
Article:
Novodvorský, P. orcid.org/0000-0002-3292-7586, Thieme, L., Laňková, I. et al. (8 more authors) (2024) The IDEAL (Insulin therapy DE-intensificAtion with iglarLixi) randomised controlled trial—study design and protocol. Diabetes Therapy, 15 (6). pp. 1461-1471. ISSN 1869-6953

https://doi.org/10.1007/s13300-024-01582-x

Diabetes Ther (2024) 15:1461–1471
https://doi.org/10.1007/s13300-024-01582-x

STUDY PROTOCOL

The IDEAL (Insulin therapy DE-intensificAtion with iglarLixi) Randomised Controlled Trial—Study Design and Protocol

Peter Novodvorský · Lenka Thieme · Ivana Laňková · Miloš Mráz · Zoltán J. Taybani · Balázs Bótyik · Péter Stella · Miroslav Vytasil · Felipe Lauand · Mireille Bonnemaire · Martin Haluzík

Received: March 8, 2024 / Accepted: April 2, 2024 / Published online: April 24, 2024

ABSTRACT

Introduction: Multiple daily injection insulin regimen (MDI) represents the most intensive insulin regimen used in the management of people with type 2 diabetes (PwT2D). Its efficacy regarding glycaemic control is counterbalanced by the increased risk of hypoglycaemia, frequently observed tendency to weight gain and necessity for frequent glucose monitoring. Recent introduction of novel antidiabetic medications with pleiotropic effects reaching far beyond the reduction of glycaemia (HbA1c), such as the glucagon-like peptide 1 receptor agonist (GLP-1 RA), has significantly widened the therapeutic options available for management of T2D. Consequently, there is currently a substantial number of PwT2D for whom the MDI regimen was initiated at a time when no other options were available. Yet, in present times, these individuals could benefit from simplified insulin regimens ideally taking advantage of the beneficial effects of the novel classes of antidiabetic medications. iGlarLixi (Suliqua®) is a once-daily fixed-ratio combination of basal insulin analogue glargine 100 U/ml and a GLP-1 RA lixisenatide.

Methods: Insulin therapy DE-intensificAtion with iglarLixi (IDEAL) is a six-centre, open-label, parallel-group, active comparator, phase IV randomised controlled trial with a 24-week active treatment period examining the efficacy and safety of MDI regimen de-intensification with once-daily administration of iGlarLixi versus MDI regimen continuation in PwT2D on a backgroud therapy with metformin ± sodium-glucose cotransporter 2 inhibitor.

Planned Outcomes: The primary objective is to compare the effects of MDI therapy de-intensification with iGlarLixi versus MDI regimen continuation regarding glycaemic control (HbA1c). Secondary objectives include detailed evaluation

P. Novodvorský · L. Thieme · I. Laňková · M. Mráz · M. Haluzík (✉)
Diabetes Centre, Institute for Clinical and Experimental Medicine (IKE M), Vídeňská 1958, 140 21 Prague 4, Czech Republic
e-mail: halm@ikem.cz

P. Novodvorský
Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

M. Mráz · M. Haluzík
First Faculty of Medicine, Charles University, Prague, Czech Republic

Z. J. Taybani · B. Bótyik
First Department of Endocrinology, Dr. Réthy Pál Member Hospital, Békes County Central Hospital, Békéscsaba, Hungary

P. Stella
Sanofi Hungary, Budapest, Hungary

M. Vytasil
Sanofi, Prague, Czech Republic

F. Lauand · M. Bonnemaire
General Medicines, Sanofi, Paris, France

of the effects of MDI regimen de-intensification with iGlarLixi on glycaemic control using standardised continuous glucose monitoring (CGM) metrics and self-monitoring of plasma glucose. Furthermore, body weight and body composition analysis, quality of life and safety profile are evaluated.
Trial Registration: ClinicalTrials.gov, identifier NCT04945070.

