CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208583Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208583
Link to EDR	\\CDSESUB1\evsprod\NDA208583\0000
Submission Date(s)	September 15, 2015
Submission Type	505(b)
Brand Name	XULTOPHY®
Generic Name	Insulin degludec and liraglutide [rDNA origin] injection
Dosage Form and Strength	Pre-filled disposable pen-injector (3 mL solution cartridge assembled in pen-injector; 300 units insulin degludec and 10.8 mg liraglutide)
Route of Administration	Subcutaneous injection
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant	Novo Nordisk
Associated INDs	109121 (Insulin Degludec/Liraglutide), 76496 (Insulin Degludec), 61040 (Liraglutide)
OCP Review Team	Sang M. Chung, Ph.D., Manoj Khurana, Ph.D., Nitin Mehrotra, Ph.D.

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Note to readers: Throughout this review, treatments are designated as follows:

- "IDeg + Lira", "IDeg+liraglutide", and "insulin degludec+liraglutide: used interchangeably to represent any dosage of the free combination therapy with insulin degludec and liraglutide
- "IDegLira", "IDeg/Lira," and "insulin degludec/liraglutide": only used for the fixed-ratio combination formulation

1 Executive Summary

The applicant has submitted NDA 208583 for XULTOPHY®, the fixed-ratio combination (FRC) of insulin degludec (IDeg) and liraglutide (Lira), as a 505(b)(1) application. The proposed indication for XULTOPHY is an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus (T2DM). XULTOPHY® is the first ever anti-diabetic FRC product that combines two subcutaneously injectable drugs IDeg and Lira in one formulation.

IDeg, a basal insulin, has been approved for both Type 1 diabetes mellitus (T1DM) and T2DM (TRESIBA®, NDA 203314), and Lira, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has been approved for T2DM (VICTOZA®, NDA 022341). The applicant refers pertinent labeling information of TRESIBA® and VICTOZA® in addition to results with XULTOPHY® as the sponsor owns both NDAs for each active ingredients.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed NDA 208583 for XULTOPHY® and found the clinical pharmacology information acceptable to support approval

1.2 Post-Market Requirements and Commitments

None

2 Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Clinical pharmacology information was assessed using results from 3 Phase 1 trials in healthy volunteers, and 5 Phase 3 trials following XULTOPHY® in T2DM. In addition, co-administration of liraglutide as add on to basal insulin was evaluated in the original NDA for Lira.

The pen-injector is the final presentation (Figure 1) and provides up to 50 dose steps in one injection where, 1 dose step contains 1 unit of IDeg and 0.036 mg of Lira (Figure 2).

Figure 1 Photographs of pen-injector for XULTOPHY®

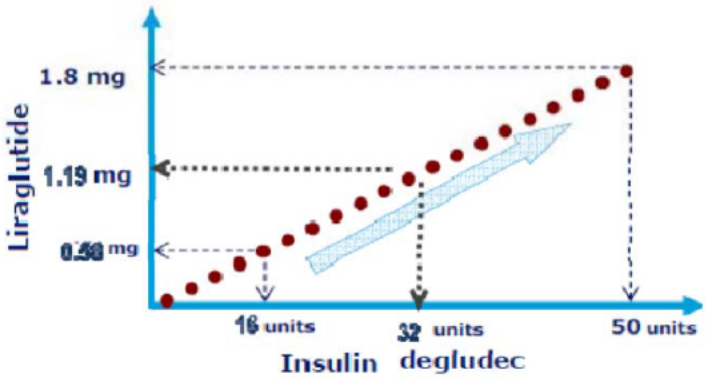
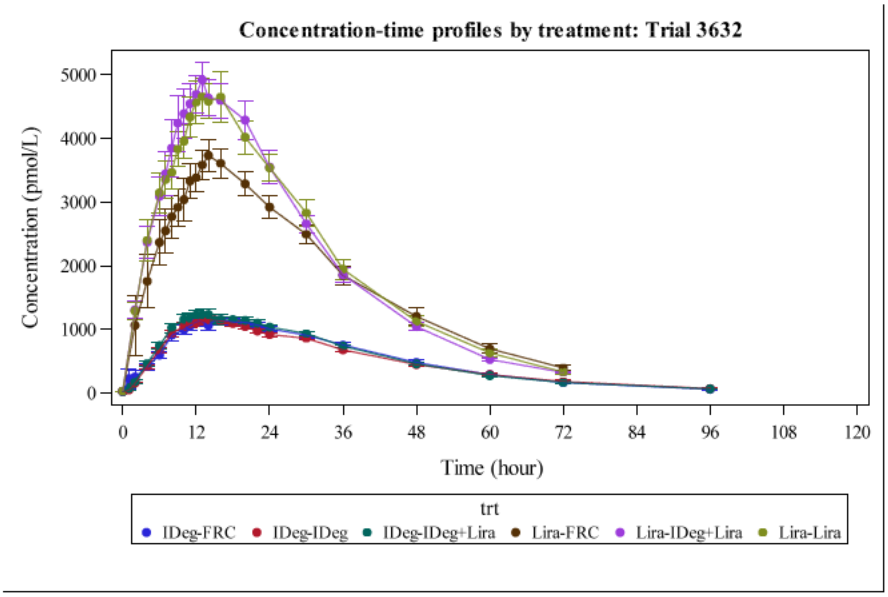


Figure 2 Schematic summary of doses of IDeg and Lira in the proposed FRC product (Source: FDA Briefing Document, Advisory Committee Meeting, May 24, 2016)

Insulin Degludec and Liraglutide Pharmacokinetics

The applicant evaluated pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of IDeg and Lira after the FRC administration compared to those after administration of IDeg alone, Lira alone or co-administration of IDeg and Lira under euglycemic clamp procedure in healthy volunteers.

IDeg exposure following FRC was not significantly different from that of IDeg alone (Figure 3). Lira maximum concentration (Cmax) following FRC was 23% lower without significant change in overall exposure (measured by area under the concentration-time curve; AUC) when compared to those of Lira alone (Figure 3).



- IDeg-FRC=insulin degludec following FRC, IDeg-IDeg+Lira=insulin degludec following co-administration of insulin degludec and liraglutide, IDeg-IDeg=insulin degludec following insulin degludec
- Lira-FRC=liraglutide following FRC, Lira-IDeg+Lira=liraglutide following co-administration of insulin degludec and liraglutide, Lira-Lira=liraglutide following liraglutide

Figure 3 IDeg or Lira concentration-time profiles following single doses in healthy subjects

Further, according to the population analyses using plasma concentration data from Phase 3 study, exposure of both IDeg and Lira was proportional to clinically relevant FRC doses, and there was no unique covariate for IDeg or Lira exposure after FRC other than body weight, which is already a known covariate affectingPK (and PD) of individual drugs (Refer to Clinical Pharmacology reviews of VICTOZA® and TRESIBA®).

Insulin Degludec and Liraglutide Pharmacodynamics

Applicant used the glucose infusion rate (GIR) data from euglycemic clamp to characterize the PD effect of IDeg alone, Lira alone and IDeg plus Lira combination treatments. While the interpretation of the GIR from the euglycemic clamp for exogenous insulin is straightforward, the interpretation of GIR data is challenging for the Lira administered alone or IDeg + Lira as part of the FRC (Figure 4), specifically in the subjects capable of secreting endogenous insulin (healthy or T2DM). The primary challenge is posed by the capability of Lira to facilitate endogenous insulin secretion in a glucose dependent manner, which could be triggered by the infused glucose under clamp experimental setting. Nevertheless, from a clinical pharmacology perspective C-peptide / endogenous insulin concentration data provide useful insight into the interference from exogenous insulin in PD effect of Lira, or in other words, whether IDeg and Lira exert their pharmacodynamic effects, in somewhat independent manner. PD data indicate that there is mutual interplay between IDeg and Lira PD effects following administration of FRC as follows:

- Insulin secretion was measured using C-peptide concentrations following a single dose of FRC or each drug given alone in healthy subjects under euglycemic clamp procedure. The C-peptide levels decreased from the baseline following insulin degludec administration. Typically the objective of clamp experiments is to measure the exogenous insulin effect by keeping the euglycemic target lower than normoglycemia to avoid triggering the endogenous insulin secretion. However, for Lira alone and FRC treatments, the C-peptide was increased from the baseline (Figure 5), and along with GIR, did not return to baseline by end of clamp procedure. PK and GIR may further explain the insulin secretion differences among treatments (Figure 4).

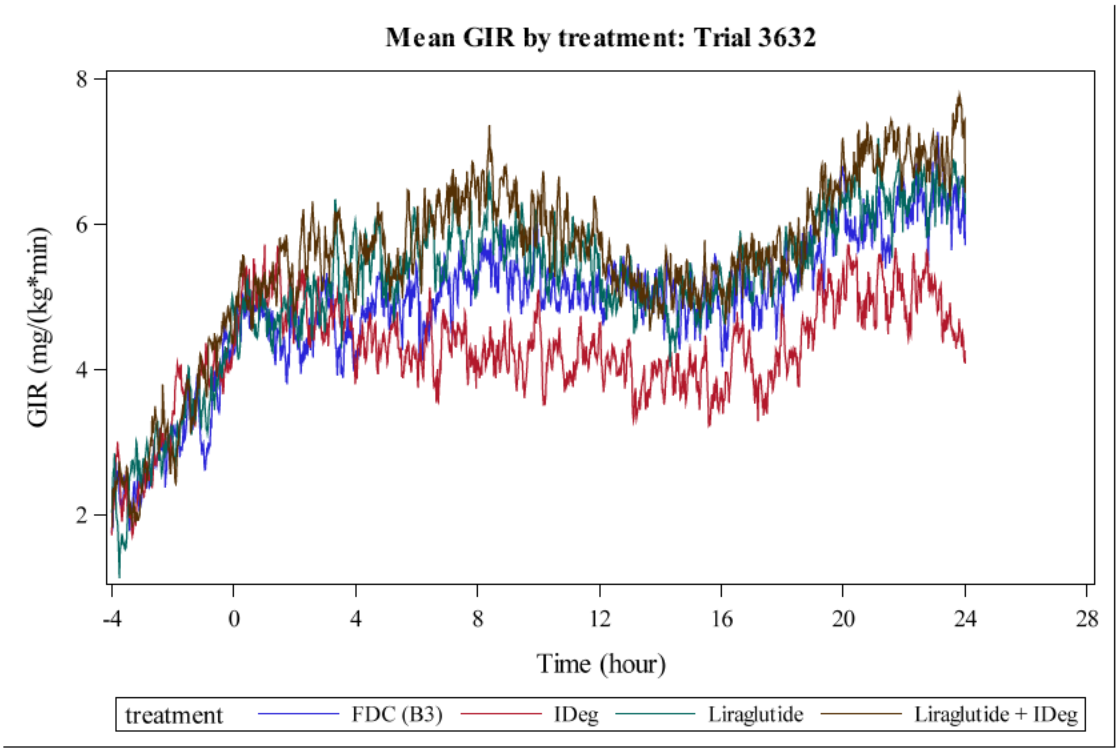


Figure 4 Mean GIR-time profiles by treatments (Trial 3632) (Note: B3 was an early clinical formulation of FRC. See the details of formulations in review section 3.2.6)

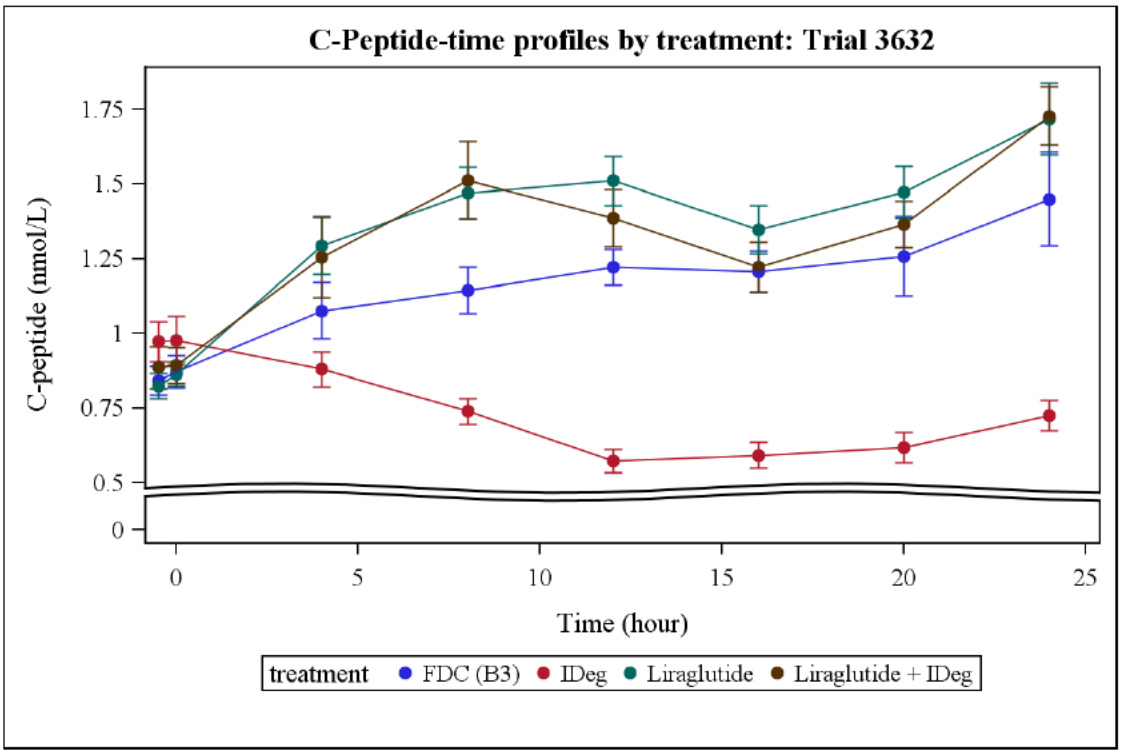


Figure 5 Mean (SE) C-peptide-time profiles after a single dose in healthy subjects (Note: B3 was an early clinical formulation of FRC. See the details of formulations in review section 3.2.6)

The C-peptide data from meal challenge evaluation in a sub-set of patients from Phase 3 trial (Trial 3697) was not informative, though a modest increase in C-peptide levels was reported in response to the IDeg and Lira administration as FRC in comparison to the administration of IDeg alone (treatment ratio for C-peptide $AUC_{0\text{-}4h}$ = 1.14 (95% CI; 1.03-1.26)).

Since there was a specific assay method for IDeg to permit independent measurement of the fasting state insulin levels, the homeostatic model assessment of beta cell functionality (HOMA-B*) provides insight into the contribution of Lira to the glycemic control from a mechanistic perspective. Estimated beta-cell functionality using HOMA-B remained unchanged following IDeg alone. However, on average HOMA-B was increased following FRC or Lira alone in patients with T2DM (Figure 6). Note that a lower HOMA-B with the FRC treatment may be related to the lower final dose of Lira attained in the FRC arm in comparison to that of Lira alone (Figure 7) though a formal dose-response relationship has not been established for HOMA-B. The total daily dose of IDeg was lower in the FRC treatment arm in comparison to the IDeg alone (Figure 7).

