CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208583Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	209583
Applicant	Novo Nordisk
Date of Submission	12 Sep 2015 Major amendment dated 24 Aug 2016
PDUFA Goal Date	12 Dec 2016 (after 3 month clock extension)
Proprietary Name / Established (USAN) names	Xultophy 100/3.6 Liraglutide injection/insulin degludec injection
Dosage forms / Strength	solution for sc injection 100 units and 3.6 mg per mL
Proposed Indication	Indicated to improve glycemic control in adults with diabetes mellitus
Recommended Action	Approval with modified indication as follows: Indicated to improve glycemic control in adults with diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily)

Cross Discipline Team Leader Review

1. Introduction

This document contains the **summary review for regulatory action** written by the Division of Metabolism and Endocrinology Products cross-discipline team leader for NDA 208583 a proposed drug/device combination product in a disposable pen injector device which contains two drugs: **liraglutide** and **insulin degludec** in a fixed-ratio solution for subcutaneous injection. This NDA is a 505(b)(1) application but not considered a new molecular entity (NME) application because the applicant, Novo Nordisk, has approved NDAs 22341 for liraglutide and 203314 for insulin degludec, respectively.

The reader is referred to the multiple discipline reviews for a more comprehensive review and detailed discussion of the development program for this NDA. This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review	Dr. Tania Condarco	21 Nov 2016
Statistical review (DBII)	Dr. Anna Kettermann	15 Jun 2016
Clinical Pharmacology (OCP) review	Drs. Chung, Khurana, and Nitin	17 Jun 2016
Nonclinical Pharmacology Toxicology review	Dr. Miyun Tsai-Turton	12 May 2016
Product Quality review	Dr. Suong Tran	9 May 2016
Division of Pediatric and Maternal Health labeling review	Dr. Carol Kasten	28 Sep 2016
DMEPA multiple reviews	Dr. Ariane Conrad	18 Apr 2016; 13 Jul 2016; 19 Aug 2016; 28 Sep 2016
Proprietary name memo	Todd Bridges	22 Sep 2016
DRISK REMS review	Dr. Amarilys Vega	14 Jul 2016; 21 Nov 2016
DEPI drug utilization review	Dr. Justin Mathew	27 Apr 2016
CDRH consult review	Dr. Sapana Patel	2 Jun 2016; 8 Sep 2016
CDRH Compliance review	Christopher Brown	5 Mar 2016
DMPP patient labeling review	Twanda Scales and Charuni Shah	29 Aug 2016
OPDP labeling review	Dr. Charuni Shah	29 Aug 2016
Clinical Inspection summary	Dr. Cara Alfaro	26 May 2016
Advisory Committee (EMDAC) meeting transcript	http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM518286.pdf	
Summary review for insulin glargine/lixisenatide NDA	Dr. Jean-Marc Guettier	21 Nov 2016

2. Background

a) Product Information

In this review insulin degludec may be abbreviated as *IDeg* and liraglutide may be abbreviated as *lira*. The proposed drug product will be abbreviated as IDegLira, and the conditionally accepted tradename for IDegLira is Xultophy 100/3.6. These terms may be used interchangeably.

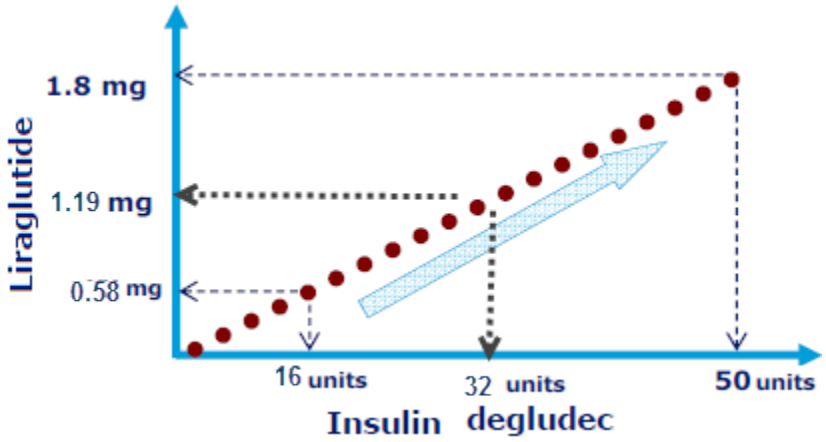
IDegLira is a fixed ratio combination product of two drugs in a disposable pen device. The two drugs are insulin degludec, a long-acting basal human insulin and liraglutide, a glucagon-like-peptide-1 receptor agonist (GLP-1).

Insulin Degludec
IDeg was approved in 2015 under the trade name Tresiba. IDeg is a long-acting insulin analog that is indicated to improve glycemic control in adults with diabetes mellitus. IDeg is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification. IDeg, like all insulins, regulates glucose metabolism by stimulating peripheral glucose uptake and by inhibiting hepatic glucose production, lipolysis and proteolysis. IDeg is to be used as a basal insulin with once daily administration. The half-life of insulin degludec, at steady state, is 25 hours independent of dose. As with all basal insulin products, the dose of IDeg is individualized based on the subjects metabolic needs, blood glucose monitoring results and glycemic goal.

Liraglutide
Liraglutide injection was approved in 2010 under the trade name Victoza. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Liraglutide is 97% homologous to native human GLP-1. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The mechanism of action for glucose lowering consists of glucose-dependent insulin secretion from pancreatic beta cells, decrease in glucagon concentration and a delay in gastric emptying. The half-life of liraglutide is 13 hours after subcutaneous injection. For all patients, liraglutide is initiated at 0.6 mg per day for one week; titration of liraglutide can continue by 0.6 mg increments to a maximum dose of 1.8 mg per day. In 2014 liraglutide injection at a higher dose (3.0 mg per day) was approved for weight management (Tradename Saxenda, NDA 206321).

IDegLira
The liraglutide and the IDeg drug substances used for the IDegLira formulation are identical to the drug substances used for the commercial Victoza and Tresiba drug products, respectively. IDegLira is packaged in a 3 mL cartridge that is assembled into a pre-filled disposable pen device using the PDS290 platform**.** The pre-filled pen contains an IDeg/liraglutide ratio of 100 units/3.6 mg per mL. Note this is a fixed ratio in that as the dose of IDegLira increases or

decreases, the ratio between the doses of the two components does not change. A consequence of this fixed ratio formulation is that one drug cannot be titrated without titration of the other drug. To the Division's knowledge, this is unique among therapeutic drug products.



Source: 2.5 Clinical overview; Adapted from Figure 1-1, page 10; modified by Dr. Condarco to show the respective doses of liraglutide for 32, and 16 units of degludec.

b) Regulatory History

U.S. regulatory history for the sought indication

Advice to the Applicant regarding the development of IDegLira was provided by The Division of Metabolism and Endocrinology Products (DMEP) during pre-submission meetings. Guidance on the overall aim of the development program was to provide Phase 3 trial data showing that both drugs contribute to the claimed effect, i.e. glycemic control, to satisfy the Agency's policy regarding fixed combination drug products as defined in Section 300.50 of Title 21 of the Code of Federal Regulations (CFR) (21 CFR 300.50) which states:

"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.

FDA recommended that the primary objective of the pivotal trial(s) should be to demonstrate superiority on HbA1c for the combination (IDegLira) over each of the individual components in order to satisfy the 'combination drug rule' as described previously. The Applicant was concerned that it would be difficult to show superiority of IDegLira to insulin degludec alone since the upper limit of the daily insulin dose in IDegLira is 50 units whereas insulin degludec alone has no upper dose limit. FDA agreed that for the purposes of addressing the combination rule it would be acceptable to limit the maximal degludec dose to 50 units, i.e. impose a dose cap. By limiting the degludec dose, the superiority of IDegLira to both individual drug constituents could be tested. The Agency noted however that instituting an insulin degludec dose limit in a clinical trial would not be reflective of a real-world scenario,

in which prescribers would be expected to titrate insulin to glycemic goals and that the clinical relevance of the findings from such a study would be limited.

FDA also expressed concern that subjects receiving less than the minimum established clinically effective dose (i.e., <1.2 mg) of liraglutide would not be expected to derive any clinical benefit from the liraglutide in the combination but would be potentially exposed to risks associated with liraglutide use. It was clear at the time that the proposed pivotal trial was designed to mostly assess the average IDeg/Lira glucose lowering effect of the drug and could not robustly address this issue.