Keywords: Complex insulin therapy simplification; Fixed-ratio combination of GLP-1 receptor agonist and basal insulin (FRC); Insulin therapy de-intensification; Insulin glargine/lixisenatide (iGlarLixi); Intensified insulin therapy (IIT); Multiple daily injections insulin regimen (MDI); Type 2 diabetes (T2D)

Key Summary Points

Multiple daily injection insulin regimen (MDI) represents the most intensive insulin regimen used in the management of people with type 2 diabetes (PwT2D), and many individuals were started on it at a time when no other treatment options were available
MDI regimen is very efficient regarding glycaemic control but is linked with increased risk of hypoglycaemia and a frequently observed tendency to weight gain, and it requires frequent glucose monitoring and insulin dose adaptations
iGlarLixi (Suliqua®) is a once-daily fixed-ratio combination of basal insulin analogue glargine 100 U/ml and a glucagon-like peptide 1 receptor agonist (GLP-1 RA) lixisenatide
Insulin therapy de-intensification with iGlarLixi (IDEAL) is the first randomised controlled trial comparing the efficacy and safety of MDI regimen simplification with once-daily administered iGlarLixi versus MDI regimen continuation in PwT2D on a backgroud therapy with metformin ± sodium–glucose cotransporter 2 inhibitor
Results from IDEAL trial are expected to provide the evidence base regarding the efficacy and safety of MDI regimen simplification with the ultimate benefit to the PwT2D currently treated with complex insulin regimens

INTRODUCTION

Multiple daily injection insulin regimen (MDI), also referred to as intensive insulin therapy (IIT), represents the most complex type of insulin regimen used in the management of people with type 2 diabetes (PwT2D). Correspondingly, MDI regimen has been the last intensification step in the therapeutic guidelines for management of hyperglycaemia in T2D after non-pharmacological interventions, use of oral antidiabetic medication(s) and basal or premixed insulins [1–5]. The major advantage of all insulin-based therapies is their rapid and dose-dependent glucose-lowering effect. This is counterbalanced by the increased risk of hypoglycaemia, a frequently observed tendency to weight gain and the necessity for frequent glucose monitoring and possible insulin dose adaptations by patients negatively affecting their compliance with therapy and quality of life. These unwanted side effects of insulin therapy become more prominent with the increased complexity of insulin regimens and increased number of injections per day.

The introduction of novel antidiabetic medications with pleiotropic effects reaching far beyond the reduction of glycaemia (HbA1c) such as glucagon-like peptide 1 receptor agonists (GLP-1 RA) or sodium–glucose cotransporter 2 inhibitors (SGLT2i) meant that insulin-based therapies were moved further down the treatment algorithms in the most relevant clinical guidelines for T2D management [1–5]. Fixed-ratio combinations of basal insulin analogues and GLP-1 RA (FRC) benefit from complementary mechanisms of action of their two components that cumulatively address seven of the eight pathophysiological processes of the DeFronzo's ominous octet [6]. Basal insulins provide control of fasting glucose, while GLP-1 RAs influence both fasting and postprandial

glycaemia and reduce food intake and glycaemia by stimulation of glucose-dependent insulin secretion, suppression of glucagon secretion, delay in gastric emptying and suppression of appetite [7]. Consequently, the glucose-lowering effect of FRCs is complemented by comparable or lower risk of hypoglycaemia compared to basal insulin therapy, neutral effect on body weight and a lower risk of gastrointestinal adverse effects compared to GLP-1-RA when used alone [8]. Because of these favourable developments, we are currently seeing a significant pool of PwT2D in whom the MDI regimen was initiated at a time when no other options were available. Yet, currently, these individuals could benefit from simplified insulin regimens ideally taking advantage of the beneficial effects of the novel classes of antidiabetic medications.