* HOMA-B (%) = 20·fasting insulin[µU/mL]/(FPG[mmol/L]-3.5) (glucose in molar units), or 360*insulin / (FPG-63) (glucose in mass units, mg/dL) (reference: D.R. Matthews *et al*., Diabetologia 28:412-419, 1985)

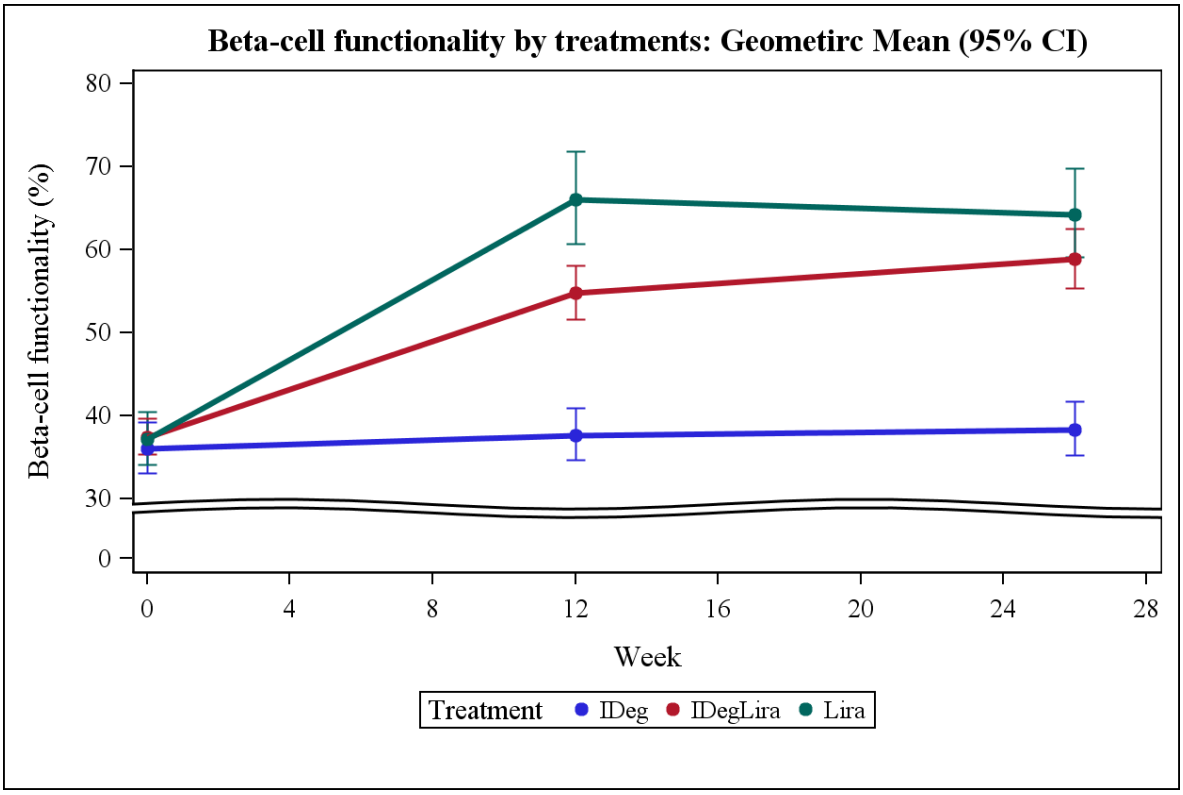


Figure 6 Mean (SE) beta-cell functionality by treatment period in T2DM

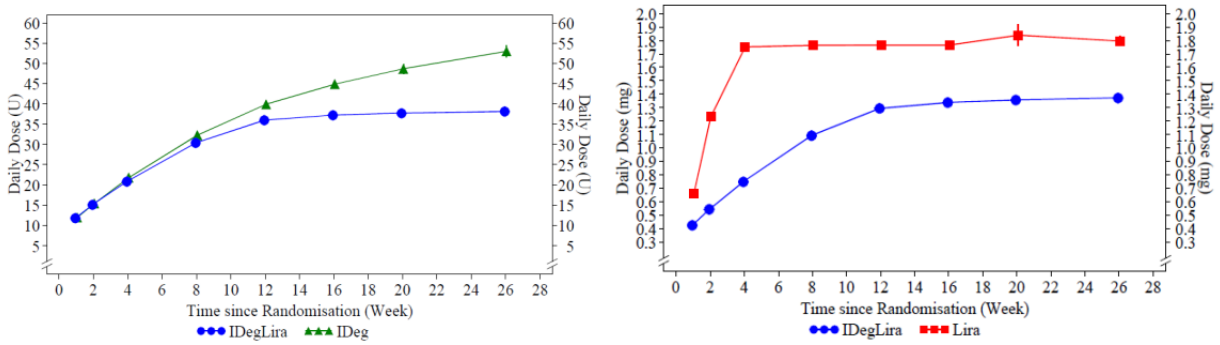


Figure 7 Daily IDeg (units, left) and Lira (mg, right) dose by treatment week (SOURCE: Figure 11-3 and 12-4, CSR Trial 3697)

Dose/Exposure-Efficacy information

For the same dose or exposure of IDeg or Lira for the FRC treatment, there was additional HbA1c reduction following FRC compared to that of IDeg or Lira administered alone according to the post-hoc analysis conducted by the sponsor (Figure 8). However, this dose-response data does not permit the assessment of dose-response relationship for the entire range of IDeg or Lira doses a patient may have been introduced during the titration of the FRC. Total daily IDeg doses were observed as supplemental dose-response data across Phase 3 trials, and there were apparent trends in the data for patients achieving greater HbA1c reduction with less (Trial 3697, Trail 3952) or similar (Trial 3912) total daily IDeg doses after FRC than those of basal insulin alone indicating a dose-sparing effect of IDeg. However, In absence of more mechanistic dose-response assessment, the interpretation of total daily IDeg dose data is limited to the qualitative assessment of contribution of IDeg and Lira to overall effect from a mechanistic perspective. Further, different titration algorithms followed across trials may influence the data differently, and in turn, distort the relationship between glycemic PD (i.e., FPG and PPG) and HbA1c across trials (see review section 3.2.1 and 3.2.2 for further details).

The dose-response of Lira was evaluated from the dedicated trials from the original NDA for Lira (i.e., Study NN2211-1310 and NN2211-1571), and the analysis results provided ED_{50} and E_{max} (HbA1c change from baseline) as 0.60 mg (95% CI; 0.21, 1.71) and -2.11% (96% CI; -2.92, -1.30). The extrapolation of same dose-response relationship of Lira under FRC administration is, however, not supported by the data from FRC administration arm for reason stated above.

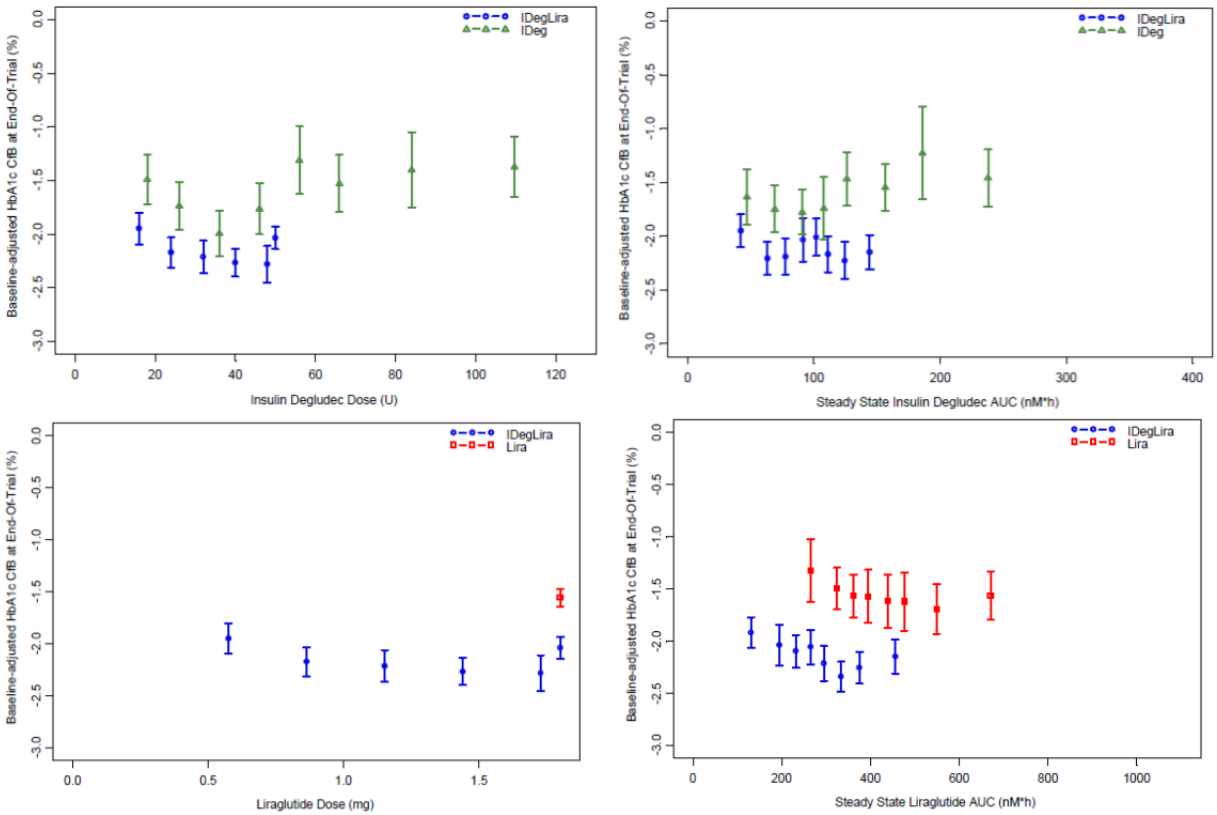


Figure 8 Effects of FRC (blue), IDeg (green) or Lira (red) on HbA1c change from baseline at end of trial versus percentiles of doses (left) and exposure at steady-state (right) (SOURCE: study-report-nn9068-3679-er)

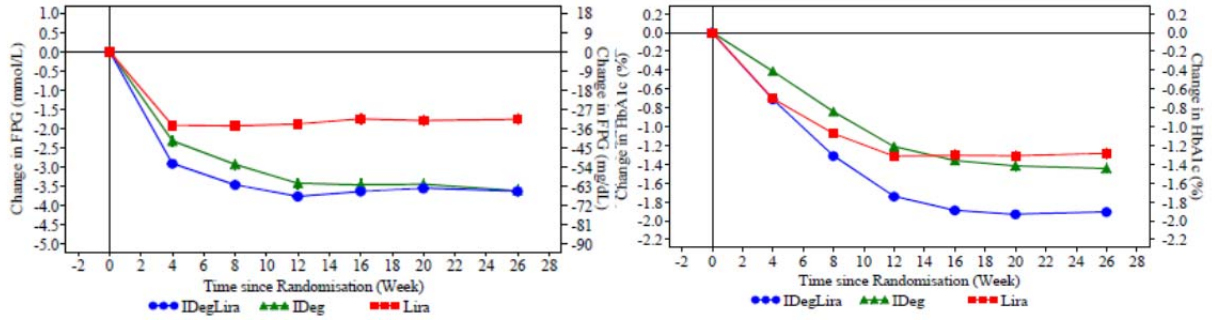
Overall, PD and dose/exposure-efficacy data indicate there is contribution of each component to the efficacy following FRC administration compared to that of single agent alone. The PK/PD data showed that IDeg did not interfere with the enhancement of glucose based insulin secretion action of Lira, when administered as FRC.

Relationship Between Pharmacodynamic and Efficacy Data

Mean HbA1c data indicate that FRC provide additional HbA1c lowering compared to each active ingredient for the same doses (Figure 8, Appendix 4.5). IDeg is known to lower primarily fasting plasma glucose (FPG). Lira PD data in VICTOZA® labeling indicate that it affects FPG and post-prandial glucose (PPG).

However, in the context of IDeg+Lira FRC product the relationship between glycemic response (i.e., FPG or PPG) and HbA1c data are not well understood particularly in the data from 2 Phase 3 trials, where HbA1c-time profiles were significantly different among treatments without apparent difference in FPG (Figure 9). IDeg or insulin glargine dosing algorithm may potentially distort the relationship between FPG and HbA1c. Alternatively, there might be significant contribution of Lira to lower HbA1c through lowering PPG after FRC administration (see PPG data in Appendix 4.7). However, systematic understanding for the quantitative correlation of PPG in the consideration of FPG to HbA1c is not known at this time.

Trial 3697



Trial 3952

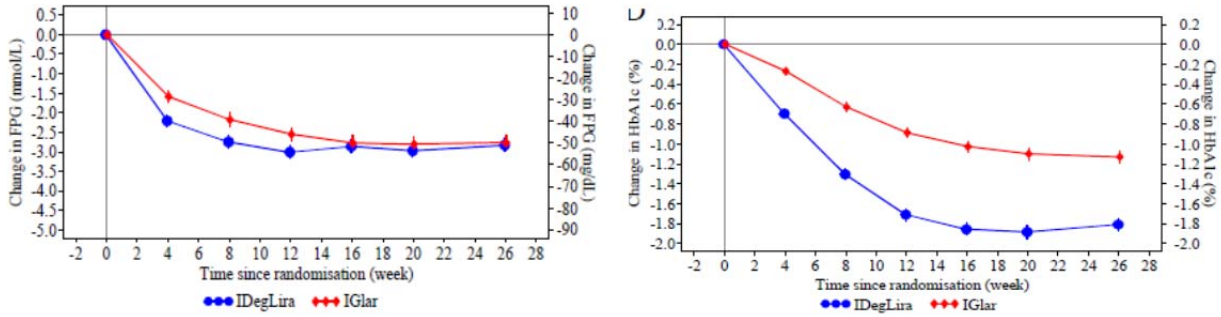


Figure 9 Mean FPG (left) and HbA1c (right) in 2 Phase 3 studies with basal insulin as a comparator

2.2 Outstanding Issues

None from the clinical pharmacology perspective.

2.3 Summary of Labeling Recommendations

To be updated

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

General regulatory background and challenge

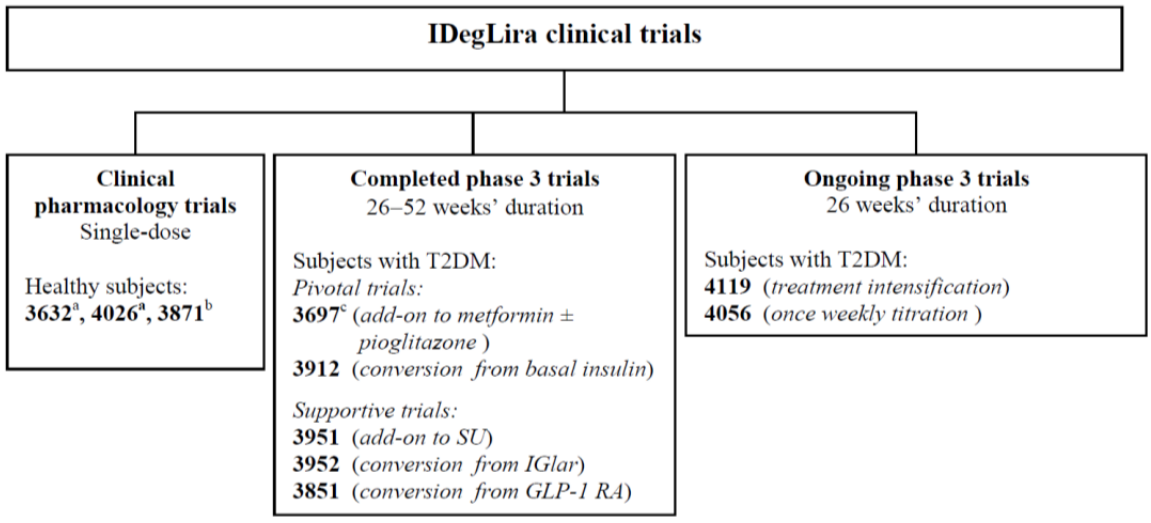
The proposed final presentation (device and FRC formulation) introduces a new paradigm for diabetic therapeutics and poses regulatory challenges as follows:

- Adequacy of HbA1c data in meeting the combination regulation (i.e., 21CFR 300.50);
  - "*two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug*"
- Clinical relevance of new titration scheme and its impact on HbA1c results
  - FRC requires simultaneous titration of both active ingredients. Contrary, each active ingredient has been approved for using different titration scheme
- Clinical relevance of secondary or exploratory endpoints, particularly body weight and dose sparing data
- Potential benefit risk ratio shift considering each active ingredients have unique adverse event (AE) (e.g., hypoglycemic events from IDeg and gastro-intestinal (GI) AEs by Lira)
- Labeling for specific indications/target patient population
- Potential medication errors because each active ingredient has different dose unit

Although each active ingredients of FRC have been approved, Advisory Committee meeting was held for XULTOPHY® to discuss the regulatory challenges on May 24, 2016. The committee supported for approval.