The NDA for IDegLira was submitted 12 Sep 2015 so the original PDUFA goal date was 12 Sep 2016. Because insulin degludec was not yet approved at the time of submission of the IDegLira NDA, the submission was considered an NME with a 12-month review clock. (Note insulin degludec/Tresiba was approved in 25 Sep 2015). A Major Amendment to the IDegLira NDA was received by the Agency on 24 Aug 2016. The review clock was extended by 3 months for a revised PDUFA goal date of 12 Dec 2016.

Pediatrics

The Applicant's iPSP (initial pediatric study plan) was agreed on 28 August 2015.

Regulatory status outside the U.S.

As of 31 Mar 2015, IDegLira was approved in the EU and Switzerland and launched in Switzerland and the United Kingdom.

3. CMC/Device

c) CMC

The Office of New Drug Products (ONDP) provided a Quality summary review with Dr. Suong Tran as Application Technical Lead. The overall Quality review recommendation is Approval including the facility review/manufacturing inspection recommendation. I agree with the assessment and conclusions of the ONDP review.

This section summarizes key aspects of the drug substance/drug product.

Drug Substance

Insulin degludec (IDeg)

The IDeg drug substance has been reviewed previously under NDA 203314. In brief, IDeg is an insulin analog produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae followed by chemical modification. IDeg differs from human

insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C-16 fatty acid has been attached.

Liraglutide (lira)

The CMC information for the drug substance lira is referred to NDA 22341. Lira is an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Lira is made by attaching a C-16 fatty acid with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor.

Drug Product

The drug product is a solution for SC injection and a fixed ratio combination drug consisting of 100 Units IDeg and 3.6 mg lira per mL. It is packaged in a 3-mL cartridge, which is then assembled in a disposable single-user multiple-dose pen injector for commercial distribution. The total pen content is 300 Units IDeg and 10.8 mg lira. The pen-injector provides up to 50 unit[1] in one injection where, 1 unit contains 1 unit of IDeg and 0.036 mg of lira.

Inactive ingredients are (per mL): glycerol 19.7 mg, phenol 5.70 mg, zinc 55 mcg, and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH (to 8.15). There is an overage (b) (4) due to expected loss during manufacture. All the excipients meet compendial requirements.

According to Dr. Tran, the drug product manufacturing process is standard for this type of dosage form and includes: (b) (4)

Cartridges are assembled into pen injectors, packaged, and labelled. Further, the drug product specification includes critical quality attributes standard for this type of drug substance (protein/peptide) and dosage form (injectable solution), and these attributes are the same as in NDAs 22341 and 203314 (actual test methods and acceptance criteria may vary to be product-specific).

Changes in manufacturing process during development have been introduced (b) (4) The changes in composition and manufacturing process introduced after phase 3 clinical trials have been evaluated and justified with respect to comparability. Bioequivalence (BE) between the formulation used for phase 3 clinical trials and the formulation intended for the market has been demonstrated. (There is a difference in the (b) (4) phase 3 formulation (b) (4) and the commercial formulation (b) (4) Comparability of the 2 formulations was confirmed via a BE study, a comparison of degradation products, and stability profiles).

[1] The unit of measure for IDegLira recommended for approval is 'units'. In the clinical development program for IDegLira the unit of measure was called 'dose steps'. Therefore, some of the primary reviews use this terminology.

The robustness of the final manufacturing process has been verified during process justification and the reproducibility has been demonstrated by manufacture of three consecutive process performance qualification batches.

Compared to the degradants in the products of NDAs 22341 and 203314, there is no new degradant in the new drug product. (b) (4)

Container closure system: The primary (product-contact) components consist of a USP type 1 glass cartridge (3-mL), with a (b) (4) rubber disc on one end and a (b) (4) rubber plunger on the other end. Extractable and leachable data are reported in the NDA with supporting safety information.

Expiration Date & Storage Conditions: 24 months at 2-8 °C, with an in-use storage for up to 21 days at room temperature or under refrigeration, based on real-time stability data for the primary batches with the commercial formulation.

d) Device

CDRH Device Review

Consultative review of the device constituent (the prefilled pen injector) was provided by the Center for Devices and Radiological Health (CDRH). Overall review of the device constituent by Dr. Sapana Patel recommended approval, and concluded that the Applicant has designed a reasonably safe and effective pen injector delivery system based on the PDS 290 pen-injector system currently used for the FlexTouch. The review assessed the design and development of the device constituent specifications, engineering risk analysis, performance studies and biocompatibility of the device constituent. Contributing reviewers included:

Robert Meyer- Engineering review of pen-injector (including dose accuracy and device malfunction)
Sarah Mollo Ph.D-Biocompatibility review of pen-injector
Patricia Beaston Ph.D. M.D. - Clinical consult

Device Description:
The device constituent PDS290 IDegLira pen-injector is similar to the currently marketed prefilled disposable insulin delivery device Flex Touch. PDS290 IDegLira pen-injector is developed for the injection of the combination product insulin degludec/liraglutide, whereas FlexTouch was developed for the injection of insulin. PDS290 IDegLira pen-injector is a pen-shaped, prefilled device containing a 3 ml cartridge with drug. Therefore the drug is not in contact with the device. Both pens are based on the same PDS290 pen-injector platform design. The design similarities are that both are pen-shaped injectors with prefilled cartridges, where the intended dose is given by turning the dose selector and pressing the button to deliver the intended dose.

The initial device proposed by the Applicant appeared as below (b) (4)

(b) (4)

During the review cycle, the Applicant was advised to change the pen dial because the Agency was considering a revised indication where the recommended starting dose would be 16 units, and because the ability to dial the IDegLira pen device to potentially sub-therapeutic doses of liraglutide, was a concern voiced at the Advisory Committee meeting. As such, DMEP recommended to the Applicant to modify the IDegLira pen to show only the priming dose and doses that were tested in the Phase 3 program.

DMEP sent the following Information Request to the Applicant: *In light of the revised indication, the recommended starting dose should be 16 units. It would be acceptable to redesign the Pen to display units starting at 10 so that clinical discretion can be used in the case of illness or other conditions necessitating a dose reduction.* (b) (4)

The Applicant responded that the scale drum component (pen dial) of the pen will be updated as requested by the Agency to display units starting at 10 so that clinical discretion can be used in the case of illness or other conditions necessitating a dose reduction. The Applicant will configure the pen dial in a manner that will provide for administration of volumes necessary to prime the pen, i.e. a priming symbol (▪▪—), consistent with the FDA approved Saxenda pen-injector which shares the same PDS290 platform with the IDegLira pen.

The revised pen dial will appear as follows:

The CDRH consultants reviewed the proposed change to the pen dial and found it acceptable.

With regard to dose accuracy CDRH included one comment to CDER in their consult report as follows: *The Sponsor has provided dose accuracy results which demonstrate the device can deliver the medication after device conditioning is applied, per specifications which are compliant with ISO 11608-1:2012 Needle-based injection systems for medical use – Requirements and test methods. The device is capable of delivering doses* (b) (4) *to 50 increments.* (b) (4) *The specifications are* (b) (4) *The Sponsor has not provided justification as to why the specification tolerances are acceptable other then they meet the standard. We defer the acceptability of the noted dose specifications to CDER.* I also note that the question of dose accuracy was addressed by Dr. Beaston in the consult report who stated that although the ISO standard allows for 100 % dose error at 1 increment (1 unit of insulin/.036 mg liraglutide) this error would be unlikely to result in harm to the patient as the recommended starting dose for IDegLira is 10 increments (10 units of insulin/.036 mg liraglutide). I agree with Dr. Beaston regarding the acceptability of the potential dosing error at the lower range.

CDRH Compliance Review

Final recommendation of approval from the Office of Compliance at CDRH was documented 3 Mar 2016. The initial submission did not contain sufficient information to make an approval determination. A response to information request received by the Agency on 26 Jan and 3 Feb 2016 adequately addressed the deficiencies. No facilities inspections were recommended.

4. Nonclinical Pharmacology/Toxicology

Dr. Miyun Tsai-Turton recommended approval of IDegLira to improve glycemic control in adults with type 2 diabetes mellitus. Please see her review dated 12 May 2016. I agree with her assessment and conclusions.