iGlarLixi (Sanofi, Paris, France) is a FRC of basal insulin analogue glargine 100 U/ml (iGlar) and a GLP-1 RA lixisenatide in a concentration of 50 mcg/ml (pen A) or 33 mcg/ml (pen B) of lixisenatide (Lixi) in a 3-ml prefilled injection pen. iGlarLixi is marketed in Europe with a brand name Suliqua® 100/50 (pen A) and Suliqua® 100/33 (pen B) [9]. iGlar is a long-acting basal insulin analogue which has a half-life of approximately 13 h, and it predominantly addresses fasting blood glucose levels [10]. Lixi is a once-daily exendin-4-based GLP-1 RA analogue based on exendin-4 which has a half-life of approximately 3–4 h with a predominant effect on postprandial glucose levels [7]. The efficacy and safety of iGlarLixi have been established in various clinical scenarios by several phase 2b/3 trials [11–15]. The other available FRC on the market, iDegLira (Xultophy®, NovoNordisk A/S, Bagsværd, Denmark), contains basal insulin degludec and the GLP-1 RA analogue liraglutide [16].

The efficacy and safety of insulin therapy de-intensification from MDI regimen into once-daily administration of iDegLira in PwT2D has been examined in prospective, non-randomised, observational studies from Hungary and Slovakia [17–19]. A pragmatic RCT from Italy assessed the feasibility of MDI insulin regimen de-intensification by its replacement with either the FRCs or a combination of basal insulin plus SGLT2i and also reported favourable outcomes [20]. The results of these trials are in line with our own clinical experience and the clinical experience of other clinicians. Yet, a formal assessment of insulin therapy de-intensification in PwT2D in a form of a standard RCT has not been done up so far. The completion of such an RCT is required to acquire data that will support the clinical practice of insulin therapy de-intensification with FRCs with the necessary evidence base. The IDEAL trial is the first RCT formally assessing the efficacy and safety of intensive insulin therapy simplification (de-intensification) with once-daily administered FRC iGlarLixi in PwT2D. For this purpose, continuous glucose monitoring (CGM) metrics reflecting the current international consensus statements on CGM data reporting [21, 22] will be employed in addition to changes in HbA1c levels.

METHODS

Study Design

Insulin therapy de-intensification with iGlarLixi (IDEAL) is a six-centre, open-label, parallel-group, active comparator, phase IV randomised controlled trial. This study has been registered on US National Library of Medicine ClinicalTrials.gov database (NCT04945070).

Study Population

Approximately 100 individuals will be recruited following the provision of signed informed consent. The main inclusion and exclusion criteria are listed in Table 1. Prior to enrollment, the protocol was reviewed and approved by the Joint Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital in Prague, Czechia, and this approval is valid for all study sites. This study is conducted in accordance with the Helsinki Declaration of 1964 and its later amendments and the ICH Good Clinical Practice Guidelines.

Table 1 Main inclusion and exclusion criteria

Inclusion criteria
Age 18–80 years
Type 2 diabetes
Treatment with MDI regimen ≥ 3 months prior to screening visit
Treatment with metformin (unless not tolerated) ± SGT2i on stable doses ≥ 3 months prior to screening visit
Total daily dose of insulin ≤ 0.8 IU/kg of body weight
Fasting c-peptide levels above the lower limit of normal range
HbA1c ≤ 75 mmol/mol (9%) or 76–86 mmol/mol (9.1–10%) (measured by local laboratory) in case of non-compliance with MDI regimen
Exclusion criteria
Other types of diabetes apart from type 2 diabetes
Use of any oral or injectable glucose-lowering agents other than those stated in the inclusion criteria within the last 3 months before screening visit
Systemic glucocorticoid use for a total duration of ≥ 1 week within 3 months before the screening visit
Medical conditions in which systemic glucocorticoid use can be expected throughout the course of the trial
History of stroke, pulmonary embolism, myocardial infarction, unstable angina or heart failure requiring hospitalisation within the last 3 months before the screening visit
Chronic heart failure (NYHA stages III–IV)
Chronic liver disease
Active malignancy
Anaemia (haemoglobin < 100 g/l) at screening visit
Clinically significant diabetic retinopathy or macular oedema likely to require treatment within the study period
History of prior GLP-1 RA discontinuation for safety/tolerability reasons or lack of efficacy
Chronic kidney disease stage IV or V (egfr < 30 ml/min/1.73 m^2)
Gastroparesis
Pregnancy or lactation
Personal or family history of medullary thyroid cancer or a condition predisposing to it
History of pancreatitis (with the exception of pancreatitis related to gallstones followed by cholecystectomy)
Inability to comply with study procedures

eGFR estimated glomerular filtration rate; *GLP-1 RA* glucagon-like peptide 1 receptor agonist; *MDI* multiple dose injections; *NYHA* New York Heart Association; *SGLT2i* sodium-glucose cotransporter 2 inhibitor