Product specific regulatory background and challenges

The applicant conducted a total 8 clinical trials to support XULTOPHY® clinical development (Figure 10).



[a] Trials 3632 and 4026 tested the IDeg/Lira ratio of 100 units/3.6 mg per mL used in phase 3 trials and intended for the market.
[b] Trial 3871 tested an alternative IDeg/Lira ratio of 100 units/(b) (4) mg per mL, which did not undergo further clinical development.
[c] The trial consisted of a 26-week main trial period followed by a 26-week extension period.

Figure 10 Schematic summary of clinical trials supporting XULTROPHY®

Potential drug-drug (IDeg vs. Lira) or formulation (FRC vs. co-administration) interactions were evaluated in 2 Phase 1 trials under the clamp procedures in healthy subjects (Figure 10, Trial 3632 and 3871). The pivotal bioequivalence (BE) of to-be-marketed (TBM) formulation referencing Phase 3 formulation was assessed (Figure 10, Trial 4026) because there were changes in compositions of TBM formulation compared to those of Phase 3 formulation.

The applicant conducted Phase 3 trials to evaluate clinical relevance of potential options for T2DM patients such as starting two drugs at once (Trial 3697 and 3951), failing basal insulin (Trial 3912 and 3952) or failing GLP-1 RA (Trail 3851) (Figure 10, Table 1, see overview of study design in Appendix 4.3, see trial endpoints in Appendix 4.4).

Table 1 Highlights of design aspects of Phase 3 trials

Trial	Primary design characteristics	T2DM patients	Reference treatment
3697*	Factorial study design	Not previously treated with GLP-1 or insulin	IDeg uncapped or Lira QD
3912*	Sequential add-on	Failing basal insulin	IDeg capped at 50 units
3952	Sequential add-on	Failing basal insulin (insulin glargine)	Insulin glargine uncapped
3851	Sequential add-on	Failing GLP-1	GLP-1 RA (Lira QD or exenatide BID)
3951	Start two drugs at once vs. placebo	Not previously treated with GLP-1 or insulin	Placebo (SU±met)**

*: pivotal trials
**: sulfonyl urea ± metformin

There are product specific challenges related to FRC class issues;

- *Adequacy of HbA1c data in meeting the combination regulation (i.e., 21CFR 300.50);*
  - Specifically, doses for GLP-1 RA lower than the approved effective dose (e.g., Lira <1.2 mg) were observed in sub-sets of patients and its contribution to HbA1c is not well understood (Figure 11)
- *Clinical relevance of new titration scheme and its impact on HbA1c results*
  - *FRC requires simultaneous titration of both active ingredients. Contrary, each active ingredient has been approved for using different titration scheme*
    - The recommended Lira starting dose is 0.6 mg because of GI tolerability, and the dose should be increased to 1.2 mg after 1 week at 0.6 mg or 1.8 mg if 1.2 mg does not result in acceptable glycemic control.
    - IDeg is recommended to start 10 units for insulin naïve T2DM patients, or the same unit dose as the total daily long or intermediate-acting insulin unit dose, and titrate the dose based on the patient's metabolic needs, blood glucose monitoring results and glycemic control goal for T1DM
- *Labeling for specific indications/target patient population*
  - The proposed dosing cap for FRC (e.g., IDeg 50/ Lira 1.8 mg) (Figure 11) and its potential limitation for patients with clinically relevant conditions (e.g., high body weight (BW))

- Relevance of trial results related to labeling for treatment naïve patients to both active ingredients, and experienced patients with an active ingredient or with both ingredients

- *Potential medication errors because each active ingredient has different dose unit*
  - mg and unit (U) for Lira and IDeg, respectively

In addition, impact of heterogeneous titration scheme (e.g., capping vs. uncapping comparator, starting doses, dosing steps or SMPG goal) across trials on HbA1c data is not well understood.

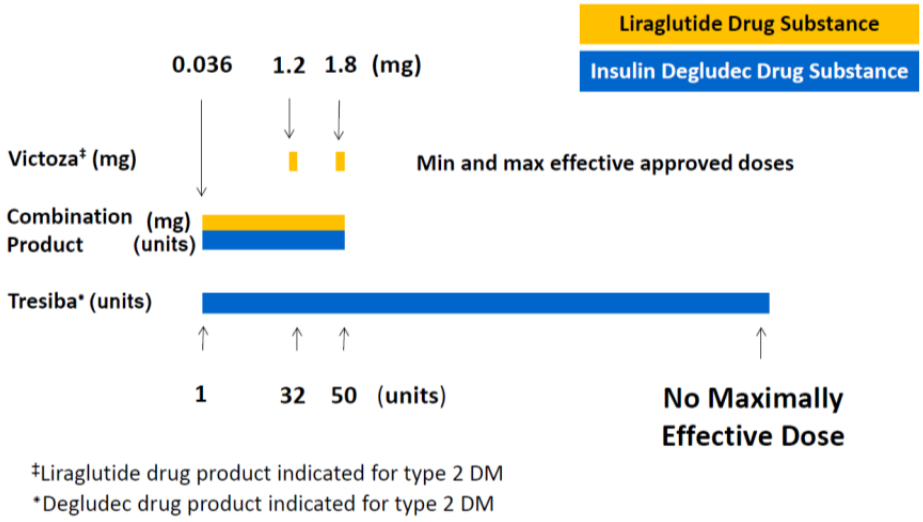
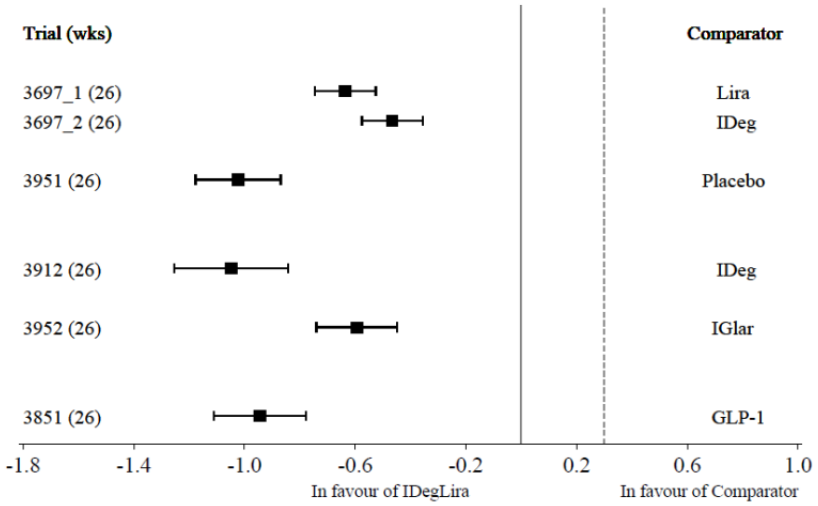


Figure 11 Proposed dosage of FRC compared to those of each active ingredients (Source; AC meeting 5/24/2016)

3.2 Clinical Pharmacology Review Questions

3.2.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness?

Results of the primary efficacy endpoint (HbA1c) indicate that FRC is superior to a comparator treatment across Phase 3 trials (Figure 12, see Appendix 4.5 for mean HbA1c change from baseline by treatment period). Refer clinical relevance of results to the review by Dr. Tania Condarco. Although it was based on post-randomization data, dose/exposure-HbA1c data indicate that there is additional HbA1c reduction after FRC compared to that of individual active ingredient for the same dose or exposure (Figure 8).



- Estimates with 95% CI
- Dotted line: non-inferiority limit used in Trial 3697 and 3952
- Solid line: superiority limit

Figure 12 Treatment differences - HbA1c (%) change from baseline - completed Phase 3 trials (Source: Figure 3-2, 2.7.2)

The relative changes among glycemic parameters (i.e., HbA1c, FPG and PPG) by treatments are not coherent across Phase 3 trials. In general, reduction of HbA1c after FRC was consistently greater than that of comparator (Figure 12). However, reduction of FPG was inconsistent among Phase 3 trials (see FPG data in Appendix 4.6). Specifically, reduction of HbA1c was not fully explained by reduction of FPG in trials with uncapped dosing for comparators (i.e., IDeg in Trial 3679 and insulin glargine in Trial 3952).

PPG may be potential bridging data to explain the difference between FPG and HbA1c; greater reduction of HbA1c with similar FPG reduction for a lower nominal IDeg dose after FRC compared to those of comparators. In this submission, PPG was measured after a standardized liquid mixed-meal, namely meal challenge study, in a sub-set (n=260) of Trial 3697, and PPG was presented as the change in $iAUC_{0\text{-}4h}$ (mmol/L) at Week 26 from baseline ($iAUC_{0\text{-}4h}$ = $AUC_{0\text{-}4h}$ (mmol*time/L) / time of observation period, where AUC was calculated using glucose concentrations after adjustment with value of 10 minute prior to the meal). There was additional PPG reduction (0.71 mmol/L (95% CI; -1.17, -0.26) or 12.81 mg/dL) after FRC compared to that of IDeg alone, whereas no significant difference (0.09 mmol/L) to that of Lira alone.

This data indicates that PPG reduction by Lira may contribute to greater HbA1c reduction without apparent difference in FPG after FRC. However, quantitative relationship between PPG (or iAUC) with HbA1c reduction is not fully understood. Therefore, clinical relevance of observed PD changes (PPG and FPG in combination) towards HbA1c reduction is unknown.

3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

XULTOPHY® is to be dosed in accordance with the individual patient's needs. However, potential impact of XULTOPHY® dosing cap (i.e., IDeg 50/Lira 1.8 mg) on therapeutic management is not well understood because patients' characteristics that require more than 50 XULTOPHY® dosing unit have not identified.

Population analysis indicates that there was no unique covariate for IDeg or Lira exposure other than already known covariates affecting individual drugs (Figure 13). Body weight or body mass index (BMI) is well-established significant covariate for both IDeg and Lira (Figure 14). Therefore, a patient with higher body weight or BMI may need more XULTOPHY® dose to reach the therapeutic goal compared to that of patient with lower body weight or BMI (Figure 15).

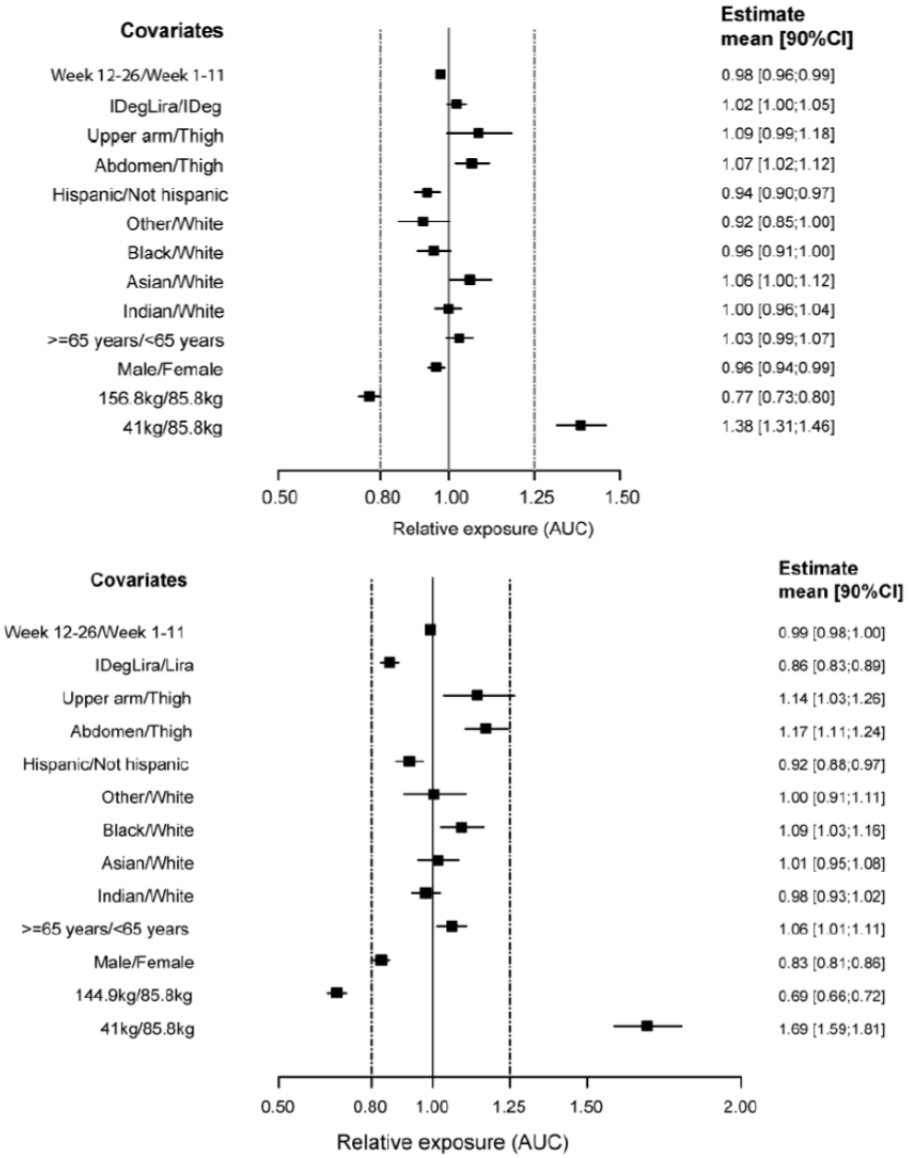


Figure 13 Forest plot of covariate analysis for IDeg (top) and Lira (bottom) (Source: Figure 3-7, 2.7.2)

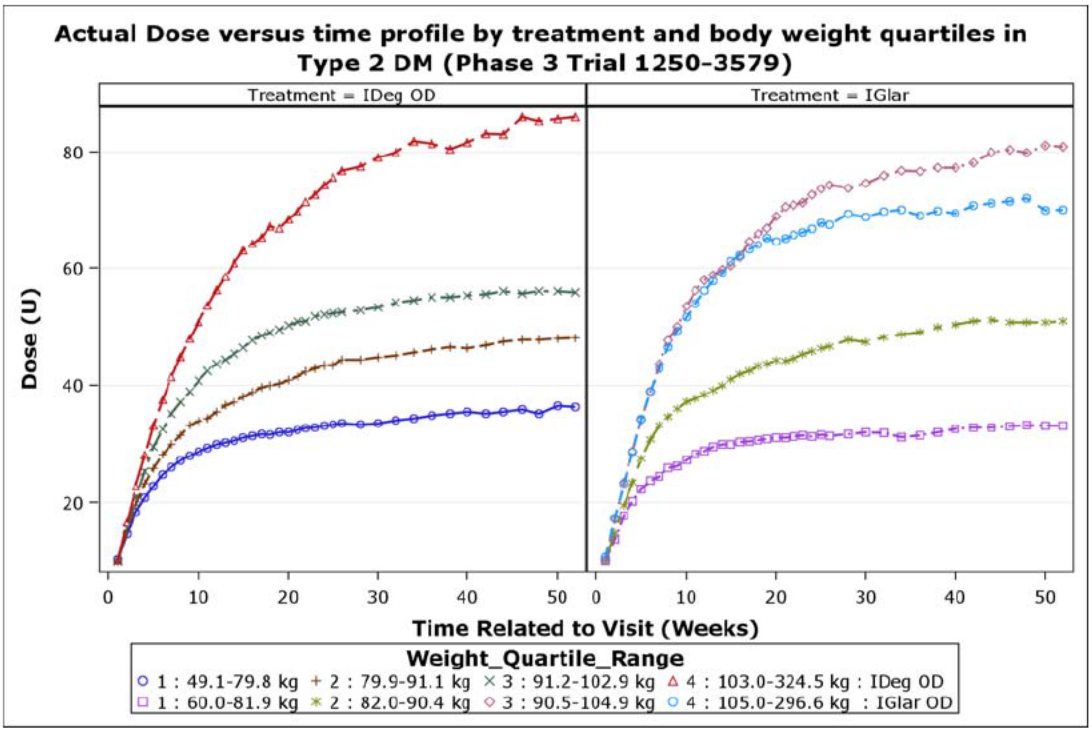


Figure 14 Effect of body weight on IDeg dose in T2DM (Source: Clinical pharmacology review for TRESHIBA (NDA 203314) by Dr. Manoj Khurana)