As the nonclinical profile of both drug components of IDegLira have been previously characterized/reviewed, the IDegLira nonclinical development program included pivotal

combination toxicity studies of up to 90 days duration in a single relevant species (Wistar rats) and local tolerance assessment in rabbits and pigs. Included in the NDA submission were one primary pharmacology study in rats, one single dose pharmacokinetic study in pigs, a series of repeat dose toxicity studies in rats which revealed no safety concern for humans, and local tolerance studies in pigs and rabbits which showed only mild inflammatory reactions.

Primary pharmacology study
In a primary pharmacology study in male Wistar rats, dose-dependent effects of IDegLira after a single dose were observed for all parameters measured, including decreases in blood glucose, food and water consumption and body weight that were consistent with those expected based on the established pharmacodynamic (PD) effects of IDeg and liraglutide as individual components.

Pharmacokinetic study
In single dose pharmacokinetic (PK) studies in pigs the PK of IDeg was shown to be similar when dosed as part of IDegLira or as IDeg alone. The PK of liraglutide when dosed as part of IDegLira showed a tendency towards lower overall Cmax compared to when dosed as liraglutide alone. However, the total dose-normalized exposure (AUC/Dose) for liraglutide as part of IDegLira was similar to that of liraglutide alone.

(b) (4)

[redacted]

Repeat dose toxicity studies in rats
In tox studies, increases in exposures of both IDeg and liraglutide were predictable, dose-proportional and sex independent. Limited systemic accumulation (<2-fold) was observed for the individual components upon repeated administration of IDegLira, which is consistent with the expected steady state concentrations considering the established half-lives of elimination and the dosing interval for the individual components.

Four- and 13-week rat toxicity studies (with local tolerance assessments) were conducted with IDegLira administered via the SC route. In the 13-week study, with the 600/960 IDeg/Lira nmol/mL formulation (the same IDeg/liraglutide ratio as the formulation for marketing), no adverse effects were observed at 20/32 nmol/kg/day, which represents 2.1-fold (for IDeg) and 3.3-fold (for liraglutide) the maximum clinical dose of 50 IU/1.8 mg IDegLira]. Dose-dependent reductions in body weight gain were observed across the dose range. No adverse drug-related histopathology findings were observed. Findings observed in the 13-week toxicity study were consistent with the known pharmacological effects of insulin and/or GLP-1 analogues. No antibodies were observed towards liraglutide, whereas antibodies against IDeg were observed at a similar frequency to what was found detected in previous IDeg studies.

The 4-week study was conducted with a different formulation than the to-be-marketed formulation. The maximum tolerated dose was exceeded, leading to premature sacrifices and dose reduction due to hypoglycemia. Histopathological findings were observed previously with insulin degludec and related to hypoglycemia, and thus, not discussed further in this review. For further information, please see Dr. Tsai-Turton's review.

Local tolerance studies in pigs and rabbits
In pigs, the histopathological changes induced by the to-be-marketed formulation of IDeg/Lira and the vehicle at the site of injection were considered to be mild, only marginally above the minimal reactions induced by saline, and therefore considered acceptable for subcutaneous administration.

The potential for local tissue reactions after single unintended intramuscular or intravenous administration of IDegLira was evaluated in rabbits. Local reactions were mild (erythema) and comparable to that of vehicle and not considered to pose any concerns for the clinical use of the product. No drug related macroscopic and microscopic changes were noted.

Genetic Toxicology

In accordance with ICH M3 (R2) no genotoxicity studies were performed with IDegLira. The genotoxicity assessments of IDeg and liraglutide were performed under IDeg NDA 203314 and liraglutide NDA 22341. In a standard genotoxicity battery of *in vitro* and *in vivo* studies, liraglutide demonstrated no genotoxic potential. Genotoxicity studies were not performed with IDeg as it is considered a biotechnology-derived product without mutagenic potential.

Carcinogenicity

No carcinogenicity studies were conducted for the IDegLira fixed ratio combination.
For IDeg, the nonclinical in vitro and in vivo studies on cell proliferation and neoplasm formation showed no adverse findings and the carcinogenic potential of IDeg was not greater than that of human insulin. For liraglutide, the carcinogenic potential was assessed in 104-week studies in mice and rats. Liraglutide caused local, injection site related fibrosarcomas in male mice at the highest dose and thyroid C-cell tumors in rodents. Studies in mice also demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells.

Reproductive toxicology

No development and reproductive toxicity studies have been conducted for IDegLira. With IDeg, minor fetal and infant effects were observed which were secondary to the lowered maternal blood glucose levels. The animal reproduction studies did not reveal any difference between IDeg and human insulin regarding embryotoxicity and teratogenicity. For liraglutide,

Dr. Tsai-Turton states that 'Liraglutide has been shown to be teratogenic in rats and has been shown to cause reduced growth and increased total major abnormalities in rabbits.' However, upon discussion with DPMH it was determined that the term teratogenic in the risk summary statement in Section 8.1 (Use in Specific Populations – Pregnancy) of the Prescribing Information may not be the most appropriate term to describe the findings observed in pregnant animals exposed to liraglutide. The signal for serious liraglutide-related embryo-fetal malformations was considered equivocal, and the remainder of drug-related findings were inconsistent with the common clinical definition of teratogenic (i.e., causing major malformations/birth defects in the embryo or fetus).

Impurities and leachables

All IDegLira impurities were within the approved limits established for liraglutide 6.0 mg/mL (Victoza) and IDeg 100 U/mL (Tresiba). Five leachables (b) (4) were identified and quantified in a long-term leachable study with IDegLira. The container closure system is considered suitable for the 100 U/mL insulin degludec and 3.6 mg/mL liraglutide drug product (IDegLira 100 U/3.6 mg per mL) with no safety concerns related to the levels of leachables observed, based on Permissible Daily Exposure levels established in ICHQ3C or the qualification threshold established by the Product Quality Research Institute.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology review team has recommended approval of IDegLira. Please see review dated 17 Jun 2016. I agree with the assessment and conclusions. No postmarketing studies are recommended.

This section summarizes key aspects of the clinical pharmacology information. The body of data includes results from 3 Phase 1 trials in healthy volunteers, as well as data generated from the 5 Phase 3 trials submitted to support safety and effectiveness. In addition, coadministration of liraglutide as add on to basal insulin has been evaluated as an Efficacy Supplement in the single entity liraglutide NDA.

The applicant evaluated pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of IDeg and lira in the fixed-ration combination (FRC) compared to those after administration of IDeg alone, lira alone or co-administration of IDeg and lira in a single dose randomized, double-blind, double-dummy, four-period crossover pharmacokinetic/pharmacodynamic euglycemic clamp study (Trial 3632), which compared the systemic exposure of insulin degludec and liraglutide following administration of the fixed-ratio combination (FRC) (Insulin degludec dose = 17 Units and liraglutide dose = 0.6 mg) to that of insulin degludec (17 Units) or liraglutide (0.6 mg) administered alone, or simultaneous administration of insulin degludec (17 Units) and liraglutide (0.6 mg) in healthy volunteers.

The OCP reviewers comment that interpretation of combination PD effect is complicated by the fact that in subjects capable of secreting endogenous insulin (such as the healthy volunteers

enrolled in the phase 1 studies) lira should cause such secretion in a glucose clamp procedure (i.e. lira should stimulate endogenous insulin secretion in the presence of glucose). However, the clamp procedure should be able to provide insight into the interference from exogenous insulin in PD effect of lira, or in other words, whether IDeg and lira exert their PD effects, in an independent manner. The results of the Clinical Pharmacology studies are discussed below.

Pharmacokinetics

IDeg exposure following administration via the FRC was not significantly different from that of IDeg alone (geometric mean ratios (GMR) for AUC and Cmax were 1.03 and 1.12, respectively). The maximum concentration (Cmax) of lira following administration *via* the FRC was 23% lower (90% CI; 0.68, 0.87) without significant change in the overall exposure (measured by area under the concentration-time curve; AUC 90% CI; 0.82, 0.96) when compared to those of lira alone.