Study Design, Randomisation and Study Interventions

Participants in this trial will be followed up for approximately 40 weeks. This includes an up to 4-week screening period, randomisation followed by a 24-week (6 months) open-label treatment period and a 12-week follow-up period. The protocol includes six on-site visits (V1–V6) and ten mandatory phone call visits (P1–P10) at pre-specified time points. Figure 1 shows the study flow chart with the timings and interventions performed at each visit.

At screening visit (V0), following the provision of written informed consent, medical history and drug history will be taken and physical examination performed. Anthropometric data will be recorded including the body composition analysis (InBody 570®, InBodyUSA, Cerritos, CA, USA). Venous blood will be taken to analyse the study-specific, safety and exploratory endpoints (see Fig. 1 and text below for further details).

At the end of the screening period, eligible participants will be randomised in a 1:1 ratio to either undergo re-education and continue with the MDI regimen or to discontinue the MDI regimen and start iGlarLixi together with lifestyle and treatment-specific education. iGlarLixi is considered an investigational medicinal product (IMP). For participants randomised to remain on MDI regimen, insulin preparations are considered to be IMPs and will be provided by the investigators during the study treatment period.

Self-monitoring of Blood Glucose (SMBG)

All participants will be provided blood glucose meters (FreeStyle Freedom Lite, Abbott Diabetes Care, Alameda, CA, USA) for the duration of the trial. During the 24-week treatment period, all participants will perform daily fasting SMBG measurements, a 4-point SMBG profile (before 3 main meals of the day and at bedtime) before each P visit and a 7-point SMBG profile (before and 120 min after the 3 main meals of the day and at bedtime) before visits V2, V3 and V5. Regular blood glucose meter downloads will take place during on-site visits. SMBG data will be used for iGlarLixi dose titration to achieve target fasting glycaemia and for insulin dose modification in the MDI arm according to investigators' clinical judgement.

Administration of iGlarLixi

For participants randomised into the iGlarLixi arm, the total basal insulin dose (in case of insulin analogues) or 50% of the previous total daily dose of insulin (TDD) (in case of human insulins) on the day before V2 will be used for the iGlarLixi starting dose calculation and pen type assignment as indicated in Table 2. Participants will be asked not to administer the morning dose of basal insulin on the day of V2 visit or halve their evening dose of basal insulin on the evening before V2 visit depending on the time of their usual basal insulin administration. Any prandial insulin dose of ≤ 8 units will be completely stopped on the day of first iGlarLixi dose administration. Prandial insulin dose exceeding eight units at any main meal will be halved at the time of iGlarLixi initiation and then discontinued within the following 2 weeks in a fashion which is left to the discretion of the investigator. iGlarLixi will be administered once daily within 1 h (ideally 30–45 min) before breakfast. No change in metformin ± SGLT2i dosage is allowed during the 24-week treatment period.

iGlarLixi Dose Titration

iGlarLixi will be up-titrated every 3 days by two dose steps (DS) containing two units of glargine 100 U/ml and 1.0 µg (pen A) or 0.66 µg (pen B) of lixisenatide with the aim of achieving self-monitored morning fasting glucose (the mean of fasting glucose values from the preceding 3 days is considered) ≤ 6 mmol/l or until reaching 60 units of glargine 100 U/ml and 20 µg of lixisenatide. Dose adjustments to avoid hypoglycaemia are allowed at any time at the discretion of the investigator.