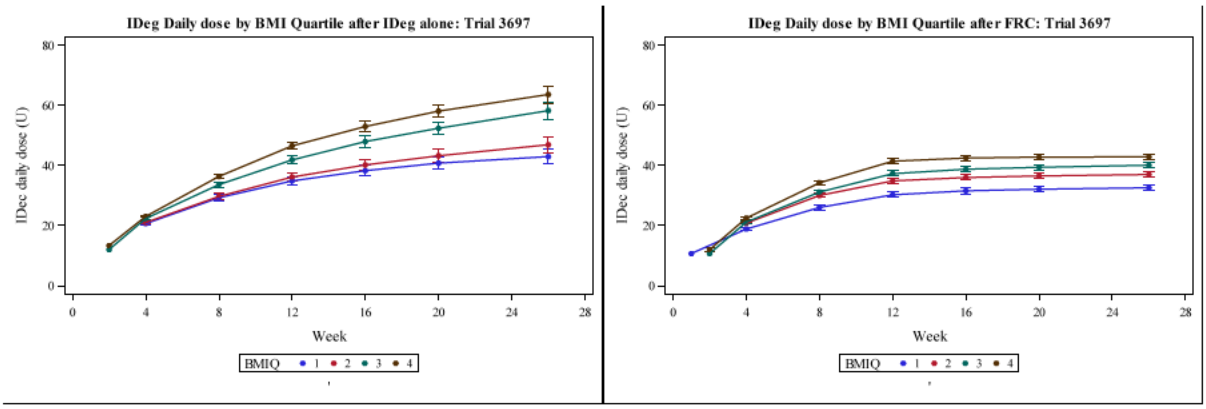


Figure 15 Effect of BMI on IDeg total daily dose following IDeg alone (left) or FRC (right) in T2DM

Weight gain following insulin and its analogs is an important factor to consider in diabetic therapeutics and management particularly related to adherence. Consistent body weight decrease was observed following FRC compared to basal insulin alone as comparator (Trial 3697, 3912 and 3952). However, clinical relevance of weight loss is not well understood because of relatively small changes (e.g., change in body weight < 5kg) (see changes in body weight during the treatment period in Appendix 4.9).

Total daily IDeg dose was evaluated to indirectly measure additional benefit of FRC based on the assumption that less IDeg dose is needed to achieve the same HbA1c change compared to that of IDeg alone if there is independent Lira contribution to the benefit following FRC, referred

as ‘dose sparing effect’. The total daily IDeg dose may be considered as supplemental dose-response for insulin and its analogs because conventional dose-response data are not available as their doses are individually titrated dependent on a blood glucose target. It was apparent that HbA1c reduction was greater with less total daily IDeg doses after FRC than those of basal insulin alone (Trial 3697, Trail 3952, Figure 16), or HbA1c reduction was greater with similar IDeg dose after FRC compared to that of IDeg alone when IDeg dose was capped (Trial 3912, Figure 16). It indicates that there was contribution from Lira to HbA1c reduction in addition to that of IDeg following FRC. However, data interpretation is not straightforward because total daily IDeg dose may be largely dependent on titration algorithms, and titration algorithms were heterogeneous between FRC and comparators. Different titration algorithms across trials may affect the relationship between glycemic PD (PPG and FPG) and HbA1c data (refer the review section 3.2.1).

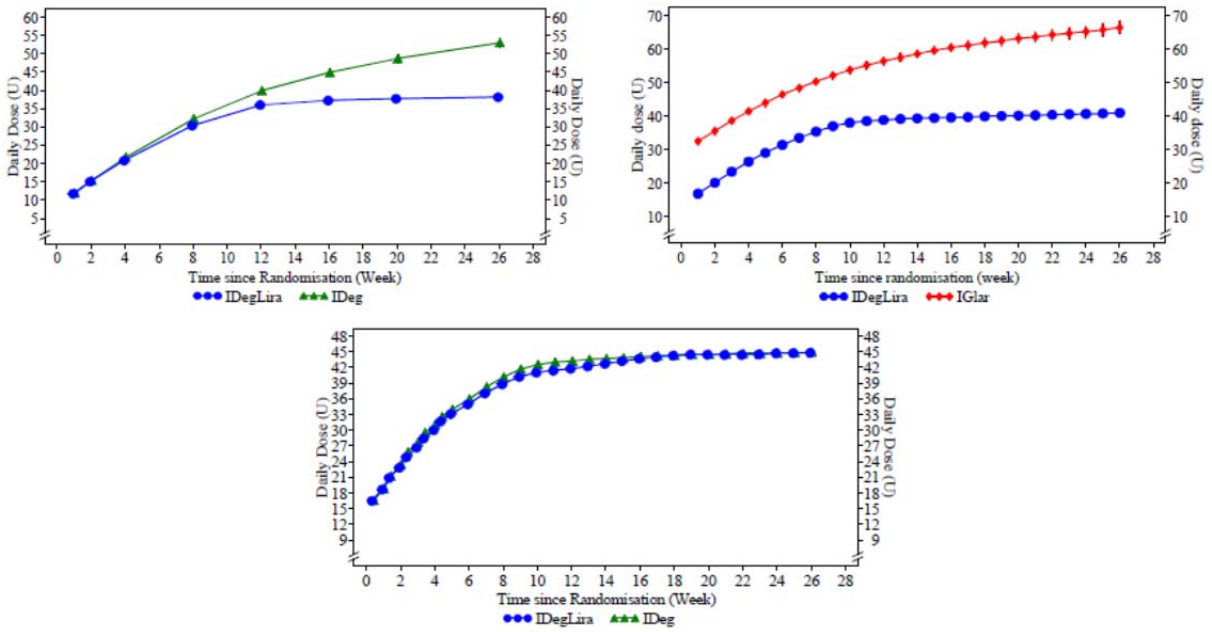


Figure 16 Total daily dose by treatment period: uncapped dosing for comparators (Trial 3697, upper left, and 3952, upper right) or capped dosing for comparator (Trail 3912, lower)

3.2.3 Are there clinically relevant drug-drug or formulation interactions, and what is the appropriate management strategy?

Drug-drug and formulation interaction potentials were assessed using a factorial study design (i.e., IDeg alone, Lira alone, co-administration of IDeg and Lira, or FRC) under clamp procedures in healthy volunteers (Trial 3632).

For IDeg, there was no apparent drug-drug or formulation interaction potential because IDeg concentration-time profiles were comparable among IDeg alone, co-administration of IDeg and Lira, or FRC, and statistical analysis indicates that IDeg AUC and Cmax after FRC met BE criteria referencing those of IDeg alone or co-administration (

Table 2, see individual PK parameters in Appendix 4.2).

For Lira, there was no drug-drug interaction potential because Lira concentration-time profiles were comparable between Lira alone and co-administration, and statistical analysis indicates that Lira AUC and Cmax after co-administration met BE criteria referencing those of Lira alone.

However, there seems formulation interaction as shown lower concentration-time profile after FRC compared to that of co-administration (Figure 3) and the trends resulted in 26% lower Cmax after FRC compared to that of co-administration (
Table 2, see individual PK parameters in Appendix 4.2). However, it is concluded that the lower Cmax may not have clinical significance because AUC was comparable between two treatments, and 26% lower Cmax alone seems not significantly undermine its efficacy as efficacy of FRC was better for the same Lira AUC compared to that of Lira alone (Figure 8).

Table 2 IDeg and Lira treatment ratios for AUC0-inf and Cmax after single-dose (dose=17 units (IDeg 17 units and Lira 0.61 mg, Trial 3632)

Compound	PK parameter	Treatment Ratio	Estimate	90% CI
IDeg	$AUC_{0\text{-inf}}$	IDegLira / IDeg	1.03	(0.99 ; 1.07)
		IDegLira / IDeg + Lira	0.98	(0.95 ; 1.02)
		IDeg + Lira / IDeg	1.05	(1.01 ; 1.09)
	C_{max}	IDegLira / IDeg	1.12	(0.99 ; 1.27)
		IDegLira / IDeg + Lira	1.04	(0.92 ; 1.18)
		IDeg + Lira / IDeg	1.08	(0.95 ; 1.22)
Lira	$AUC_{0\text{-inf}}$	IDegLira / Lira	0.89	(0.82 ; 0.96)
		IDegLira / IDeg + Lira	0.89	(0.83 ; 0.97)
		IDeg + Lira / Lira	0.99	(0.92 ; 1.07)
	C_{max}	IDegLira / Lira	0.77	(0.68 ; 0.87)
		IDegLira / IDeg + Lira	0.74	(0.66 ; 0.84)
		IDeg + Lira / Lira	1.03	(0.91 ; 1.16)

PD data indicate that there was potential Lira effect on glucodynamics in addition to that of IDeg after FRC administration at the given dose (i.e., 17 unit IDeg and 0.61 mg Lira) (see section 2.1.2). However, its clinical relevance is not well understood.

Population PK analysis indicates that IDeg and Lira exposure was proportional to FRC dose within the clinically relevant range (Figure 17). Estimates of population PK analysis after FRC are comparable to those of each ingredient alone (Table 3). Therefore, population analysis further supports no apparent drug-drug or formulation interactions after FRC.

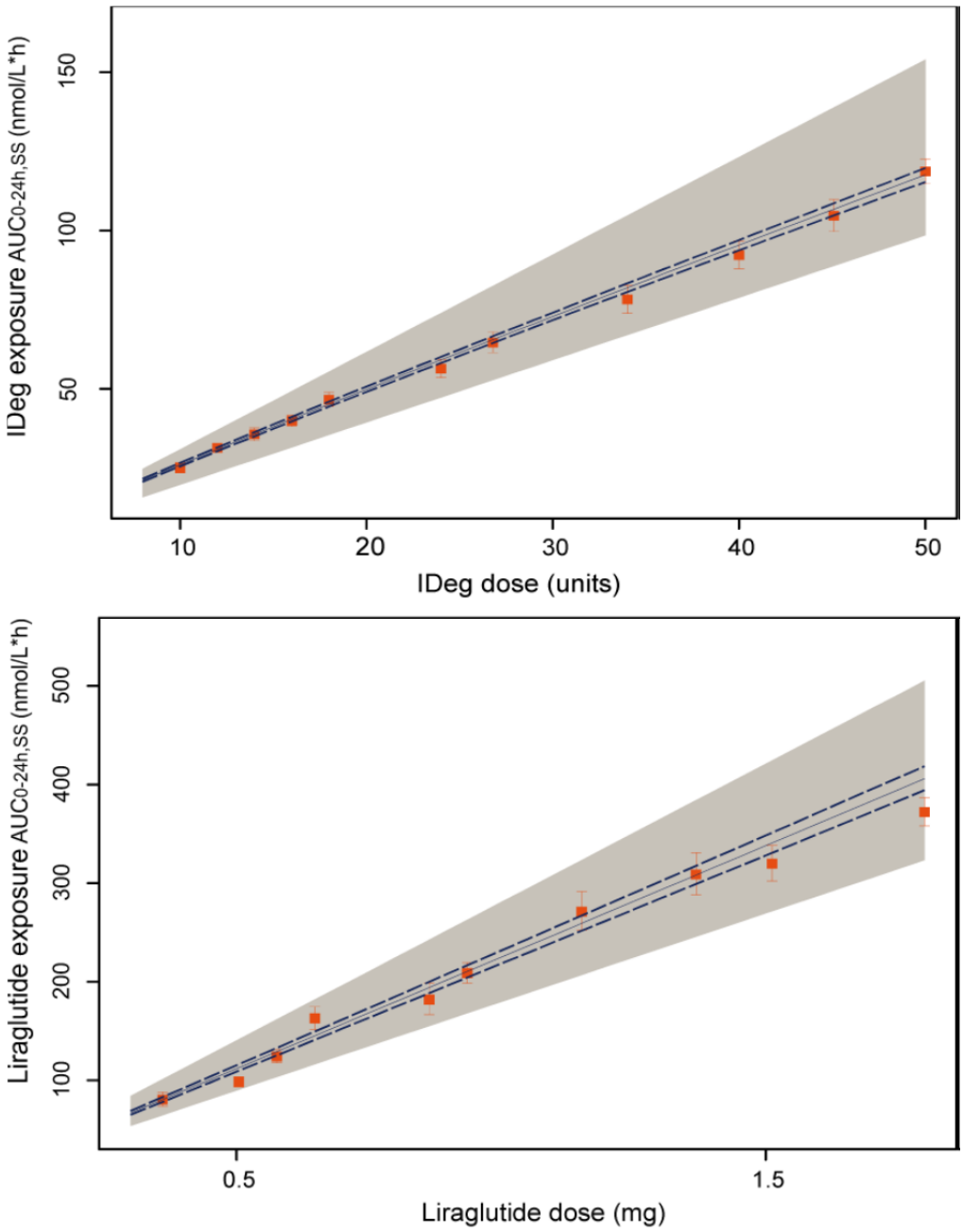


Figure 17 IDeg (upper) or Lira (lower) exposure versus dose at steady-state IDegLira (source: Figure 3-5 & 3-6, 2.7.2)

Table 3 IDeg and Lira estimates for a reference subject from the population analysis

Treatment	V/F (L) Population mean (CV%)	CL/F (L/h) Population mean (CV%)
IDegLira		2.51 (22.4)
	23.4 (94.7)[a]	
IDeg		2.56 (22.4)

Note: The hypothetical reference subject was of median body weight (85.8 kg), non-Hispanic White female, <65 years of age, dosed in the thigh, Weeks 1–11.

[a] Common estimates for IDegLira and IDeg due to sparseness of sampling (see Section 1.3.8).

V/F: volume of distribution. CL/F: clearance. CV: coefficient of variation.

Treatment	V/F (L) Population mean (CV%)	CL/F (L/h) Population mean (CV%)
IDegLira		1.37 (27.7)
	29.3 (105)[a]	
Liraglutide		1.18 (27.7)

Note: The hypothetical reference subject was of median body weight (85.8 kg), non-Hispanic White female, < 65 years of age, dosed in the thigh, Weeks 1–11.

[a] Common estimates for IDegLira and liraglutide due to sparseness of sampling (see Section 1.3.8).

V/F: volume of distribution. CL/F: clearance. CV: coefficient of variation.

3.2.4 Does the available clinical pharmacology information provide the pivotal bridging?

Yes, BE of TBM formulation (IDegLira V2) was demonstrated referencing Phase 3 formulation (IDegLira B5). Components and composition of TBM formulation are summarized compared to those of other formulation used during the clinical development in this review section 3.2.2.

PKs of IDeg and Lira were estimated after the TBM or Phase 3 formulation (Table 4) under clamp procedures in a 2-way cross-over with healthy subjects (see Synopsis in Appendix 4.1).

Table 4 Investigation formulations for Trial 4026: TBM (IDegLira V2) vs. Phase 3 formulation (IDegLira B5)

Trial Product	Dose	Batch Number
Insulin degludec/Lira B5	17 Dose steps (17 units IDeg and 0.61 mg Lira)	BW56288
Insulin degludec/Lira V2	17 Dose steps (17 units IDeg and 0.61 mg Lira)	CW58106

Plasma concentration – time profiles of IDeg and Lira were comparable between formulations (Figure 18) and statistical analysis for BE assessment indicates that TBM is bioequivalent to Phase 3 formulation (
Table 5).

