ISRCTN56991780 https://doi.org/10.1186/ISRCTN56991780

Efficacy and safety of using insulin glargine 300 U/mL in patients with type 2 diabetes on basal insulin and oral antidiabetic drugs failing to achieve their blood sugar targets

Submission date
03/07/2019

Recruitment status
No longer recruiting

Registration date
03/07/2019

Overall study status
Completed

Last Edited
27/09/2022

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 lifestyle changes and oral antidiabetic drugs. However, type 2 diabetes is a progressive disease and therefore, in many cases insulin treatment is also needed. An often used way to start insulin treatment in type 2 diabetes is to add one shot of basal insulin per day to the oral antidiabetic drugs used. Taking 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 achieving 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 heart disease. Several newer types of insulins have been developed which reduce the risk of hypoglycemia compared with older types of insulin. The aim of this study is to find out whether switching the basal insulin to insulin glargine 300 units per milliliter, a newer basal insulin, in people with type 2 diabetes who already use another basal insulin as add-on to oral antidiabetic drugs and who did not reach their target blood sugar levels, allows more people to achieve their blood sugar targets safely, i. e. with low risk for hypoglycaemia, in daily clinical practice.

Who can participate?
Patients aged 18 or over with type 2 diabetes who use oral antidiabetic drugs and a basal insulin other than insulin glargine 300 units per milliliter and are treated by a German, Austrian or Swiss physician.

What does the study involve?
Participants are elected by their treating physician to join this study, if the physician has already decided to switch an existing basal insulin treatment to insulin glargine 300 units per milliliter independent of the participation in this study. Participants are treated by their physician as usual and visit their doctor in the usual time intervals (in Germany, Austria and Switzerland usually every 3 months for diabetes patients). The physician documents several parameters at the first

visit, when the basal insulin is switched, 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 TOP-2 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, Austria and Switzerland, where people with type 2 diabetes are treated.

When is the study starting and how long is it expected to run for?
October 2014 to December 2017

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

Who is the main contact?
Prof. Dr Jochen Seufert, MD, chief physician of Division of Endocrinology and Diabetology, Department of Medicine II, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Hugstetter Strasse 55, D-79106 Freiburg, Germany, email: office-seufert.med@uniklinik-freiburg.de

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
GLARGL07590

Study information

Scientific Title
Initiation of insulin glargine 300 U/mL in type 2 diabetic patients after failure of pre-existing BOT treatment with any other basal insulin

Acronym
TOP-2

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 switched from a basal insulin supported oral therapy (BOT) other than insulin glargine 300 U/mL to a 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. Germany: approved 16/04/2015, Ethik-Kommission der Albert-Ludwigs-Universität Freiburg / Ethical committee of Albert Ludwig University Freiburg (Engelberger Str. 21, D-79106 Freiburg, Germany; Tel: +49 (0)761 270 72600; www.ethik-Kommission.uniklinik-freiburg.de), ref: 152/15
2. Austria: approved 17/08/2015, Ethikkommission der Stadt Wien / Ethical committee of the city of Vienna (Magistratsabteilung 15 - Gesundheitsdienst der Stadt Wien, Magistrat der Stadt Wien; Thomas-Klestil-Platz 8, 1030 Wien, Austria; Tel: +43 (0)1 4000 87754; Email: ethikkommission@ma15.wien.gv.at), ref: EK 15-187-VK
3. Switzerland: approved 19/08/2015, Ethikkommission Thurgau / Ethical committee Thurgau (Kantonale Ethikkommission, Spitalcampus 1, 8596 Münsterlingen, Switzerland; Tel: + 41 (0)71 686 22 44), ref: KEKTGOV2015/22

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 NIS; at baseline, approximately 6 and approximately 12 months after starting insulin glargine 300 U/mL therapy. Baseline documentation (documentation 1) had to start immediately after switching to insulin glargine 300 U/mL in patients with T2DM failing to achieve their glycemic targets on a pre-existing BOT treatment with any other basal insulin. This had to occur after the physician had decided independently of the participation in this study 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 (documentation 2), and the last measurements were documented approximately 12 months thereafter (documentation 3). Besides this, all 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 clinical 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 NIS. Titration algorithm was also left at the investigator's discretion. Participating physicians were distributed equally all over Germany, Austria and Switzerland to allow for a representative sample of German, Austrian and Swiss patients with T2DM switching the basal insulin component of their BOT regimen.

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 planned to document and analyze about 3,000 patients in this NIS (2,500 patients from Germany and 250 from Austria and Switzerland, each). The planned number of participating sites was 665. Participating doctors were mostly to be general practitioners, family physicians and internists (office based) in Germany and Switzerland and diabetologists/endocrinologists in Austria as the kind of physicians who usually start and follow-up basal insulin therapy in patients with T2DM. Also, diabetologists were to be included in the study. The practices were to be distributed equally all over Germany, Austria and Switzerland to allow for geographical representativeness.

Intervention Type
Other

Primary outcome measure
Fasting blood glucose (FBG) 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 two FBG values ≤ 110 mg/dL (≤ 6.1 mmol/L) within the respective observational period.

Response rates were summarized with frequency distribution and, in addition, adjusted frequency distribution considering only patients with nonmissing data. Exact 95% confidence intervals (CI) according to Clopper-Pearson were calculated.

Secondary outcome measures

Unless stated otherwise, measured at baseline, and after 6 and 12 months:
1. Absolute change in HbA1c [%]
2. Absolute change in fasting blood glucose (FBG) [mg/dL]
3. Response rate 6 and 12 months after start of insulin glargine 300 U/mL treatment defined by:
3.1. Either reaching two FBG values ≤110 mg/dL (≤6.1 mmol/L) or at least once the predefined individual HbA1c target value
3.2. Reaching at least one HbA1c value [%] equal or less to the predefined individual HbA1c target value
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 (≤6.1mmol/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 [mg/dL]
8. Absolute change in body weight [kg]
9. Absolute change in daily insulin doses (number of units per day and number of units per kg

body weight [BW] per day) and number of dose modifications per visits; baseline and monthly documentation until month 12.
10. Values and absolute changes for blood lipids [mg/dL] (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
27/12/2017

Eligibility

Key inclusion criteria
1. Patients with type 2 diabetes (basal insulin and oral antidiabetic drugs) with any basal insulin except insulin glargine 300 U/mL
2. Adults and seniors: age at least 18 years, no upper age limit
3. HbA1c between 7.5% to 10.0%
4. Fasting blood glucose > 130 mg/dL
5. 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
3000

Key exclusion criteria
1. Type 1 diabetes
2. Contraindications for therapy with insulin glargine 300 U/mL
3. Existing insulin therapy with basal and bolus Insulin (i.e. basal-bolus insulin therapy, premixed 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
Austria

Germany

Switzerland

Study participating centre
University of Freiburg
Prof. Dr. Jochen Seufert
Division of Endocrinology and Diabetology
Department of Medicine II
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Sponsor information

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Sponsor type
Industry

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https://ror.org/03ytdtb31

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 subgroup analyses (age groups, responder) are planned for the beginning of 2020

Intention to publish date
01/04/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available on reasonable request from Katrin Pegelow (Katrin.Pegelow@sanofi.com) and Cornelia Dorn (Cornelia.Dorn@sanofi.com).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	conference abstract	01/04/2016		No	No
Abstract results	conference abstract	26/04/2018		No	No
Abstract results	conference abstract	01/05/2018		No	No
Results article		01/12/2018	19/04/2021	Yes	No
Results article		13/09/2021	09/08/2022	Yes	No
Protocol file	version 2.0	21/04/2015	27/09/2022	No	No