Study period	Screening period			Treatment period												Follow-up
VISIT	V0	V1	V2	P1	P2	P3	P4	P5	P6	P7	V3	P8	P9	P10	V4	V5	V6
	↑	↑	↑	☎	☎	☎	☎	☎	☎	☎	↑	☎	☎	↑	↑	↑	↑
WEEK	-4	-2	0	0	1	2	3	5	8	10	13	15	18	22	23	24	36
DAY (at least 3 days apart)	-28±3	-14±3	0±3	3±1	7±2	14±2	21±5	30±5	50±7	70±7	90±7	110±7	130±7	150±7	161±3	168±3	252+7
Informed Consent	x																
Inclusion/Exclusion Criteria	x																
Medical history (incl. surgical, diabetes, cardiovascular & allergy history, medication history, alcohol & smoking habits, demography)	x																
Physical Examination	x															x	
Height	x																
Body weight and Vital signs	x										x					x	x
Body composition analysis	x															x	
Randomisation			x														
Dispense/collect study diary + BG meter		x														x	
DTSQs			x													x	
ADDQoL			x													x	
HABS			x													x	
DTSQc																x	
Dispense/collect IMP			x								x					x	
IMP compliance check; collecting and counting used and unused pens											x					x	
iGlarLixi dose adjustment				x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispensation/ Placement CGM of blinded device		x													x		
Collect CGM device and upload data			x													x	
SMBG																	
Fasting SMBG daily			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
4-point SMBG profile from previous day				x	x	x	x	x	x	x		x	x	x	x		
7-point SMBG profile from previous day			x								x					x	
BG meter download											x					x	
Laboratory testing																	
HbA_{1c}	x										x					x	x
Fasting Plasma Glucose	x										x					x	x
C-peptide	x																
Safety laboratory																	
Pregnancy testing (WOCBP only)	x																
Hematology, Clinical Chemistry	x										x					x	
Exploratory endpoints	x																
AE/SAE/Hypoglycemia	To be assessed and reported (if any) throughout the study																
Injection site reactions, hypersensitivity reactions	To be assessed and reported (if any) throughout the study																

Fig. 1 Study flow chart. *ADDQoL* Audit of Diabetes Dependent Quality of Life Questionnaire; *DTSQc* Diabetes Treatment Satisfaction Questionnaire change; *DTSQs* Diabetes Treatment Satisfaction Questionnaire static; *HABS* Hypoglycemia Attitudes and Behavior Scale; *IMP* investigational medicinal product; *P* phone call study visits; *SMBG* self-monitoring of blood glucose; *V* on-site study visits; *WOCBP* women of childbearing potential

Table 2 Starting dose of iGlarLixi (Suliqua®)

Previous daily basal insulin dose*		≥ 10 to < 20 units/day	≥ 20 to < 30 units/day	≥ 30 to ≤ 50 units/day
Initial suliqua dose	Suliqua 100/50 (pen A)	≥ 10 to < 20 dose steps/day	20 dose steps/day	
	Suliqua 100/33 (pen B)			30 dose steps/day

*Recommendation for basal insulin once-daily except glargine 300 U/ml (Toujeo®). For participants receiving Toujeo®, reduce the dose by 20% and then choose a starting dose according to the table

Rescue Therapy

For participants in the iGlarLixi arm, MDI regimen should be re-initiated in case of repeatedly detected fasting hyperglycaemia > 14 mmol/l on 3 consecutive days not reacting to iGlarLixi up-titration which is subsequently confirmed by a laboratory fasting blood glucose (FBG) measurement or in case of repeatedly detected hyperglycaemia > 17 mmol/l at any time on 3 consecutive days not reacting to iGlarLixi up-titration. Short-term (up to 10 days) uses of rapid-acting insulin therapy (for example due to acute illness or surgery) will not be considered rescue therapy.

Multiple Daily Injection (MDI) Arm

Participants who have been performing self-titration of their insulin doses are allowed to perform regular insulin dose adjustments throughout the duration of the study. Insulin dose adjustments by IDEAL investigators will only be conducted during on-site visits according to clinical practice of the site. No change in metformin ± SGLT2i dosage is allowed during the 24-week treatment period.