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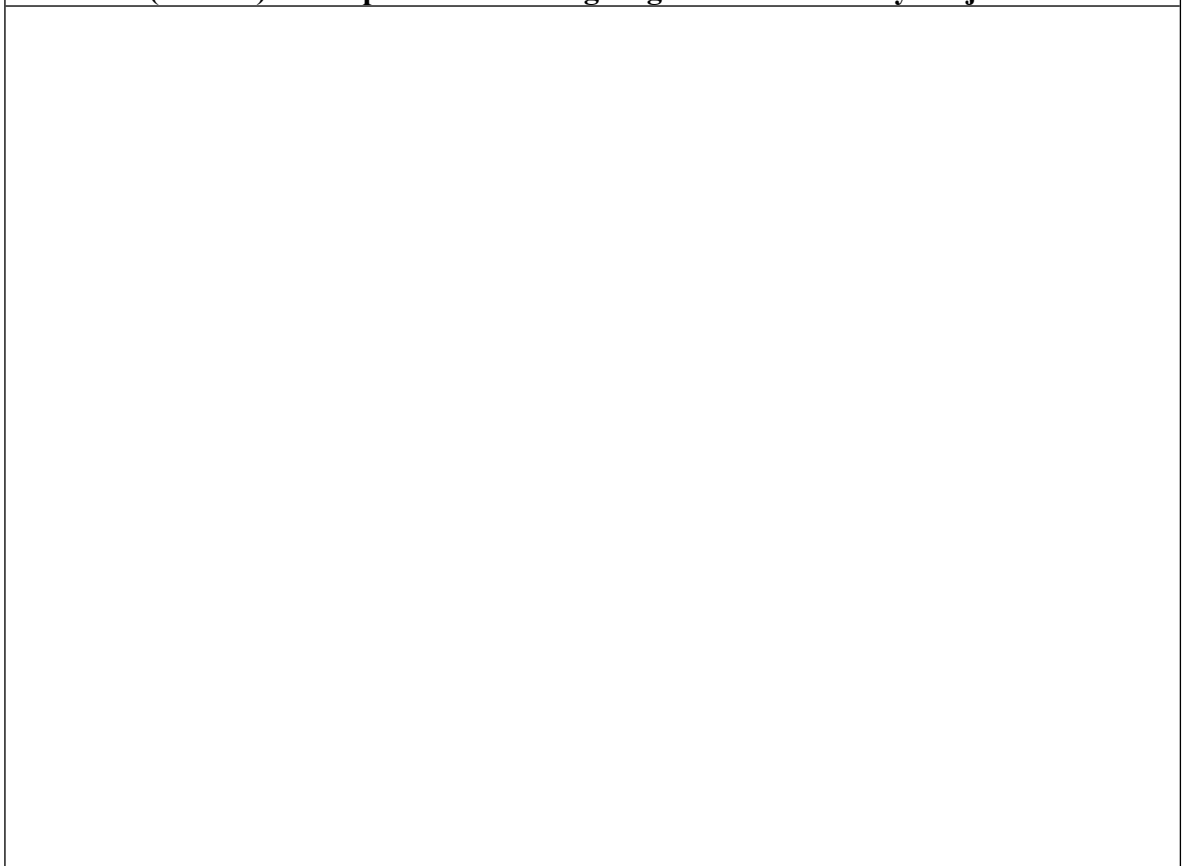
Insulin degludec or liraglutide concentration (top), GIR (middle) and blood glucose (bottom) - time profiles following single doses in healthy subjects



- 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

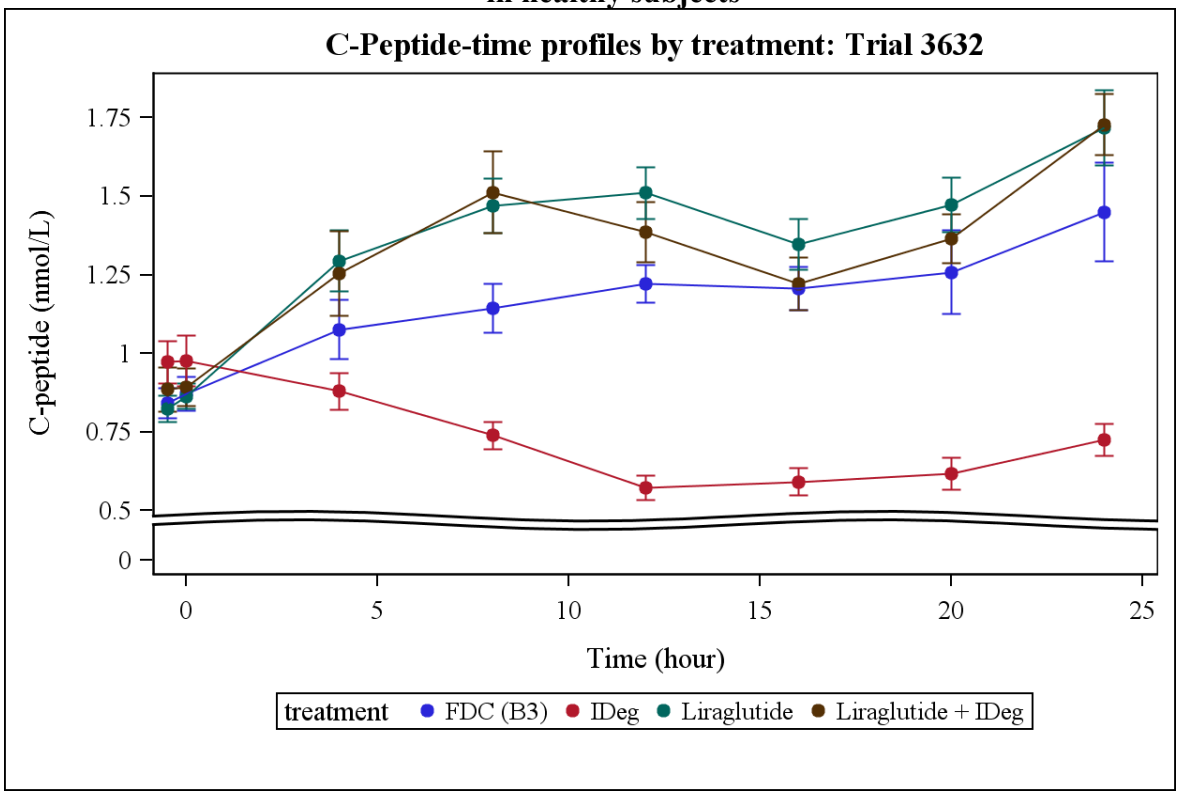
Source: Clinical Pharmacology Review

In the population PK analyses using plasma concentration data from Phase 3 studies, exposure of both IDeg and lira was proportional to clinically relevant FRC doses, and there was no unique covariate for IDeg or lira exposure with the FRC other than body weight, which is already a known covariate affecting PK (and PD) of the individual drugs.

Pharmacodynamics

The applicant used the glucose infusion rate (GIR) data from euglycemic clamp to characterize the effect of IDeg alone, lira alone and IDeg plus lira combination. C-peptide levels (representing endogenous insulin secretion) decreased from baseline following insulin degludec administration. This decline in C-peptide following insulin administration is a usual observation in the euglycemic clamp studies. For lira alone and the FRC treatments, the C-peptide was increased from the baseline and along with GIR, did not return to baseline by the end of clamp procedure suggesting that there is net positive stimulation of endogenous insulin release by liraglutide in the presence of inhibition action by insulin degludec after FRC administration.

C-peptide versus time profiles following a single dose of FRC (FDC(B3)), liraglutide alone, insulin degludec alone, and insulin degludec plus liraglutide (separate injections) in healthy subjects



Source: Clinical Pharmacology Review

The OCP reviewers concluded that the C-peptide data from meal challenge evaluation in a sub-set of patients from Phase 3 trial (Trial 3697) was not sufficiently informative to

determine the PD effect of lira when administered with IDeg, 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 AUC0-4h = 1.14 (95% CI; 1.03-1.26)). Although the results are consistent with the PK/PD results, the clinical relevance of C-peptide and insulin data, and the magnitude of post-prandial glucose (PPG) change towards HbA1c reduction observed with different treatments (e.g. different titration regimens, glucose lowering over time) cannot be fully understood.

The dose-efficacy 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 ED50 and Emax (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 the same dose-response relationship of lira when administered in combination with IDeg in the FRC, however, is not scientifically justified, and the same dose-response cannot be assumed for the dose range of the liraglutide component when insulin degludec and liraglutide are administered as the fixed ratio combination. This has implications for conclusions regarding 'contribution to claimed effect' of lira at lower doses that may be administered to some insulin sensitive patients using IDegLira in the care setting.