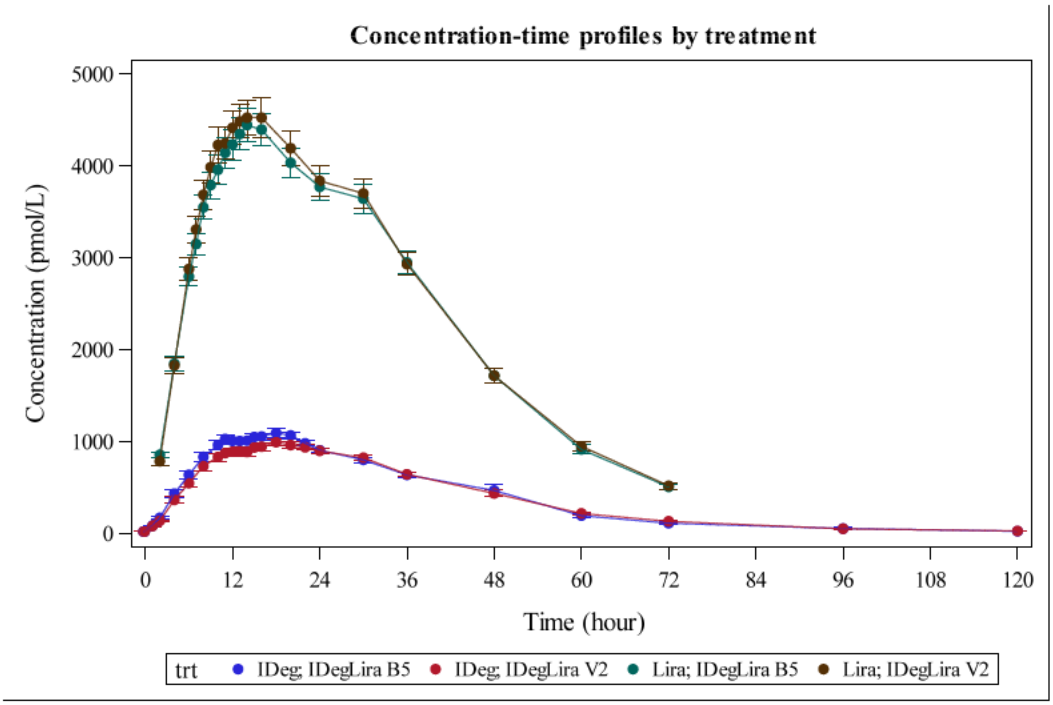


Figure 18 Mean (SE) concentration–time profiles of IDeg or Lira by treatments (Trial 4026)

Table 5 Summary of IDeg and Lira PK, and statistical analysis for BE assessment (treatment ratio – V2/B5 (90%CI)) (Source: Table 11-1, CSR)

Compound	PK parameter		N	Estimate
IDeg	$AUC_{0\text{-}tz}$ (pmol*h/L)	IDegLira V2	48	40466
		IDegLira B5	48	42750
		Treatment ratio		0.947 (0.914, 0.980)
	Cmax (pmol/L)	IDegLira V2	49	1106
		IDegLira B5	49	1274
		Treatment ratio		0.869 (0.802, 0.941)
Lira	$AUC_{0\text{-}tz}$ (pmol*h/L)	IDegLira V2	48	168853
		IDegLira B5	48	167024
		Treatment ratio		1.01 (0.978, 1.045)
	Cmax (pmol/L)	IDegLira V2	49	4668
		IDegLira B5	49	4689
		Treatment ratio		0.995 (0.938, 1.056)

Although the trial was under clamp procedures, the application indicated that PD (e.g., GIR) was not adequately assess in the trial because the procedure was just to ensure safety. The PD was further confounded by meal consumption during the trial (Figure 19). However, the PK data alone without PD data were sufficient for IDeg or Lira BE assessment because bioanalytical studies for both compounds did not have significant interference against endogenous insulin or GLP-1.

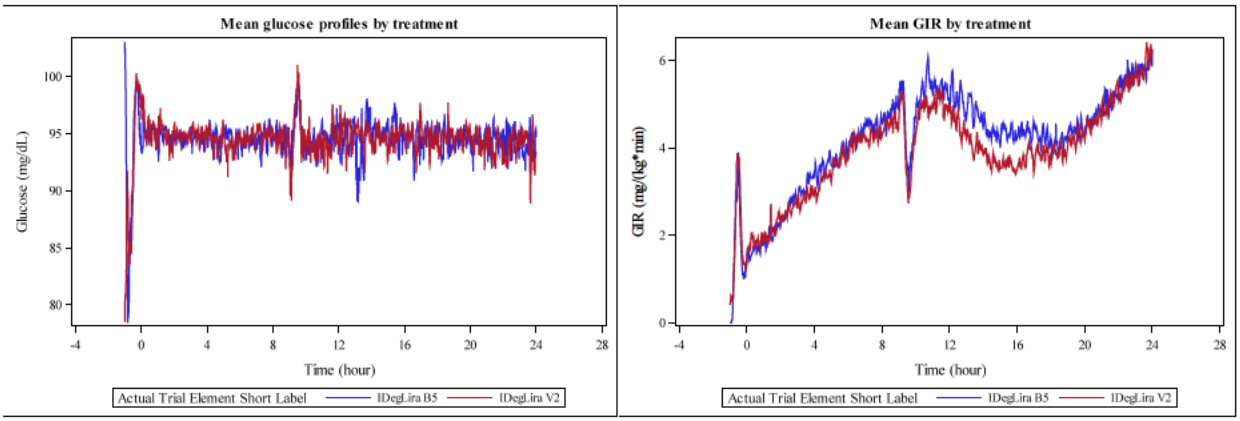


Figure 19 Mean glucose concentration- (left) and GIR- (left) time profiles (Trial 4026)

3.2.5 Were bioanalytical studies acceptable?

Yes, both IDeg and Lira were measured adequately without significant cross-reactivity against endogenous analogs or between two active ingredients.

A sandwich enzyme-linked immunosorbent assay (ELISA) specific for IDeg and Lira were developed. Validation parameters for IDeg and Lira are summarized in Table 6 and Table 7.

Table 6 Summary of validation parameters for IDeg in human serum (Source: Table 1-3, 2.7.1)

Parameter	Results	Study ID
Range	LLOQ = 20 pM ULOQ = 1000 pM	AA81207 and ZZ29613
Accuracy	Within the limits of 80−120% (75−125% at LLOQ and ULOQ)	AA81207
Dilution linearity	Dilution up to 5000 fold within the limits of 80−120%	ZZ29613
Precision	Within the limits of ≤20% (≤25% at LLOQ and ULOQ)	AA81207 and ZZ29613
Stability	5 cycles of freezing and thawing at -20°C and -80°C 139 days at -80°C 763 days at -20°C 379 days at -20°C (IDeg in the presence of liraglutide)	AA81207 AA96132
Stability	5 cycles of freezing and thawing at -20°C and -80°C 4.5 months at -80°C 9 months at -20°C	AA81207
Interference	No interference of liraglutide up to 400.000 pM	208117
Hemolysis	No influence ≤5%	AA81207

LLOQ: Lower limit of quantification. ULOQ: Upper limit of quantification. IDeg: insulin degludec

Table 7 Summary of validation parameters for Lira in human serum (Source: Table 1-5, 2.7.1)

Parameter	Results	Study ID
Analytical range	LLOQ =30.0 pM ULOQ= 4500 pM	212136
Accuracy	Within the limits of 80 - 120% (75-125% at LLOQ)	212136
Dilution linearity	Samples diluted up to 1:116081 within the limits of 80% - 120%	212136
Precision	Within the limits of ≤20% (≤25% at LLOQ)	212136
Stability	4 cycles of freezing and thawing 126 days at -80°C 731 days at -20°C 732 days at -20°C (liraglutide in the presence of IDeg) Ambient temperature for up to24 hours 4°C for up to 24 hours	212136
Interference	No interference of IDeg for up to 15000 pM	212136
Hemolysis	No influence	212136

LLOQ: Lower limit of quantification; ULOQ: Upper limit of quantification; IDeg: insulin degludec

The specificity information provided by the applicant for insulin glargine, insulin detemir, insulin aspart and human insulin indicates that cross-reactivity was not observed for the four compounds up to 5000 pM.

Bioanalytical report indicates that cross-reactivity with native GLP-1 was eliminated by degradation of endogenous GLP-1 by pre-incubation of the plasma sample (4 hours at 37°C). Lira was shown to remain intact at these conditions.

Bioanalytical report indicates that there was no potential interference of Lira or IDeg in the IDeg- or Lira specific ELISA assay, respectively.

The Office of Study Integrity and Surveillance (OSIS) recommends accepting the pivotal BE data (Trial 4026) without on-site inspection because OSIS recently inspected the bioanalytical sites (see Memorandum by OSIS in Appendix 4.10).

3.2.6 What are the highlights of the formulation as they relate to clinical pharmacology review?

The application conducted the pivotal bioequivalence study because there were changes in compositions for to-be-marketed formulation compared those of Phase 3 formulation (Table 8).

Table 8 Formulations of IDegLira used in clinical trials

	IDegLira (A3)	IDegLira (B3)	IDegLira (B5) (Phase 3)	IDegLira (V2) (To-be-marketed)
Fixed ratio	IDeg/Lira 100 units (b) (4) mg per mL	IDeg/Lira 100 units/3.6 mg per mL	IDeg/Lira 100 units/3.6 mg per mL	IDeg/Lira 100 units/3.6 mg per mL
Drug substance per mL				
Insulin degludec	100 units, 600 nmol	100 units, 600 nmol	100 units, 600 nmol	100 units, 600 nmol
Lira	(b) (4) mg, (b) (4) nmol	3.6 mg, 960 nmol	3.6 mg, 960 nmol	3.6 mg, 960 nmol
Other ingredients per mL				
Phenol	(b) (4)			5.70 mg
Glycerol				19.7 mg
Zinc (b) (4)				55.0 µg
Hydrochloric acid	q.s.	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.
Water for injection	to make 1 mL	to make 1 mL	to make 1 mL	to make 1 mL
pH	(b) (4)	(b) (4)	(b) (4)	8.15
Trial: Phase 1	3871	3632	4026	4026
Phase 3			3697, 3912, 3851, 3951, 4119 (ongoing)	4056 (ongoing)

4 Appendices

4.1 Pivotal Study Synopsis: Study NN9068-4026

CTR synopsis

Clinical Trial Report synopsis - ICH E3 Section 2

Trial registration ID-number NCT01916174	**UTN** – U1111-1137-3809 **EudraCT number** – 2012-005468-93
TITLE OF TRIAL A trial to demonstrate bioequivalence between two insulin degludec/liraglutide formulations, B5 and V2, in healthy subjects	
INVESTIGATOR Dr. med. Christoph Kapitza, CEO, PROFIL Institut für Stoffwechselforschung GmbH	
TRIAL SITE PROFIL Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, D-41460 Neuss, Germany	
PUBLICATIONS No publications were available at the time of this clinical trial report synopsis.	
TRIAL PERIOD Initiation date: 05 August 2013 Completion date: 04 November 2013	**DEVELOPMENT PHASE** Phase 1
DATA CUT-OFF DATE The results presented reflect the data available in the clinical database as of 03 January 2014.	
OBJECTIVES **Primary objective** • To demonstrate bioequivalence between two formulations of insulin degludec/liraglutide (IDegLira), B5 and V2 **Secondary objectives** • To compare the pharmacokinetic properties between two formulations of IDegLira, B5 and V2, with respect to IDeg and liraglutide • To evaluate safety and tolerability following single dose administration of two formulations of IDegLira, B5 and V2	
METHODOLOGY This was a single centre, randomised, double-blind, single dose, two-period crossover trial in healthy subjects. The trial was designed to compare bioequivalence of IDegLira B5 and V2 and to investigate the pharmacokinetics, safety and tolerability of single dose administration of the two IDegLira formulations. The trial period consisted of 4 visits: A screening visit (Visit 1; 2-28 days prior to first dosing), two dosing visits (Visit 2-3; separated by a wash-out period of 7-15 days between dosings) and one follow-up visit (Visit 4). At Visit 2 the subjects were randomly allocated to a sequence of two single dose administrations (either B5 followed by V2 or V2 followed by B5) on two separate dosing visits. At each of the two dosing visits subjects were to stay in-house for the first 24 hours after trial product administration (or longer if deemed necessary by the investigator). A safety glucose infusion was performed during the first 24 hours after each dosing in order to avoid hypoglycaemic episodes. The concentration-time profile of IDeg was determined for 120 hours and concentration-time profile of liraglutide for 72 hours	
NUMBER OF SUBJECTS PLANNED AND ANALYSED A total of 50 healthy subjects were planned for randomisation. A total of 64 subjects were screened of which 50 subjects, 32 males and 18 females, were randomized and exposed to trial products. A total of 48 subjects completed the trial.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION Healthy men and women between 18 and 55 years of age with a BMI between 18.5 and 27.0 kg/m^2, body weight between 60 and 90 kg and fasting plasma glucose below 6.1 mmol/L were eligible for participation.	

Key exclusion criteria included pregnancy or inadequate contraceptive methods (female), donation of blood or plasma >500 ml within 3 months before screening, history or presence of cancer, or any clinically significant cardiovascular, respiratory, metabolic, renal, hepatic, gastrointestinal, endocrine (incl. diabetes), haematological, dermatological, venereal, neurological, psychiatric diseases or other major disorders that might have impact on the trial, as judged by the investigator, drug or alcohol abuse and use of any medication except paracetamol, acetylsalicylic acid, contraceptives and vitamins, within 2 weeks before screening.

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Two IDegLira formulations were used in this trial:

Trial Product	Dose	Batch Number
Insulin degludec/liraglutide B5	17 Dose steps (17 units IDeg and 0.61 mg liraglutide)	BW56288
Insulin degludec/liraglutide V2	17 Dose steps (17 units IDeg and 0.61 mg liraglutide)	CW58106

All trial products were provided in 3 ml Penfill® cartridges for subcutaneous administration using a NovoPen® 4 device.

DURATION OF TREATMENT

The subjects received one single injection at each of the two dosing days, one of each trial product.

CRITERIA FOR EVALUATION – PHARMACOKINETICS

The criteria for evaluation of pharmacokinetics were the concentrations of insulin degludec in serum and liraglutide in plasma after administration of IDegLira formulations.

The pharmacokinetic endpoints were derived from the 120 hour concentration-time curves of insulin degludec and the 72 hour concentration-time curves of liraglutide

CRITERIA FOR EVALUATION – SAFETY

The criteria for evaluation of safety were adverse events, physical examination, vital signs, evaluation of local tolerability, plasma glucose measurements, hypoglycaemic episodes, clinical laboratory tests, body weight and BMI.

STATISTICAL METHODS

Power calculation

Using data from a previous trial (NN9068-3632), it was calculated that 45 subjects were needed to complete the trial to demonstrate bioequivalence with a combined power of 90% assuming a ratio of 1 between IDegLira B5 and V2.

Analysis sets

All 50 subjects were included in the full analysis set (FAS) and the safety analysis set (SAS). Analyses of pharmacokinetic endpoints were based on the FAS, analyses of safety endpoints were based on the SAS. The two withdrawn subjects only contributed partially to the pharmacokinetic endpoints because some data were not evaluable at both dosing visits.

Primary endpoints

In this trial, there were 4 co-primary endpoints derived from the individual IDeg and liraglutide concentration profiles: $AUC_{IDeg,0\text{-}tz,SD}$, $C_{max,IDeg,SD}$, $AUC_{Lira,0\text{-}tz,SD}$ and $C_{max,Lira,SD}$. These were analysed using an analysis of variance (ANOVA) approach. Log transformed values were used in order to account for heteroscedasticity. The statistical model for each endpoint had treatment, period, sequence and subject within sequence as fixed effects. To establish equivalence for the primary endpoints, the ratios between the two treatments were estimated and the corresponding 90% confidence intervals (CIs) were constructed.

Bioequivalence was considered to be demonstrated if the 90% CI for the treatment ratios were all fully within the interval [0.80; 1.25] for all 4 co-primary endpoints.

The analysis of the co-primary endpoint was repeated with an adjustment for actual drug content. Before breaking the blinding, it was decided to perform a sensitivity analysis using the same methods and models as the primary analysis. The sensitivity analysis excluded a subject randomised in error and data points that were deemed implausible by the study group in a blinded review.