Continuous Glucose Monitoring (CGM)

Two periods of blinded CGM monitoring (Freestyle Libre Pro iQ®, Abbott Diabetes Care, Alameda, CA, USA) will be performed during the course of the study, namely during the screening period (CGM started at V1 visit) and at the end of the 24-week treatment period (CGM started at V4 visit). Participants and investigators will be able to assess and discuss CGM read-outs at the end of each CGM period at V2 and V5 visit, respectively. No personal CGM/FGM devices can be used during the time when the study-specific CGM takes place. Participants should not initiate CGM/FGM monitoring during the course of the study but can use their previously introduced CGM/FGM devices outside the study-specific CGM periods.

Patient-Reported Outcomes

Participants will be administered a set of questionnaires during the course of the trial, namely the Diabetes Treatment Satisfaction Questionnaire static (DTSQs) and Diabetes Treatment Satisfaction Questionnaire change (DTSQc), Hypoglycemia Attitudes and Behavior Scale (HABS), and the Audit of Diabetes Dependent Quality of life (ADDQoL) questionnaire to assess multiple patient-reported outcomes. The authors have purchased the licence to use the DTSQs, DTSQc and ADDQoL questionnaires in this trial from the Health Pscyhology Research Ltd. (HPR).

Exploratory Outcomes

As a part of the study protocol parameters related to low-grade inflammation, hepatic steatosis and adipose tissue metabolism will be assessed including selected cytokines and chemokines and their receptors, adipokines, hepatokines, fibroblast growth factors and others.

PLANNED OUTCOMES

Study Objectives

The primary objective of the IDEAL trial is to compare the effects of MDI therapy simplification (de-intensification) with iGlarLixi versus MDI regimen continuation in relation to glycaemic control (HbA1c) in individuals with T2D. Secondary objectives include evaluation of such insulin therapy simplification on the following aspects of diabetes care: CGM-related outcomes, data from self-monitoring of plasma glucose (fasting and post-prandial glycaemia), body weight and composition, treatment burden, quality of life, and safety profile.

Endpoints

The primary endpoint is the mean change in HbA1c from baseline to 24 weeks (6 months) after randomisation. Secondary endpoints include: mean change in percentage of time spent in the following glycaemic ranges: time in range (TIR) (3.9–10.0 mmol/l, respectively, 70–180 mg/dl), time above range (TAR) (> 10.0 mmol/l, respectively, > 180 mg/dl), time below range (TBR) (< 3.9 mmol/l, respectively, < 70 mg/dl), level 1 hyperglycaemia (> 10.0–13.9 mmol/l, respectively, > 180–250 mg/dl), level 2 hyperglycaemia (> 13.9 mmol/l, respectively, > 250 mg/dl), level 1 hypoglycaemia (3.9–3.0 mmol/l, respectively, 70–54 mg/dl) and level 2 hypoglycaemia (< 3.0 mmol/l, respectively, < 54 mg/dl), mean change in sensor glucose and glycaemic variability expressed as coefficient of variation (%CV), mean change in FPG, mean change in PPG (calculated as the mean of the three 2-h post-prandial glucose levels between baseline and end of treatment period) and mean change in anthropometric characteristics (body weight, BMI, waist circumference and body composition analysis). All listed endpoints are comparisons of the change (baseline vs. end of the treatment period) between the two arms of the trial unless stated otherwise. Safety endpoints include proportion of participants who experienced at least one (self-reported) hypoglycaemic episode and proportion of participants who experienced at least one level 3 (severe) hypoglycaemia requiring external assistance from baseline to end of treatment period, hypoglycaemia event rate (expressed as number of episodes per participant-year) from baseline to end of treatment period, and number of participants with adverse events (AE) and serious adverse events (SAE) from baseline to end of treatment period. Exploratory endpoints include measurements of factors related to low-grade inflammation, hepatic steatosis and adipose tissue metabolism (e.g. cytokines and chemokines and their receptors, adipokines and hepatokines, fibroblast growth factors and others).