Data Quality/Integrity

The OCP review also contains the recommendation from OSIS (Office of Study Integrity and Surveillance) that the data from the submitted NDA should be accepted without on-site inspection.

6. Clinical Microbiology

Please see section 3 (CMC). There were no Clinical Microbiology deficiencies that would preclude approval.

7. Clinical/Statistical- Efficacy

Dr. Condarco (Clinical) and Anna Kettermann (Statistical) recommend approval of IDegLira. The Applicant submitted 5 new phase 3 trials conducted in patients with type 2 diabetes mellitus (T2DM) as evidence of efficacy: 2 pivotal trials (3697 and 3912) and 3 other supportive studies that evaluated IDegLira in other T2DM populations (3851, 3951, and 3952).

Phase 3 trial design overview
The designs of the five trials are summarized below.

Summary of trial design: phase 3 studies					
Trial Number	**3697 (pivotal)**	**3912 (pivotal)**	**3851**	**3951**	**3952**
Objective	IDegLira vs. IDeg vs. lira (3 arm factorial study)	IDegLira vs. IDeg with dose cap	IDegLira vs. GLP-1 analog alone	IDegLira vs. placebo	IDegLira vs. insulin glargine
HbA1c entry criteria	7-10%	7.5-10%	7-9%	7-9%	7-10%
Blinding	Open	Blind	Open	Blind	Open
Control	Active (IDeg and lira)	Active (IDeg)	Active (exenatide and lira)	Placebo	Active (glargine)
Duration	26 weeks + **26 week extension**	26 weeks	26 weeks	26 weeks	26 weeks
Background therapy	Met ± Pio	Met	Met ± SU ± pio	Met ± SU	Met
Randomization ratio	2:1:1 (IDegLira:IDeg:lira)	1:1	2:1	2:1	1:1
Population	Add on to OAD **Insulin naive**	Previous insulin users	Previous GLP1 analog users	Add on to OAD **Insulin naive**	Previous insulin users
Hypothesis test	NI to IDeg and Superiority to lira	Superiority	Superiority	Superiority	NI

Met= metformin ≥1500 mg/day or maximum tolerated dose, Pio=pioglitazone ≥ 30 mg/day, SU= sulfonylurea at (1/2 max of approved dose), IDegLira= insulin degludec and liraglutide, lira=liraglutide, IDeg=insulin degludec, OADs=oral antidiabetic drugs, FAS=Full analysis set, NI=non-inferiority
Source: FDA created table

IDegLira was evaluated in adult subjects with established type 2 diabetes mellitus. Trials had HbA1c entry criteria ranging from 7-10%. Detailed study-specific inclusion and exclusion criteria are discussed in Dr. Condarco's Clinical Review. Inclusion and exclusion criteria were on par with what is typically observed for diabetes phase 3 trials and do not affect interpretation of trial results.

All trials were randomized controlled and had a parallel-group design. Three trials were open-labeled (3697, 3851, and 3952); two trials, one pivotal trial, (3912) and a placebo controlled trial, (3951) were double-blinded trials in which visually identical cartons and pen devices for investigational drug products were used.

The comparators varied. The pivotal trial 3697 was a factorial 3-arm study in which IDeg with no dose cap was compared to both individual components alone. Trial 3912 had the comparator IDeg capped at a maximum dose of 50 units per day, trial 3951 was a placebo-controlled trial, 3851 compared IDegLira to a GLP-1 analog, and trial 3952 compared IDegLira to insulin glargine.

The randomization ratio varied in the IDegLira program. Two trials had 1:1 randomization (3912 and 3952) of IDegLira to comparator. The remaining trials had 2:1 randomization ratio for IDegLira: to comparator with the exception of trial 3697, which had 3 arms and a ratio of 2:1:1 of IDegLira: IDeg: liraglutide.

All five trials were 26 weeks in duration, with an additional 26-week controlled extension for trial 3697.

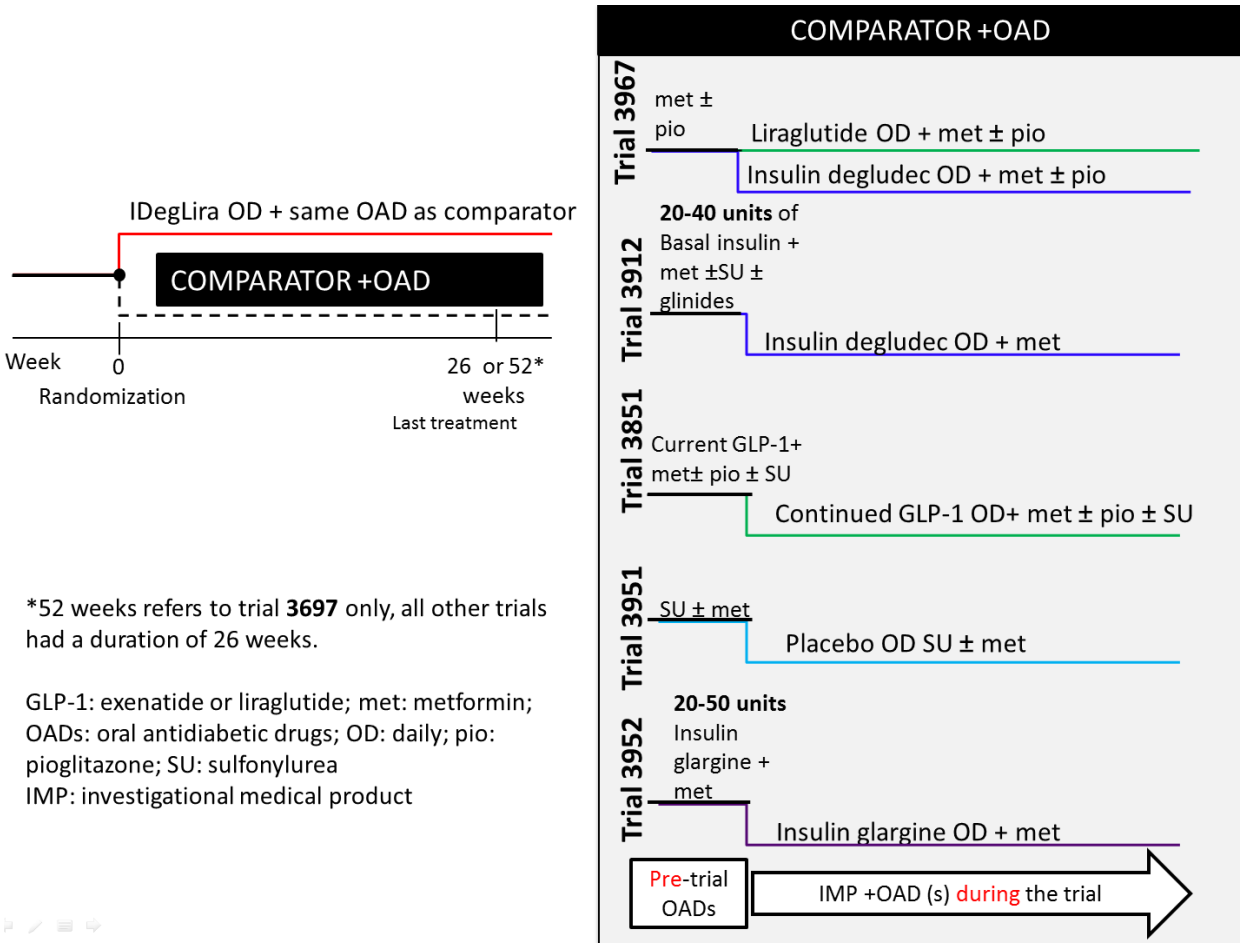
The IDegLira program evaluated the product under differing treatment scenarios, i.e. different background therapies. Two trials were conversion from pre-trial basal insulin (3912 and 3952) -thus *non*-insulin naïve; two trials were add on to OADs, other than metformin (3697 and 3951) in insulin naïve subjects, and one trial was a conversion from GLP-1 analog (3851).