Secondary endpoints

The following key secondary pharmacokinetic endpoints were derived from the individual IDeg and liraglutide concentration profiles: $AUC_{IDeg,0-\infty,SD}$, $t_{max,IDeg,SD}$, MRT_{IDeg}, $AUC_{Lira,0-\infty,SD}$, $t_{max,Lira,SD}$ and MRT_{Lira}. All secondary endpoints were compared between the IDegLira formulation using descriptive statistics except $AUC_{IDeg,0-\infty,SD}$ and $AUC_{Lira,0-\infty,SD}$ which were analysed using the same approach as for the primary endpoints.

Additional secondary pharmacokinetic endpoints

Before breaking the blinding, it was decided to calculate secondary endpoints in addition to those stated in the protocol: The percentage of AUC extrapolated and the number of subjects with extrapolated AUC >20%

Safety endpoints

The number of treatment-emergent adverse events, injection site reactions, treatment-emergent hypoglycaemic episodes as well as the changes in laboratory parameters, vital signs, physical examination, body weight, BMI and FPG were evaluated using descriptive statistics.

DEMOGRAPHY OF TRIAL POPULATION

50 healthy subjects of both genders were randomised, 32 males and 18 females. 47 subjects were White, 1 subject was Black or African American and 2 subjects were Asian non-Indian. The subjects' mean age was 38.9 years (range 18 – 53 years) and their mean BMI was 24.0 kg/m^2 (range 19.5 – 27.7 kg/m^2).

PHARMACOKINETIC RESULTS

- IDegLira V2 and IDegLira B5 were confirmed to be bioequivalent as the 90% CI of the treatment ratio IDegLira V2/IDegLira B5 was fully within the interval [0.80 ; 1.25] for all 4 co-primary endpoints. For IDeg the treatment ratios were $AUC_{IDeg,0-tz,SD}$: 0.95 $[0.91 ; 0.98]_{90\% CI}$ and $C_{max,IDeg,SD}$: 0.87 $[0.80 ; 0.94]_{90\% CI}$. For liraglutide the treatment ratios were $AUC_{Lira,0-tz,SD}$: 1.01 $[0.98 ; 1.04]_{90\% CI}$ and $C_{max,Lira,SD}$:1.00 $[0.94 ; 1.06]_{90\% CI}$.
- Adjusting for actual drug content and sensitivity analysis supported the conclusion of bioequivalence.
- No marked differences between the two IDegLira formulations were seen for secondary endpoints.

SAFETY RESULTS

- In total, 47 adverse events (AEs) were reported in 23 subjects, the most frequent being headache (21 events), vomiting (7 events) and nausea (6 events). There were no severe events and all subjects recovered.
- No SAEs, MESIs or AEs leading to withdrawal were reported.
- No injection site reactions were reported
- No clinically significant changes in vital signs, physical examination and laboratory parameters were identified from screening to follow-up
- One confirmed hypoglycaemic episode was reported. All hypoglycaemic episodes reported occurred under the clamp procedure or within one hour after disconnection from the clamp device. No severe hypoglycaemic episodes were reported. No nocturnal hypoglycaemic episodes were reported.

CONCLUSIONS

- Bioequivalence between IDegLira B5 and IDegLira V2 was confirmed, since the 90% CI of the treatment ratios for the four co-primary endpoints were all fully within the interval [0.80; 1.25]
- In general, the pharmacokinetic endpoints were similar between IDegLira B5 and IDegLira V2
- No safety issues were identified in this trial. Safety profiles for IDegLira B5 and IDegLira V2 were comparable.

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and FDA 21 CFR 312.120.

4.2 Pharmacokinetic endpoints of IDeg (upper) and Lira (lower) in IDegLira single-dose trials in healthy subjects

Trial ID, Report Location, Design	N (M/F)	IDegLira Fixed-ratio)	Treatment and Dose	$AUC_{IDeg,0-\infty,SD}$ Geom. mean (CV%) (pmol·h/L)	$AUC_{IDeg,0-24h,SD}$ Geom. mean (CV%) (pmol·h/L)	$AUC_{IDeg,0-96h/0-120h/0-\infty,SD}$ Geom. mean (CV%) (pmol·h/L)	$C_{max,IDeg,SD}$ Geom. mean (CV%) (pmol/L)	$t_{max,IDeg,SD}$ Median (CV%) (h)	$t_{½,IDeg,SD}$ Harm. mean (CV%) (h)	$CL/F_{IDeg,SD}$ Geom. mean (CV%) (L/h)	$MRT_{IDeg,SD}$ Geom. mean (CV%) (h)	$V_z/F_{IDeg,SD}$ Geom. mean (CV%) (L)
NN9068-3632 M 5.3.1.2 RND, DB, CO	24 (24/0)	IDeg/lira 100 units/3.6 mg per mL	Single s.c. doses of -IDegLira (17 units/0.6 mg) -IDeg (17 units) -Liraglutide (0.6 mg) -IDeg (17 units)+ liraglutide (0.6 mg)	50231 (15) 48837 (12) - 51177 (14)	19994 (26) 19899 (22) - 21427 (25)	$AUC_{IDeg,0-96h,SD}$: 48549 (15) 47094 (10) - 49239 (14)	1339 (43) 1195 (22) - 1285 (31)	15.5 (38) 13.5 (26) - 14.0 (28)	13.7 (36) 14.4 (34) - 14.6 (37)	2.0 (15) 2.0 (12) - 2.0 (14)	33.4 (25) 33.3 (23) - 33.4 (24)	41.9 (31) 44.6 (28) - 43.4 (37)
NN9068-4026 M 5.3.1.2 RND, DB, CO	50 (32/18)	IDeg/lira 100 units/3.6 mg per mL	Single s.c. doses of IDegLira (17 units/0.6 mg) -Formulation V2 -Formulation B5	 41375 (21) 43481 (18)	 - -	$AUC_{IDeg,0-tz,SD}$: 40466 (22) 42750 (18)	 1106 (28) 1274 (31)	 18.0 18.0	 14.4 (27) 12.4 (31)	 2.5 (18) 2.4 (17)	 32.8 (19.8) 30.7 (22.7)	 52.9 (31) 44.5 (32)
NN9068-3871 M 5.3.1.2 RND, DB, CO, BE	24 (24/0)	IDeg/lira 100 units (b) (4) per mL	Single s.c. doses of -IDegLira (17 units/1.0 mg) -IDeg (17 units) -Liraglutide (1.0 mg)	56593 (16) 51401 (15) -	- - -	$AUC_{IDeg,0-120h,SD}$: 55355 (17) 50484 (15) -	1774 (43) 1723 (35) -	16.0 14.0 -	11.9 11.2 -	1.8 (17) 2.0 (15) -	30.5 (25) 28.4 (26) -	- - -

Trial ID, Report Location, Design	N (M/F)	IDegLira Fixed-ratio	Treatment and Dose	$AUC_{lira,0-\infty,SD}$ Geom. mean (CV%) (pmol·h/L)	$AUC_{lira,0-24h,SD}$ Geom. mean (CV%) (pmol·h/L)	$AUC_{lira,0-72h/0-tz,SD}$ Geom. mean (CV%) (pmol·h/L)	$C_{max,lira,SD}$ Geom. mean (CV%) (pmol/L)	$t_{max,lira}$ Median (CV%) (h)	$t_{½,lira,SD}$ Harm. mean (CV%) (h)	$CL/F_{lira,SD}$ Geom. mean (CV%) (L/h)	$MRT_{lira,SD}$ Geom. mean (CV%) (h)	$V_z/F_{lira,SD}$ Geom. mean (CV%) (L)
NN9068-3632 M 5.3.1.2 RND, DB, CO,	24 (24/0)	IDeg/lira 100 units/3.6 mg per mL	Single s.c. doses of -IDegLira (17 units/0.6 mg) -IDeg (17 units) -Liraglutide (0.6 mg) -IDeg (17 units)+ liraglutide (0.6 mg)	136859 (30) - 154472 (29) 152922 (26)	62300 (40) - 80238 (34) 83265 (35)	$AUC_{lira,0-72h,SD}$: 126626 (30) - 146984 (30) 146563 (27)	3943 (46) - 5133 (38) 5296 (35)	14.0 (25) - 13.0 (23) 13.0 (21)	15.2 (28) - 13.7 (24) 13.6 (14)	1.2 (30) - 1.0 (29) 1.0 (21)	31.4 (22) - 27.8 (17) 26.8 (12)	26.4 (32) - 20.8 (40) 20.7 (27)
NN9068-4026 M 5.3.1.2 RND, DB, CO	50 (32/18)	IDeg/lira 100 units/3.6 mg per mL	Single s.c. doses of IDegLira (17 units/0.6 mg) -Formulation V2 -Formulation B5	 180253 (27) 177905 (25)	 - -	$AUC_{lira,0-tz,SD}$: 168853 (26) 167024 (24)	 4667 (32) 4690 (24)	 14.0 14.0	 14.3 (20) 14.0 (20)	 0.9 (29) 0.9 (30)	 31.6 (13.8) 31.4 (12.6)	 19.0 (29) 19.0 (34)
NN9068-3871 M 5.3.1.2 RND, DB, CO, BE	24 (24/0)	IDeg/lira 100 units (b) (4) per mL	Single s.c. doses of -IDegLira (17 units/1.0 mg) -IDeg (17 units) -Liraglutide (1.0 mg)	233028 (27) - 270268 (24)	- - -	$AUC_{lira,0-72h,SD}$: 220080 (26) - 258153 (25)	6604 (24) - 8678 (37)	13.0 (25) - 13.0 (21)	13.7 (20) - 12.3 (27)	1.2 (27) - 1.0 (24)	31.0 (13) - 28.1 (17)	- - -

4.3 Overview of completed Phase 3 trials

Trial	Trial description and treatment	Subject population	Antidiabetic therapy at screening	Randomised IDegLira: comp.	No. of subjects eligible for analysis*
3697 'OAD users' 26 weeks + 26 weeks extension[a]	IDegLira vs. IDeg and liraglutide in separate, parallel treatment arms (open-label). All three treatments as add-on to metformin ± pioglitazone. IDegLira and IDeg[b]: starting dose of 10 dose steps and 10 units, respectively, dosed once daily and titrated twice weekly to an FPG target of 4.0-5.0 mmol/L (72-90 mg/dL). Maximum IDegLira dose of 50 dose steps. Liraglutide[c]: Weekly dose increase of 0.6 mg/day until reaching the target dose of 1.8 mg/day Metformin: ≥ 1500 mg/day or MTD Pioglitazone: ≥ 30 mg/day	T2DM subjects inadequately controlled on metformin ± pioglitazone (screening HbA_{1c} 7.0-10.0%, both inclusive). BMI ≤ 40 kg/m^2	Metformin ± pioglitazone	2:1:1	IDegLira: 833 IDeg: 413 Liraglutide: 414
3951 'OAD users' 26 weeks	IDegLira vs. placebo (double-blinded), both in combination with SU ± metformin. IDegLira[a]: starting dose of 10 dose steps, dosed once daily and titrated twice weekly to an FPG target of 4.0-6.0 mmol/L (72-108 mg/dL) Maximum IDegLira dose of 50 dose steps SU: ≥ half of maximum approved dose according to local label Metformin: ≥ 1500 mg/day or MTD	T2DM subjects inadequately controlled on SU ± metformin (screening HbA_{1c} 7.0-9.0%, both inclusive). BMI ≤ 40 kg/m^2	SU ± metformin	2:1	IDegLira: 289 Placebo: 146
3912 'basal insulin users' 26 weeks	IDegLira vs. IDeg (double-blinded), both in combination with metformin. IDegLira and IDeg: starting dose of 16 dose steps and 16 units, respectively. Both were dosed once daily and titrated twice weekly to an FPG target of 4.0 -5.0 mmol/L (72 -90 mg/dL). Maximum IDegLira dose of 50 dose steps and IDeg dose of 50 units. Metformin: ≥ 1500 mg/day or MTD.	T2DM subjects inadequately controlled on basal insulin + metformin ± SU or glinides (screening HbA_{1c} 7.5-10.0%, both inclusive). BMI ≥ 27 kg/m^2	Basal insulin + metformin ± SU/glinides. Basal insulin: 20-40 units/day. SU and glinides: ≥ half of maximum approved dose according to local label	1:1	IDegLira: 199 IDeg: 199
3952 'basal insulin users' 26 weeks	IDegLira vs. IGlar, both in combination with metformin (open-label). IDegLira[a]: starting dose of 16 dose steps, dosed once daily and titrated twice weekly to an FPG target of 4.0 -5.0 mmol/L (71 -90 mg/dL). Maximum IDegLira dose of 50 dose steps. IGlar: starting dose equal to pre-trial dose, titrated twice weekly to FPG 4.0 -5.0 mmol/L (71-90 mg/dL). No maximum dose. Metformin: ≥ 1500 mg/day or MTD.	T2DM subjects inadequately controlled on IGlar + metformin (screening HbA_{1c} 7.0-10.0%, both inclusive). BMI ≤ 40 kg/m^2	IGlar + metformin IGlar: 20-50 units/day.	1:1	IDegLira: 278 IGlar: 279
3851 'GLP-1 RA users' 26 weeks	IDegLira vs. GLP-1 RA, both in combination with metformin ± SU ± pio (open-label). IDegLira[a]: starting dose of 16 dose steps, dosed once daily and titrated twice weekly to an FPG target of 4.0-5.0 mmol/L (72-90 mg/dL) Maximum IDegLira dose of 50 dose steps. GLP-1 RA: maintenance of pre-trial dose and treatment schedule Metformin, pioglitazone, SU: maintenance of pre-trial doses	T2DM subjects inadequately controlled on GLP-1 RA + metformin ± SU ± pio (screening HbA_{1c} 7.0-9.0%, both inclusive). BMI ≤ 40 kg/m^2	GLP-1 RA+ metformin ± SU ± pioglitazone GLP-1 RAs: liraglutide 1.8 mg/day or MTD; exenatide 10 µg BID or MTD Metformin: ≥ 1500 mg/day or MTD Pioglitazone: ≥30 mg SU: ≥ half of maximum approved dose according to local label	2:1	IDegLira: 292 GLP-1 RA: 146

[a] The process of entering the 26-week trial extension as well as the number of subjects entering/completing the extension are described in Section 1.2.11.6.

[b] One dose step of IDegLira is equivalent to 1 unit IDeg and 0.036 mg liraglutide.

[c] Liraglutide was started at 0.6 mg/day and escalated weekly in 0.6 mg increments to a maximum dose of 1.8 mg/day. Thereafter, the 1.8 mg/day was to be maintained until the end of treatment.

* 18 subjects (3 from Trial 3697 and 15 from Trial 3912) were excluded from analysis; see Section 1.2.11.4.

Abbreviations: BID = twice a day; BMI = Body mass index; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycosylated haemoglobin; IDeg = insulin degludec; IDegLira = insulin degludec/liraglutide; IGlar = insulin glargine; MTD = maximum tolerated dose; pio = pioglitazone; PRO = patient-reported outcomes; RA = receptor agonist; SU = sulphonylurea; T2DM = type 2 diabetes mellitus.