STATISTICAL CONSIDERATIONS

Sample Size

One hundred participants (50 per arm) will be included. We expect an approximately 10% drop-out rate with the number of analysed participants being approximately 90 (45 in each arm). The expected standard deviation (SD) for the 6-month change from baseline in HbA_{1C} is 0.9% based on the Lixilan-L trial results [13]. Given these parameters, the treatment effect, expressed as the least square (LS) mean difference between arms, will be estimated with an expected precision of ± 0.372%.

Statistical Analysis

The full analysis set (FAS) will include all patients who have received at least one dose of the IMP and had at least one post-baseline assessment of any efficacy variables, regardless of their compliance with the study protocol and procedures. The primary outcome of mean change in HbA1c from baseline to end of treatment period and other continuous variables will be evaluated using the mean difference between treatment groups and a 95% confidence interval (CI). For variables that are not normally distributed, a median difference between groups and a bootstrapped 95% CI will be used. Proportional variables will be reported as an odds ratio with a 95% CI.

Descriptive summary statistics, including the number, mean and SD, will be computed for each treatment group. For non-normally distributed variables, medians and the first and third quartile will be used. To compare the differences between groups, two-sample *t*-tests will be used for normally distributed data, Mann-Whitney *U* tests for non-normal data and Fisher's exact test for proportional data. Hypothesis tests will be two sided, when possible, and will use a significance level of 0.05. The Holm method will be used to control for type I errors for multiple testing. Statistical analysis will be performed with the R statistical software.

STRENGTHS AND LIMITATIONS

The main strength of the IDEAL trial is the employment of a standard RCT design to test the efficacy and safety of intensive insulin therapy simplification with once-daily iGlarLixi in PwT2D. Its further strengths include the robustness of the protocol, close safety follow-up and use of CGM technology, which will allow for complex assessment of overall glycaemic control. The limitations of this trial include its open-label design which is, given the type of investigational drugs, unavoidable. Furthermore, this is a five-centre trial from a single European country (Czech Republic) and, due to its demographic characteristics, it is likely to include mostly participants of European descent. A multi-centre international trial with inclusion of participants from different racial backgrounds would have provided data from a more diverse population and would have been more generalizable. Despite these limitations, we believe that the results of this RCT will provide a solid evidence base for an effective and safe clinical practice of the MDI regimen de-intensification with iGlarLixi in PwT2D.

CONCLUSION

The IDEAL trial is the first RCT formally assessing the efficacy and safety of intensive insulin therapy simplification (de-intensification) with once-daily administered FRC iGlarLixi in PwT2D treated with MDI regimen. The results of this trial are likely to complement the already existing data from prospective observational studies regarding such therapy simplification with the ultimate aim of benefitting the individuals with T2D.

Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Peter Novodvorsky, Lenka Thieme, Ivana Lankova, Milos Mraz, Zoltan J. Taybani, Balazs Botyik, Peter Stella, Miroslav Vytasil, Felipe Lauand, Mireille Bonnemaire, and Martin Haluzikparticipated in the writing, reviewing and editing of the manuscript and had final responsibility for approving the published version. The authors declare no medical writing/ editorial assistance during the write-up and submission of this manuscript.

Funding. This is an investigator-initiated study which is supported by Sanofi. The Rapid Service Fee was funded by the authors.