The phase 3 trials had similar withdrawal criteria:

- The subject could withdraw at any time without explanation
- The subject could be withdrawn at the discretion of the investigator due to safety concerns or if judged non-compliant with trial procedures.
- Pregnancy or intention of becoming pregnant
- If the investigator suspected acute pancreatitis.
- If the fasting SMPG values taken on three consecutive days or if any of the FPG samples analyzed by the central laboratory exceeded:

Baseline - week 6: >270 mg/dL
Week 7- week 12: >240 mg/dL
Week 13 - week 26 (to week 52 in trial 3697): >200 mg/dl

Schematic of IDegLira phase 3 studies



Source: Figure created by Dr. Condarco (Clinical Reviewer)

Dosing and titration of investigational drugs

Starting Dose

The starting dose of IDegLira varied in each trial reflecting the population enrolled.

Summary of dosing procedures: phase 3 studies					
	3697 (pivotal)	**3912 (pivotal)**	**3851**	**3951**	**3952**
Objective	IDegLira vs. IDeg vs. lira (3 arm factorial study)	IDegLira vs. IDeg with dose cap	IDegLira vs. GLP-1 analog alone	IDegLira vs. placebo	IDegLira vs. insulin glargine
Starting dose **IDegLira (insulin units) [liraglutide]**	10 [0.36 mg lira]	16 [0.6 mg lira]	16 [0.6 mg lira]	10 [0.36 mg lira]	16 [0.6 mg lira]
Comparator Insulin	10 units	16 units			Same as pretrial
Comparator GLP-1	0.6 mg		Same as pre-trial		

Maximum dose					
IDegLira	50 dose steps	50 dose steps	50 dose steps	50 dose steps	50 dose steps
Comparator insulin	No limit	**50 units**			No limit
Comparator GLP-1	1.8 mg lira		Kept at pretrial dose		

Source: FDA created table

In 3697 and 3951 (insulin naïve subjects) the starting dose of IDegLira was 10 dose steps (10 units of IDeg and 0.36 mg of liraglutide). In non-insulin naïve subjects (3912 and 3952) and previous GLP-1 analog users (3851), the starting dose of IDegLira was 16 dose steps (16 units of IDeg and 0.6 mg of liraglutide).

A notable difference between the two trials that evaluated patients who had been using insulin pre-trial (3912 and 3952) is that in trial 3912 the comparator (IDeg) was started at a lower dose than the pre-trial dose but at the same dose as IDegLira insulin dose; while in trial 3952 the starting dose of the comparator (glargine) remained equal to the pre-trial daily dose (i.e., a unit to unit switch).

Maximum dose

The maximum dose (**Error! Reference source not found.**) for all IDegLira treated subjects was 50 dose steps which is the maximum dose that can be delivered by the prefilled pen device. The pivotal trial 3912 which was intended to demonstrate superiority of IDegLira over IDeg alone had a dose cap of 50 units of IDeg. In other trials, IDeg was to be titrated to glycemic goals.

Titration schedule and algorithm for IDegLira and comparator insulin

For all trials, the adjustment of IDegLira and comparator insulin (or placebo) was performed twice weekly. Adjustments were based on the mean of the 3 preceding fasting SMPG (self-monitored plasma glucose) values obtained prior to dosing. In all studies, if SMPG value was above the pre-specified goal, a dose step upward of 2 was recommended, and if SMPG value was below the pre-specified goal, a dose step downward of 2 was recommended. Of note, the same titration targets were maintained for the 26 week extension period of trial 3697.

The fasting SMPG goals for IDegLira were the same for 3 trials (3697, 3912, and 3851), with a goal of fasting SMPG 72-90 mg/dL. Trial 3952 had a goal of fasting SMPG 71-90 mg/dL. Trial 3951 had a goal of fasting SMPG 72-108 mg/dL.

Titration algorithm for IDegLira, comparator insulin, and placebo	
SMPG (mg/dL)	Dose change (dose units)
Below goal	-2
Goal [a]	0

Above goal	+2
[a] 72-90 mg/dL- goal for 3697, 3912 and 3851 71-90 mg/dL- goal for 3952 72-108 mg/dL- goal for 3951 Titration was performed twice weekly	

Titration of non-insulin (GLP-1 analog) comparators
In trial 3851 the dose of non-insulin comparator (pre-trial GLP-1 agonist) was to remain constant throughout the duration of the trial. In 3697, the dose of liraglutide was titrated to a maximum dose of 1.8 mg, as per the Victoza label.

Titration monitoring committee
A titration committee composed of Novo Nordisk members monitored patients' adherence to the titration algorithm by monitoring and reviewing the titration doses in a blinded fashion. Deviations from the titration algorithm were discussed with the trial site, while keeping the treatment blinded. However the final decision of dose adjustment was based on clinical judgment at the discretion of the investigator.

Study procedures and visits

In all phase 3 trials the overall study procedures and visits were similar. Each trial consisted of a 2-week screening period, a 26-week main treatment period and a follow-up visit-1 week after end of treatment. Weekly (or bi-weekly for the first 5 weeks in 3912) visits/phone contacts were scheduled to occur during the 26-week treatment period. During all site visits, withdrawal criteria were reviewed, and patients were assessed for adverse events, and dose level and dosing frequency of OADs and investigational drug were evaluated. At designated site visits, vital signs, blood work (including HbA1c, FPG and safety blood work) were measured. In all trials, patients were to continue a stable dose of protocol-allowed OADs.

Week 26 was the last treatment visit (with the exception of those who participated in the extension of trial 3697). For subjects continuing in the 3697 extension period subjects continued with weekly telephone or site visit contact until conclusion of the trial. At the last treatment visit, subjects were instructed to transfer from the trial product to any kind of antidiabetic therapy. If a subject was prematurely withdrawn from the trial, the investigator was to perform all procedures for the last visit and if possible, the follow-up visit.

Subject demographics and disease characteristics

Overall baseline subject demographics and disease characteristics

Baseline demographic and disease characteristics for the pool (N=3488) of subjects from all 5 phase 3 trials who were randomized to IDegLira or comparator are shown below. These data are intended to provide an overview of the subject characteristics for the efficacy evaluation in the IDegLira program. Demographics by individual trial are presented subsequent to this overview.

The mean age of subjects in the overall IDegLira program was 57 years, slightly more than half (52.7%) were male, and the mean BMI was 31.8 kg/m^2. Close to 16% were Hispanic, 75% were White, 6.2% were Black or African American, and 17.3% were Asian. The mean duration of diabetes was 8.7 years and the mean HbA1c at baseline was 8.2%. A history of diabetic neuropathy, retinopathy and nephropathy was reported in 25.4%, 12% and 6.5% respectively. The mean eGFR was 88.3 mL/min/1.73m^{2}and 6.2% of patients had an eGFR less than 60 mL/min/1.73m^2.

Baseline demographic and disease characteristics of phase 3 trials - FAS			
		IDegLira (N=1891) N(%) or mean SD	**Comparator [a](N=1597) N(%) or mean SD**
Age (years)		57.0 (9.9)	56.7 (10.0)
Male		997 (52.7 %)	795 (49.8 %)
Body weight (Kg)		89.5 (18.7)	89.0 (18.3)
BMI (kg/m^2)		31.8 (5.0)	31.9 (5.0)
Ethnicity			
Hispanic or Latino		300 (15.9 %)	311 (19.5 %)
Race			
White		1418 (75.0 %)	1173 (73.5 %)
Black or African American		118 (6.2 %)	91 (5.7 %)
Asian [b]		328 (17.3 %)	303 (19.0 %)
American Indian or Alaska Native		3 (0.2 %)	2 (0.1 %)
Other		24 (1.3 %)	26 (1.6 %)
Duration of Diabetes (years)		8.7 (6.1)	8.8 (6.4)
HbA1c (%)		8.2 (0.8)	8.3 (0.9)
FPG (mg/dL)		165.0 (43.9)	165.8 (48.3)
Diabetes complications [e] (based on data from diabetes complications form)			
Any complication [d]		689 (36.4%)	515 (32.2%)
Diabetic neuropathy		481 (25.4%)	365 (22.9%)
Diabetic retinopathy		227 (12.0%)	169 (10.6%)
Diabetic nephropathy		122 (6.5%)	82 (5.1%)
Macroangiopathy		118 (6.2%)	82 (5.1%)
Other commonly reported concomitant illnesses (i.e. reported in >10% of patients)			
Hypertension		1320 (69.8%)	1102 (69.0%)
Hyperlipidemia		453 (24.0%)	361 (22.6%)
Dyslipidemia		433 (22.9%)	356 (22.3%)
Obesity		291 (15.4%)	255 (16.0%)
Osteoarthritis		226 (12.0%)	213 (13.3%)
Hypercholesterolemia		230 (12.2%)	179 (11.2%)
Depression		205 (10.8%)	137 (8.6%)
Menopause		190 (10.0%)	171 (10.7%)
Gastroesophageal reflux disease		194 (10.3%)	163 (10.2%)
Pretrial anti-diabetic regimen			
3697 main and ext)	1 OAD	693 (83.2%)	684 (82.7%)
	2 OADs	140 (16.8%)	143 (17.3%)
	>2 OADs	0 (0.0%)	0 (0.0%)
3912	1 OAD	95 (47.7%)	98 (49.2%)
	2 OADs	104 (52.3%)	101 (50.8%)
	>2 OADs	0 (0.0%)	0 (0.0%)
	Total insulin dose	0.3 (0.1%)	0.3 (0.1%)

