alcohol abuse.
7. Dementia or general incapacity to understand the content of the observational study.

Date of first enrolment
12/06/2015

Date of final enrolment
31/12/2016

Locations

Countries of recruitment
Germany

Switzerland

Study participating centre
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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
Sanofi-Aventis Deutschland GmbH

Results and Publications

Publication and dissemination plan
Full publications planned in high-impact peer-reviewed journals:
1 full publication planned for Q3/2019.
2 full paper on sub group analyses (age groups, responder) are planned for beginning of 2020.

Intention to publish date
26/06/2019

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	conference abstract	04/05/2016		No	No
Abstract results	conference abstract	26/04/2018		No	No
Abstract results	conference abstract	01/05/2018		No	No
Results article	results	01/05/2020	02/04/2020	Yes	No
Protocol file	version 2.0	21/04/2015	27/09/2022	No	No
Results article		03/07/2020	04/07/2024	Yes	No