Declarations

Conflict of Interest. Peter Novodvorsky has served on speaker panels for Novo Nordisk, Eli Lilly, Sanofi, Boehringer-Ingelheim, Mundipharma, Krka, Viatris, Novartis, Abbott and Medtronic; on advisory panels for Sanofi and Boehringer-Ingelheim; received honoraria or consulting fees from Merck and Eli Lilly; and received travel grants from Sanofi, Novo Nordisk, Berlin Chemie, Boehringer-Ingelheim and Eli Lilly. Zoltán J. Taybani received honoraria for speaking at meetings from Novo Nordisk, Sanofi, Eli Lilly, AstraZeneca, Boehringer Ingelheim and Novartis, Balázs Bótyik received honoraria for speaking at meetings from Novo Nordisk, Sanofi, Eli Lilly, AstraZeneca, Boehringer Ingelheim and Novartis, Martin Haluzik has served on advisory panel for Eli Lilly, Novo Nordisk, Sanofi, AstraZeneca, Mundipharma; and has served as

a consultant for Eli Lilly, Novo Nordisk, Sanofi, Astra Zeneca, Mundipharma; and has received research support for AstraZeneca, Eli Lilly, Bristol-Meyers Squibb; and has received honoraria or consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Johnson. Felipe Lauand, Mireille Bonnemaire and Miroslav Vytasil are employees and shareholders of Sanofi. All other authors of this work have no relevant conflict of interest to disclose.

Ethical Approval. Prior to enrollment, the protocol was reviewed and approved by the Joint Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital in Prague, Czech Republic, and this approval is valid for all study sites. This study will be conducted in accordance with the Helsinki Declaration of 1964 and its later amendments and the ICH Good Clinical Practice Guidelines. All participants will be asked to provide written informed consent to participate in the study.

REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55(6):1577–96.
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58(3):429–42.
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669–701.
4. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487–93.
5. Davies MJ, Aroda VR, Collins BS et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753–86.
6. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–95.
7. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8(12):728–42.
8. Novodvorsky P, Haluzik M. An update on the safety of insulin-GLP-1 receptor agonist combinations in type 2 diabetes mellitus. Expert Opin Drug Saf. 2021. https://doi.org/10.1080/14740338.2021.1978974.
9. Sanofi. Suliqua summary of product characteristics 2020. Available from: https://www.medicines.org.uk/emc/product/9871/smpc. Accessed 28 Feb 2024.
10. Hilgenfeld R, Seipke G, Berchtold H, Owens DR. The evolution of insulin glargine and its continuing contribution to diabetes care. Drugs. 2014;74(8):911–27.
11. Rosenstock J, Diamant M, Aroda VR, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy:

the LixiLan proof-of-concept randomized trial. Diabetes Care. 2016;39(9):1579–86.

12. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016;39(11):2026–35.

13. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. Diabetes Care. 2016;39(11):1972–80.

14. Blonde L, Rosenstock J, Del Prato S, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: the LixiLan-G randomized clinical trial. Diabetes Care. 2019;42(11):2108–16.

15. McCrimmon RJ, Al Sifri S, Emral R, et al. Advancing therapy with iGlarLixi versus premix BIAsp 30 in basal insulin-treated type 2 diabetes: design and baseline characteristics of the SoliMix randomized controlled trial. Diabetes Obes Metab. 2021;23(6):1221–31.

16. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2(11):885–93.

17. Taybani Z, Botyik B, Katko M, Gyimesi A, Varkonyi T. Simplifying complex insulin regimens while preserving good glycemic control in type 2 diabetes. Diabetes Ther. 2019;10(5):1869–78.

18. Taybani ZJ, Botyik B, Gyimesi A, Katko M, Varkonyi T. One-year safety and efficacy results of insulin treatment simplification with IDegLira in type 2 diabetes. Endocrinol Diabetes Metab. 2023;6(1):e390.

19. Martinka E, Dravecka I, Tkac I. Switching from multiple insulin injections to a fixed combination of degludec and liraglutide in patients with type 2 diabetes mellitus: results from the simplify study after 6 months. Diabetes Ther. 2023;14(9):1503–15.

20. Giugliano D, Longo M, Caruso P, et al. Feasibility of simplification from a basal-bolus insulin regimen to a fixed-ratio formulation of basal insulin plus a GLP-1RA or to basal insulin plus an SGLT2 inhibitor: BEYOND, a randomized. Pragmatic Trial Diabetes Care. 2021;44(6):1353–60.

21. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–603.

22. Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol. 2023;11(1):42–57.