Baseline demographic and disease characteristics of phase 3 trials - FAS			
		IDegLira (N=1891) N(%) or mean SD	**Comparator [a](N=1597) N(%) or mean SD**
	(u/kg): Total insulin dose (u):	29.0 (7.7%)	29.2 (7.7%)
3851	1 OAD 2 OADs >2 OADs	217 (74.3%) 68 (23.3%) 7 (2.4%)	108 (74.0%) 36 (24.7%) 2 (1.4%)
3951	1 OAD 2 OADs >2 OADs	30 (10.4%) 259 (89.6%) 0 (0.0%)	17 (11.6%) 129 (88.4%) 0 (0.0%)
3952	1 OAD 2 OADs >2 OADs Total insulin dose (u/kg): Total insulin dose (u):	278 (100%) 0 (0.0%) 0 (0.0%) 0.4 (0.1%) 31.2 (10.0%)	279 (100%) 0 (0.0%) 0 (0.0%) 0.4 (0.1%) 31.9 (10.3%)
Oral antidiabetic drug class			
Biguanide n(%) Metformin n (%) Mean (SD) daily dosing in mg		 1858 (98.3%) 1954.1 (469.0)	 1578 (98.8%) 1943.0 (447.7)
Glinide n (%) Repaglinide n (%) Mean (SD) daily dosing in mg		 4 (0.2%) 9.8 (2.9)	 2 (0.1%) 9.0 (4.2)
Sulfonylurea n(%) Glibenclamide n (%) Mean (SD) daily dosing in mg Gliclazide n (%) Mean (SD) daily dosing in mg Glimepiride n (%) Mean (SD) daily dosing in mg Glipizide n (%) Mean (SD) daily dosing in mg Glyburide n (%) Mean (SD) daily dosing in mg Gliquidone n (%) Mean (SD) daily dosing in mg		 87 (4.6%) 13.5 (4.5) 104 (5.5%) 105.6 (61.7) 188 (9.9%) 5.0 (4.4) 76 (4.0%) 18.0 (6.7) 1 (0.1%) 10.0 (–) 0 (0.0%) 0	 47 (2.9%) 13.2 (4.5) 59 (3.7%) 117.1 (65.3) 114 (7.1%) 4.6 (1.9) 56 (3.5%) 18.1 (7.7) 0 (0.0%) 0 2 (0.1%) 120.0 (0.0)
Thiazolidinedione n(%) Pioglitazone n (%) Mean (SD) daily dosing in mg		 154 (8.1%) 32.1 (6.8)	 148 (9.3%) 32.9 (6.2)
Insulin used at baseline [f]			
Insulin glargine n (%) Mean (SD) daily dosing in units		363 (19.2%) 30.6 (9.7)	367 (23.0%) 31.3 (9.8)
Insulin detemir n (%) Mean (SD) daily dosing in units		32 (1.7%) 32.5 (7.2)	35 (2.2%) 31.3 (7.2)
Insulin neutral protamine Hagedorn n (%) Mean (SD) daily dosing in units		79 (4.2%) 28.1 (7.2)	71 (4.4%) 28.2 (7.8)
Biosynthetic human insulin (BHI) n (%) Mean (SD) daily dosing in units		0 (0.0%) 0	1 (0.1%) 30.0 (–)
Human insulin (HI) n (%) Mean (SD) daily dosing in units		0 (0.0%) 0	2 (0.1%) 20.0 (0.0)
Insulin aspart (IAsp) n (%) Mean (SD) daily dosing in units		0 (0.0%) 0	1 (0.1%)[g] 20.0 (–)
Mean eGFR (mL/min/1.73 m2)			

Baseline demographic and disease characteristics of phase 3 trials - FAS		
	IDegLira (N=1891) N(%) or mean SD	**Comparator [a](N=1597) N(%) or mean SD**
of patients with eGFR <60 mL/min/1.73m^2	118 (6.24%)	108 (6.76%)
of patients with eGFR <30 mL/min/1.73 m^2	1 (0.05%)	0 (0.00%)

a: comparators comprise the pooled dataset containing all comparators used across the 5 trials (insulin degludec, insulin glargine, liraglutide, GLP-1 analog and placebo).
b: in Trials 3851, 3951 and 3952, no data on Asian subclasses (Indian vs. non-Indian) were collected. Hence, only data for the race 'Asian' are presented in this table.
d: subjects with one or more diabetes complication
e: some of these subjects may also be included in the diabetes complications data presented above based on the medical history.
f: in Trial 3912, the basal insulin was unknown for 5 subjects but follow-up has documented that these were 4 subjects on insulin glargine and 1 subject on NPH insulin. In Trial 3952, one subject was administered insulin detemir at screening and randomized in error. The dose was unknown.
g: Subject 765003, Trial 3912, was randomized in error because he was administering IAsp at screening. The subject completed the trial.
h: according to the CKD-EPI equation
Source: information request received 12/21/15: \\cdsesub1\evsprod\NDA208583\0008\m1\us\111-info-amendment\re-fda-ir-20151214.pdf

Baseline demographics and disease characteristics by phase 3 trial

For each individual trial, the treatment groups were well matched across treatment arms with respect to baseline demographic characteristics; see

. Some small imbalances were noted; however these are not likely to have affected the overall efficacy results. For example, in trial 3951 a small imbalance was noted in the country of residence (41.8% in the placebo group were from the United States vs. 30.8% in the IDegLira group). There was also a slight difference in body weight between treatment groups. The body weight at baseline was ~2kg lower for subjects in the IDegLira group compared to the placebo group. However, the BMI was slightly higher in the placebo group (32 kg/m^2) compared to the IDegLira group (31.2 kg/m^2). See also the Statistical Summary.

The baseline demographics and disease characteristics varied by trial consistent with enrollment criteria. These differences are summarized below.

Trials enrolling Insulin naïve subjects:
In trial 3697 (factorial study), subjects were slightly younger than in the other trials, with a mean age of 55 years. Subjects in trial 3951 (IDegLira vs. placebo) had the highest mean age (60.4 years). The duration of diabetes was also shorter for trial 3697 (mean 6.8 years) than for trial 3951 (mean 9.12 years). In both trials, close to half of participants were male. The majority of patients were White (61.9% for 3697; 75.4% for 3951), with smaller representation of other races and ethnic groups. The mean BMI was similar in the two trials ~ 31 kg/m^2. The average HbA1c was higher for trial 3697 at 8.3%, compared to trial 3951 at 7.9%.

Trials enrolling non-insulin naïve subjects:
The mean age in trials 3912 (IDegLira vs. IDeg) and 3952 (IDegLira vs. IGlar) was similar (57 - 59 years) with similar duration of diabetes ~ mean of 11 years. In both trials, close to half of participants were male. The majority of patients were White (77.4% for trial 3912 and 94.6% for trial 3952), with smaller representation of other races and ethnic groups. The mean BMI was slightly higher for trial 3912 (33.7 kg/m^2) than trial 3952 (31.7 kg/m^2).The average HbA1c was higher for 3912 at 8.8%, compared to 3952 at 8.3%.

Trial enrolling previous GLP-1 users:
For trial 3851 (IDegLira vs. GLP-1), subjects had a mean age of 58.3 years, with a mean duration of diabetes of 10.4 years, with ~half of patients being male. More than 90% of subjects were White with smaller representation of other races and ethnic groups. The mean BMI was 32.9 kg/m^2 with an average HbA1c of 7.8%. There were similar proportions of subjects taking exenatide (20.5%) and liraglutide (79.5%) randomized to each treatment group. The dose of exenatide (mean~ 18 mcg) and liraglutide (mean 1.7 mg) was similar between treatment groups at randomization.