4.4 Primary, secondary confirmatory and selected pre-specified secondary endpoints in the completed Phase 3 trials

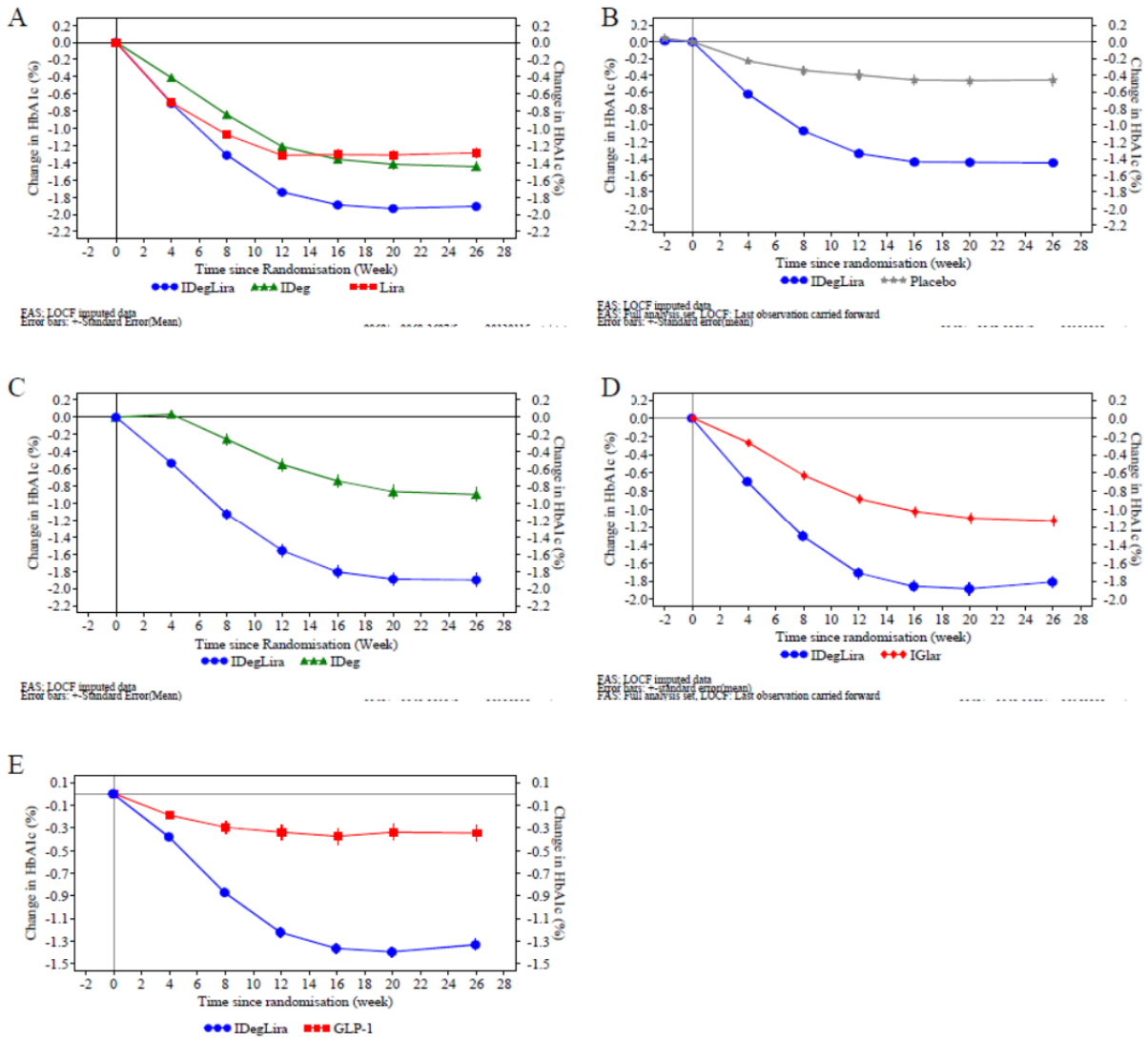
Endpoints	OAD users		Basal insulin users		GLP-1 RA users
	Trial 3697	**Trial 3951**	**Trial 3912**	**Trial 3952**	**Trial 3851**
HbA_{1c}	X[a]	X[a]	X[a]	X[a,b]	X[a]
Responders for HbA_{1c} targets	X[c]	X[c]	X[c]	X[c]	X[c]
Insulin dose	X[b]		X[c]	X[c]	
FPG	X[c]	X[c]	X[c]	X[c]	X[c]
Post-prandial glucose AUC increment based on meal test	X[b]				
9-point SMPG profile	X[c]	X[c]	X[c]	X[c]	X[c]
CGM measurement	X[c]				
Hypoglycaemic episodes	X[b]			X[b]	
Body weight	X[b]	X[c]	X[c]	X[b]	X[c]
Beta cell function/diabetes-related assessments	X[c]	X[c]	X[c]	X[c]	X[c]
Withdrawal due to ineffective therapy		X[c]	X[c]		X[c]
Patient-reported outcomes				X[c]	X[c]

[a]Primary endpoint; [b]Pre-specified confirmatory secondary efficacy endpoint; [c]Pre-specified supportive secondary endpoint

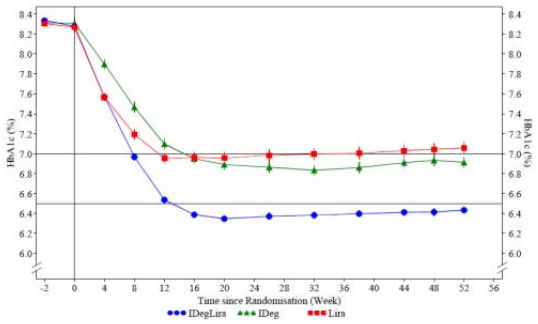
Post-prandial AUC increment and CGM measurements were performed in a subset of 260 subjects in Trial 3697

Abbreviations: AUC = area under the curve; CGM = continuous glucose monitoring; FPG = fasting plasma glucose; HbA_{1c} = glycosylated haemoglobin; SMPG = self-measured plasma glucose

4.5 Mean HbA1c change from baseline to 26 weeks (Source: Figure 3-1, 2.7.3)



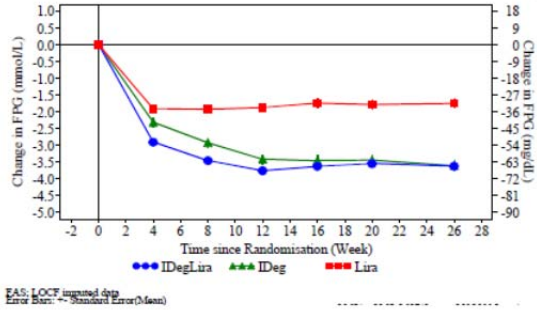
A) Trial 3697 B) Trial 3951 C) Trial 3912 D) Trial 3952 and E) Trial 3851



(Trial 3697-ext)

4.6 Mean fasting plasma glucose change from baseline to 26 weeks (Source: Figure 3-5, 2.7.3)

A



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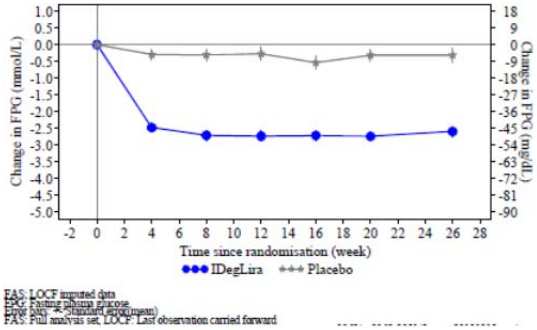

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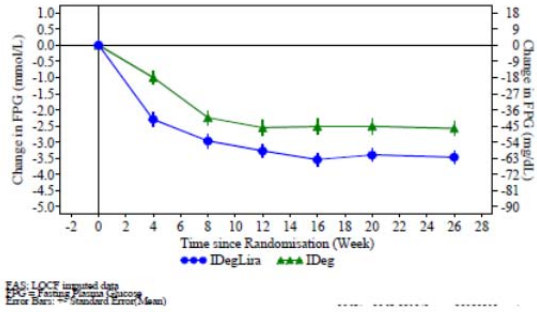

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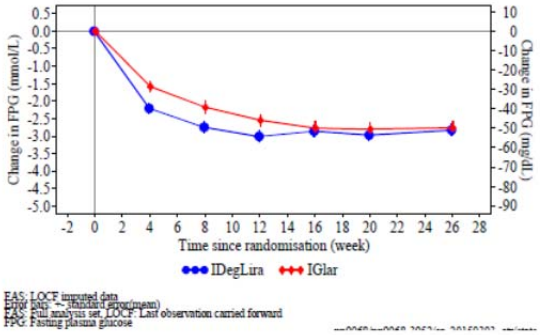

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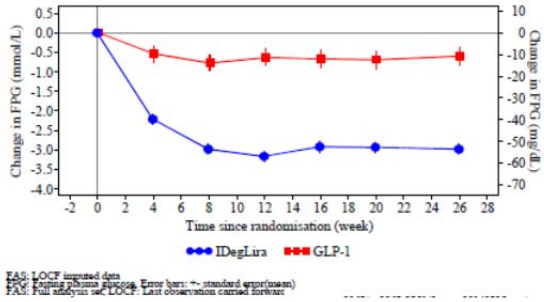
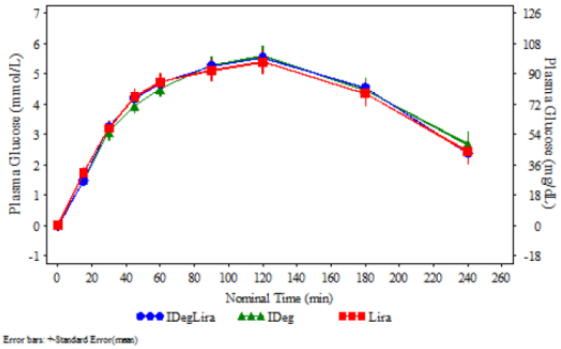
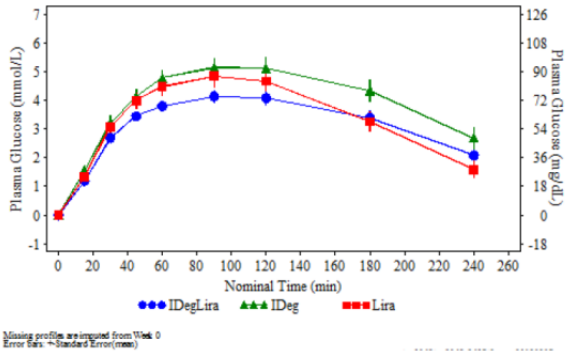


4.7 Post-prandial glucose in meal challenge study (Trial 3697)

4.7.1 Incremental mean post-prandial glucose in meal challenge at baseline (top) and after 26 weeks (bottom) (Source: Figure 3-6, 2.7.3)



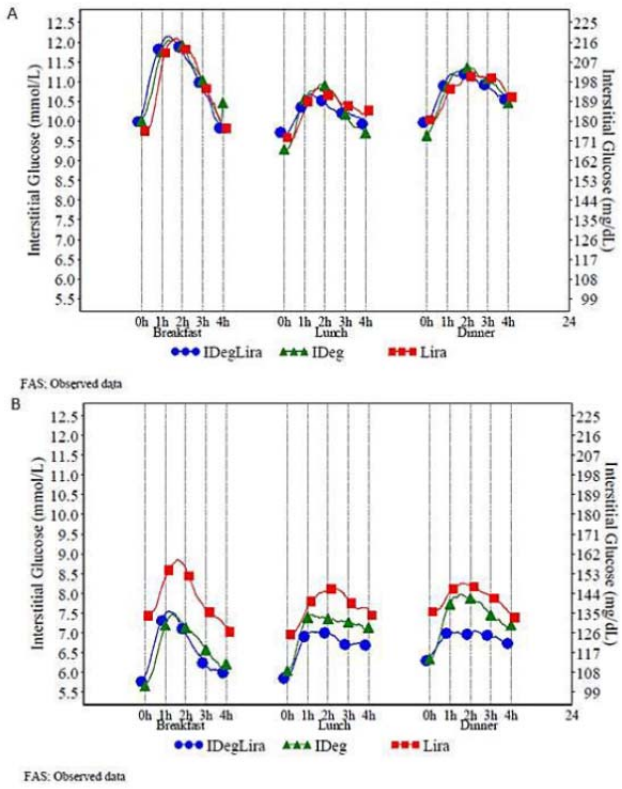


4.7.2 Post-prandial glucose AUC (Source: Table 3-25, 2.7.3)

	FAS	N	Estimate	SE	95% CI	P-value	Adjusted Significance Level
Change from Baseline in iAUC 0-4h (mmol/L)							
LSMeans							
IDegLira	131	128	-0.87	0.13			
IDeg	64	63	-0.16	0.19			
Lira	65	61	-0.78	0.19			
Treatment contrast							
IDegLira - IDeg			-0.71		[-1.17 ; -0.26]	0.0023	0.0500
IDegLira - Lira			-0.09		[-0.56 ; 0.37]	0.7001	
Change from Baseline in iAUC 0-4h (mg/dL)							
LSMeans							
IDegLira	131	128	-15.74	2.39			
IDeg	64	63	-2.93	3.40			
Lira	65	61	-14.10	3.48			
Treatment Contrast							
IDegLira - IDeg			-12.81		[-21.00 ; -4.61]	0.0023	0.0500
IDegLira - Lira			-1.64		[-10.01 ; 6.73]	0.7001	

N= Number of subjects contributing to analysis. CI= Confidence Interval
SE= Standard Error of the Mean. iAUC= Incremental area under curve
Missing data are imputed using LOCF.
Change in iAUC 0-4h Glucose is analysed using an ANCOVA method with treatment, country, baseline HbA_{1c} stratum, and previous OAD treatment as fixed effects, and baseline response as covariate. The Holm-Bonferroni method is used to calculate the Adjusted Significance Level for IDegLira-IDeg treatment contrast taking into account the analyses of body weight, insulin dose and hypoglycaemic episodes.

4.7.3 Post-prandial interstitial glucose profile (CGM) (Source: Figure 3-, 2.7.3)



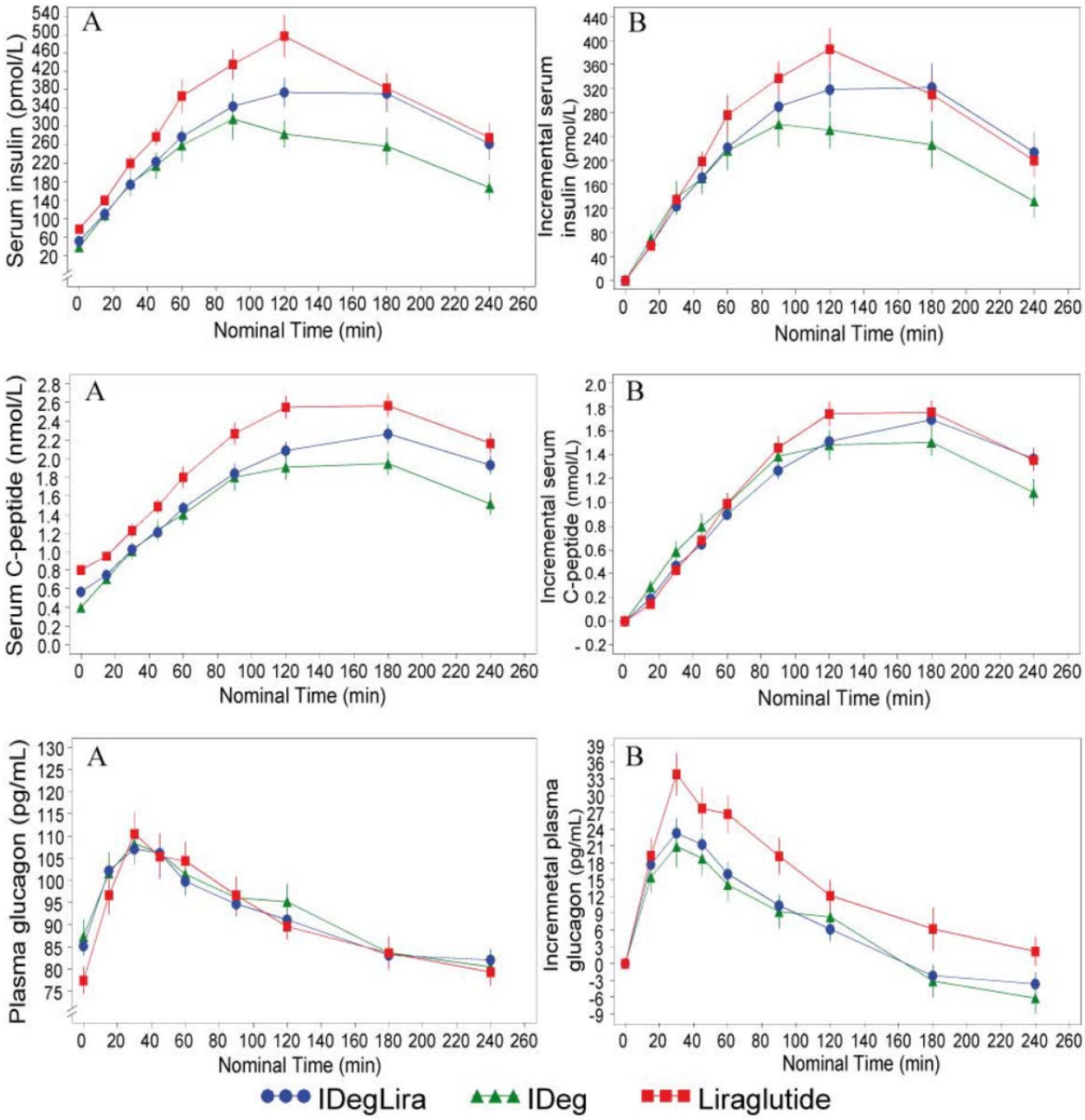
A: Baseline, B: Week 26

4.7.4 Post-prandial increment of 9-point SMPG at end of trial (Source: Table , 2.7.3)

	Treatment difference IDegLira - Basal insulin		Treatment difference IDegLira - GLP-1 RA		Treatment difference IDegLira - Placebo	
Trial (wks)	Estimate 95% CI	p-value	Estimate 95% CI	p-value	Estimate 95% CI	p-value
SMPG increment (All meals) (mmol/L)						
3697 (26)	-0.45 [-0.63; -0.28]	<0.0001	0.06 [-0.11; 0.23]	0.4835		
3697-ext (52)	-0.39 [-0.57; -0.21]	<0.0001	0.10 [-0.08; 0.27]	0.2924		
3951 (26)					0.04 [-0.28; 0.35]	0.8190
3912 (26)	-0.37 [-0.69; -0.04]	0.0260				
3952 (26)	-0.24 [-0.50; 0.03]	0.0790				
3851 (26)			0.17 [-0.14; 0.47]	0.2858		
SMPG increment (All meals) (mg/dL)						
3697 (26)	-8.20 [-11.30; -5.10]	<0.0001	1.10 [-1.99; 4.20]	0.4835		
3697-ext (52)	-6.99 [-10.20; -3.77]	<0.0001	1.72 [-1.48; 4.92]	0.2924		
3951 (26)					0.67 [-5.06; 6.39]	0.8190
3912 (26)	-6.63 [-12.47; -0.80]	0.0260				
3952 (26)	-4.29 [-9.07; 0.50]	0.0790				
3851 (26)			2.98 [-2.50; 8.46]	0.2858		

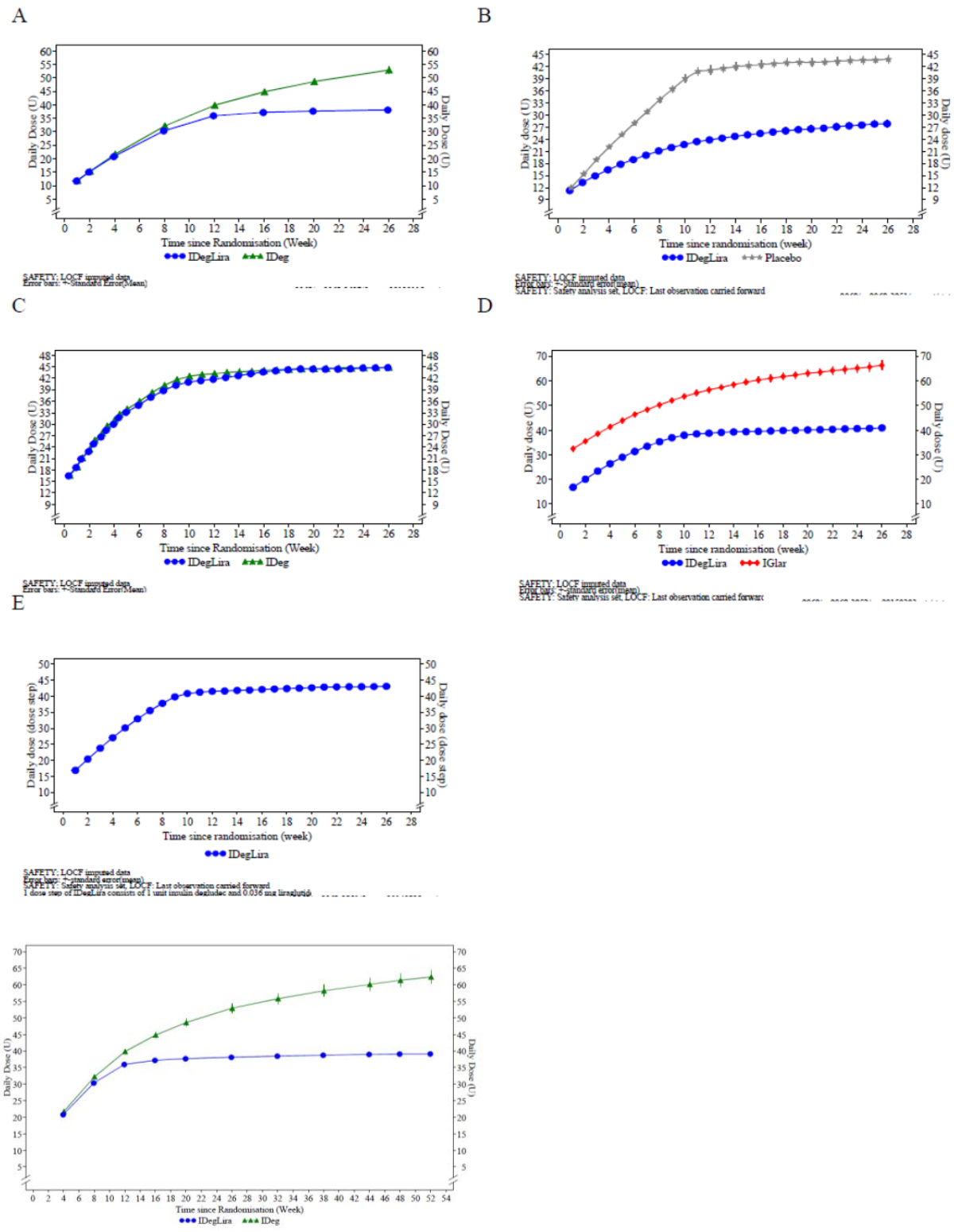
Data are based on trials NN9068-3697, NN9068-3697-ext, NN9068-3951, NN9068-3912, NN9068-3952, and NN9068-3851.
CI: confidence interval; wks: weeks; SMPG: self measured plasma glucose.
Basal insulin: IDeg (NN9068-3697, NN9068-3697-ext, NN9068-3912) and IGlar (NN9068-3952)
GLP-1 RA: Liraglutide (NN9068-3697, NN9068-3697-ext) and Liraglutide/Exenatide (NN9068-3851)
ANOVA with treatment, region/country, relevant stratification factors as fixed effects, and baseline response as covariate.
Contrast: estimated treatment difference between IDegLira and comparator
End of trial: last visit before follow-up visit
Missing data are imputed using last observation carried forward.

4.7.5 Postprandial insulin, C-peptide and glucagon after 26 weeks of treatment (Source: Figure 3-10, 2.7.2)



A) mean plot and B) incremental mean plot

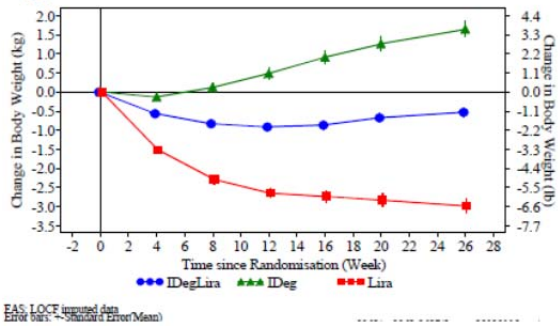
4.8 Mean daily insulin dose by treatment week (Source: Figure 3-4, 2.7.3)



(Trial 3697-ext)

4.9 Mean body weight change from baseline by treatment week (Source: Figure 3-10, 2.7.3)

A



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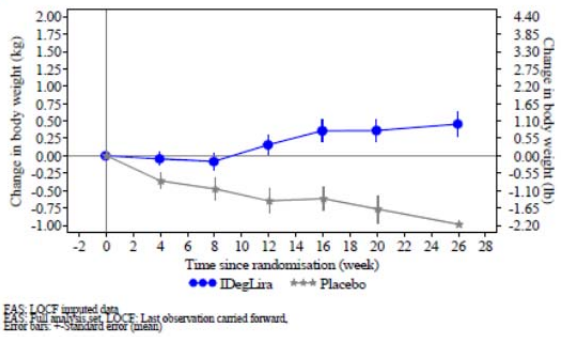

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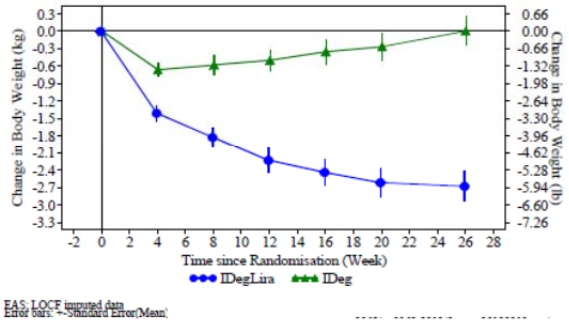

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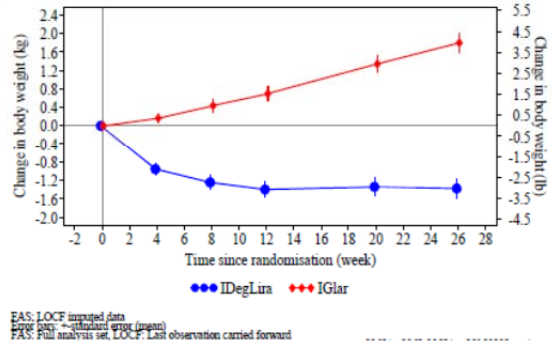

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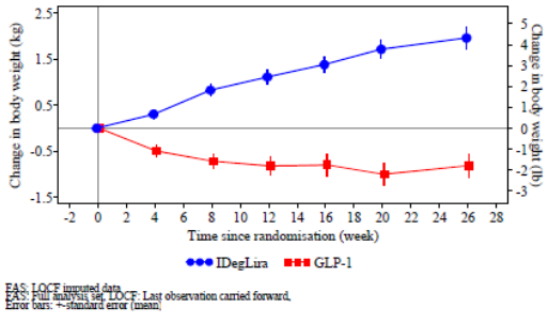


4.10 OSIS Memorandum

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/21/2015

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 208583

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)
Analytical		

Nicola M. Nicol -S

Digitally signed by Nicola M. Nicol -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola M. Nicol -S
Date: 2015.12.22 11:36:00 -05'00'

Reference ID: 3864379

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANG M CHUNG
06/17/2016

NITIN MEHROTRA
06/17/2016

MANOJ KHURANA
06/17/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208583	**SDN**	
Applicant	Novo Nordisk	**Submission Date**	September 14, 2015
Generic Name	Insulin degludec and liraglutide [rDNA origin] injection	**Brand Name**	XULTOPHY
Drug Class			
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		
Dosage Regimen	Once daily		
Dosage Form	Solution	**Route of Administration**	Subcutaneous injection
OCP Division	DCP2	**OND Division**	DMEP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Sang M Chung	Manoj Khurana (Acting)
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	11/13/2015	**74-Day Letter Date**	11/27/2015
Review Due Date	5/13/2016	**PDUFA Goal Date**	9/14/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: BE study (Trial 4026) is pivotal bridging study for Phase 3 trial and intended commercial formulation.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		

☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		2	• Trial 3871: PK/PD study following clamp procedures • Trial 3632: PK study
☑ Bioequivalence		1	• Trial 4026
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	2	Trial 3871 / Trial 3632 / Trial 4026
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☑ Healthy Subjects		1	Trial 3871: PK/PD
☑ Patients		1	Trial 3697: Phase 3 study
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		1	Trial 3697
☑ Exposure-Efficacy		1	Trial 3697
☑ Exposure-Safety		1	Trial 3697

Total Number of Studies	**In Vitro**		**In Vivo**	4
Total Number of Studies to be Reviewed				4

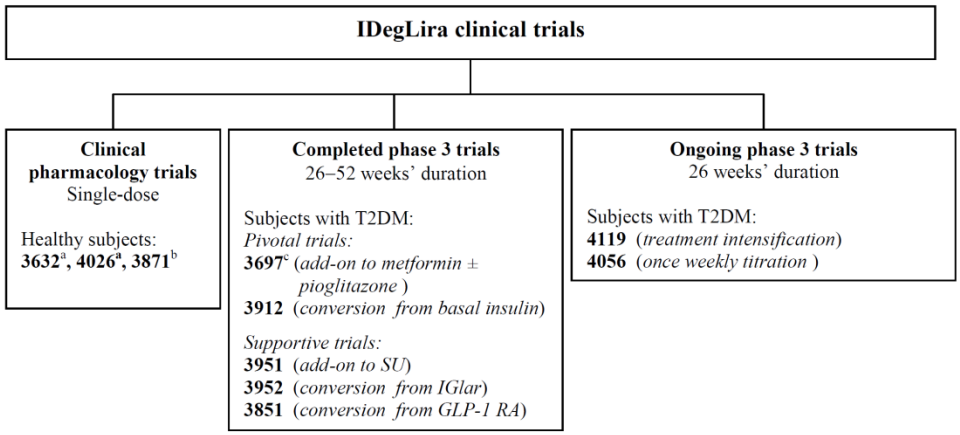
Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	Trial 4026
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	Trial 3832: DDI between insulin degludec and liraglutide
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Trial 3832
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was	☑Yes ☐No ☐N/A	

previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☑No ☐N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

The sponsor submitted this original NDA for XULTOPHY as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The sponsor provided the clinical pharmacology information primarily from 4 clinical trial results: 3 Phase 1 trials (Trial 3632, 4026 and 3871) and 1 Phase 3 trial (Trial 3697) as shown below:



[a] Trials 3632 and 4026 tested the IDeg/liraglutide ratio of 100 units/3.6 mg per mL used in phase 3 trials and intended for the market.
[b] Trial 3871 tested an alternative IDeg/liraglutide ratio of 100 units/6.0 mg per mL, which did not undergo further clinical development.
[c] The trial consisted of a 26-week main trial period followed by a 26-week extension period.

The sponsor also referred the following NDAs for individual components:

- NDA 203314 for TRESIBA® (insulin degludec) approved dated 9/25/2015
- NDA 022341 for VICTOZA® (liraglutide) approved dated 1/25/2010

The sponsor proposed a once-daily, subcutaneous injection of a fixed ratio combination of insulin degludec and liraglutide and XULTOPHY will be available as a 3 mL pre-filled, multi-dose pen containing 100 units insulin degludec and 3.6 mg liraglutide per mL.

The proposed to-be-marketed formulation was bridged to clinical formulations through the BE study (Trial 4026). Due to the pivotal nature of BE study, the inspection for the bioanalytical and clinical studies has been requested to OSIS through DMEP.

Potential clinical pharmacology review questions have been identified as follows:

- Are there adequate dose-response data supporting the proposed dosing? (Note that liraglutide starting dose for VICTOZA is 0.6 mg, and it is 0.36 mg with XULTOPHY).
- Are there adequate exposure-response data supporting the proposed dosing?
- Is the population PK analysis adequate to support the proposed labeling related to specific populations?
- Does the pivotal BE study results adequately support the bridging between Phase 3 and intended commercial formulation?

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANG M CHUNG
11/06/2015

MANOJ KHURANA
11/06/2015