Baseline demographics and disease characteristics in phase 3 trials – FAS

	TRIAL 3697			TRIAL 3912		TRIAL 3952		TRIAL 3951		TRIAL 3851	
Characteristic	**IDegLira (N=833)**	**IDeg (N=413)**	**Liraglutide (N=414)**	**IDegLira (N=199)**	**IDeg (N=199)**	**IDegLira (N=278)**	**IGlar (N=279)**	**IDegLira (N = 289)**	**Placebo (N=146)**	**IDegLira (N=292)**	**GLP-1 (N=146)**
Age (Years)											
Mean (SD)	55.1(9.9)	54.9(9.7)	55.0(10.2)	56.8(8.9)	57.5(10.5)	58.4(9.8)	59.1(9.3)	60.0(9.6)	59.4(10.8)	58.3(9.9)	58.4(8.8)
Min-max	27.8-83.8	24.0–79.1	24.4–81.6	31.4–76.9	29.5–85.8	29.2–81.7	27.6–80.4	27.6–87.	27.3–84.5	22.0–77.9	37.8–78.3
Sex: Male, n (%)	435(52.2)	200(48.4)	208(50.2)	112(56.3)	106(53.3)	143(51.4)	137(49.1)	154(53.3)	154(53.3)	153(52.4)	71(48.6)
Race											
White	513(61.6)	257(62.2)	258((62.3)	157(78.9)	151(75.9)	262(94.2)	265(95.0)	217(75.1)	111(76.0)	269(92.1)	131(89.7)
Black or African American	72(8.6)	23(5.6)	28(6.8)	9(4.5)	10(5.0)	6(2.2)	5(1.8)	16(5.5)	13(8.9)	15(5.1)	12(8.2)
Asian	228(27.3)	120(29.1)	116(28.1)	33(16.6)	36(18.1)	9(3.2)	9(3.2)	52(18.0)	20(13.7)	6(2.1)	2(1.4)
American Indian or Alaskan native	2(0.2)	2(0.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)
Native Hawaiian or Pacific Islander	0(0.0)	0(0.0)	1((0.2)	0(0.0)	1(0.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other	18(2.2)	11(2.7)	11(2.7)	0(0.0)	1(0.5)	1(0.4)	0(0.0)	4(1.4)	2(1.4)	1(0.3)	1(0.7)
Ethnicity											
Hispanic or Latino	127(15.2)	67(16.2)	56(13.5)	16(8.0)	24(12.1)	107(38.5)	133(47.7)	24(8.3)	16(11.0)	26(8.9)	15(10.3)
Not Hispanic/ Latino	706(84.8)	345(83.5)	357(86.2)	183(92.0)	175(87.9)	171(61.5)	146(52.3)	265(91.7)	130(89.0)	266(91.1)	131(89.7)
Unknown	0(0.0)	1(0.2)	1(0.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
HBA1c (%)											
Mean (SD)	8.3(0.9)	8.3(1.0)	8.3(0.9)	8.7(0.7)	8.8(0.7)	8.4(0.9)	8.2(0.9)	7.9(0.6)	7.9(0.6)	7.8(0.6)	7.7(0.6)
Min-max	6.0–11.0	6.6–11.3	6.4–12.6	7.2–12.3	7.3–10.9	6.4–11.6	5.9–10.8	6.3–9.5	6.5–9.1	6.7–9.2	6.6–9.7
FPG(mg/dL)											
Mean (SD)	165.6(43.4)	169.2(47.8)	162.7(47.3)	174.6(52.6)	172.1(55.8)	160.5(47.51)	159.8(51.96)	164.4(38.9)	164.7(37.5)	161.7(38.2)	169.1(41.7)
Min-max	48.6-333.3	84.7-349.5	55.9-421.6	54.1 - 344.1	75.7 - 538.7	64.9 - 367.6	57.7 -336.9	79.3- 331.5	70.3 - 261.3	50.5 - 286.5	86.5 - 333.3
Diabetes duration(years)											
Mean(SD)	6.6(5.1)	7.0(5.3)	7.2(6.1)	10.3(6.0)	10.9(7.0)	11.6(7.4)	11.3(6.6)	9.0(5.5)	9.3(6.5)	10.4(5.8)	10.4(5.8)
Min-max	<0.1–35.1	<0.1–32.3	<0.1–53.9	0.8–30.4	0.8–40.4	0.3–47.6	0.4–44.6	<0.1–38.3	0.5–44.8	<0.1–31.3	<0.1–31.9
Basal insulin dose(units)											
IDet: mean (SD)				32.5(7.2)	31.3(7.2)						
IGlar: mean (SD)				28.6(8.1)	29.2(7.7)	31(10)	32(10)				
Other: mean (SD)				28.1(7.2)	28.1(7.8)						

Data are mean (SD) or number (%). **Abbreviations**: FAS=full analysis set, FPG=fasting plasma glucose, HbA1c=glycosylated hemoglobin, max=maximum value, min=minimum value, OAD=oral antidiabetic drug, SD=standard deviation, IDet: insulin detemir, IGlar: insulin glargine, GLP-1=GLP-1 analog
Source: 2.7.3 Summary of Clinical Efficacy page 66-67, Table 3-1 and 3-2

Subject Disposition

The completion rate for each treatment arm ranged from 76% to 95%. Subjects who withdrew were not followed after the time of drug discontinuation for collection of HbA1c data. Therefore, missing data were considered in analyses of the primary efficacy endpoint conducted by both the Applicant and the FDA. These are discussed in detail the Statistical Summary, but to summarize, the FDA statistical reviewer concluded that missing data did not affect confidence in the conclusions of the hypothesis testing, i.e. superiority, for the phase 3 trials. Withdrawals due to adverse events are discussion in the Review of Safety.

Trial 3697- (factorial study) - disposition
Of the 1663 subjects that were randomized, 13.2% withdrew during the trial. Similar percentages of withdrawal were seen in the IDegLira and IDeg groups (11.8% and 11.6%, respectively) while the liraglutide group had the highest rate of withdrawal (17.6%). In all treatment groups, most of the withdrawals were due to meeting withdrawal criteria (close to 8-9% of withdrawals in each group). Of the subjects that withdrew due to meeting withdrawal criteria, about half of each group withdrew without explanation or due to noncompliance/safety concern; there were 2 subjects in the IDegLira group (only) who were withdrawn due to withdrawal criteria of acute pancreatitis.

Trial 3912 - (IDegLira vs. IDeg) - disposition
Of the 413 subjects randomized, 16.2% withdrew during the trial. The withdrawal rate was lower for IDegLira vs. IDeg (15.5% vs. 17%). In all treatment groups, the most common reason for withdrawal was due to "other." The Applicant described these "other" as withdrawal due to a site closure and subjects that were randomized in error. Of the subjects that withdrew due to 'withdrawal criteria,' more than half of the subjects in each treatment group withdrew without an explanation. One subject (0.5%) in the IDegLira and five subjects (2.4%) in the IDeg group were withdrawn due to continuous high SMPG.

Trial 3952 - (IDegLira vs. IGlar) - disposition
Of the 557 subjects that were randomized, 7.5% withdrew during the trial. IDegLira had twice the withdrawal rate as those randomized to IGlar (10.1% vs. 5% respectively). The withdrawals due to withdrawal criteria and due to adverse events were proportionally larger for IDegLira than IGlar. Most of the withdrawals due to withdrawal criteria were "without an explanation" and "randomized in contravention to the inclusion/exclusion criteria."

Trial 3951 - (IDegLira vs. placebo) - disposition
Of the 435 subjects who were randomized, 16.8% withdrew during the trial. There was a larger proportion of subjects in the placebo group who withdrew (24%) than in the IDegLira group (13.1%). Most of the withdrawals in both groups were due to "other": for IDegLira 4.8%, while for placebo 8.9%. Within the "other" category, there was a higher withdrawal rate in the placebo group for the category "lack of drug effect" (5.5%) while there was a higher rate of withdrawal for IDegLira for "recurrent hypoglycemia" (0.7%).

A larger proportion of subjects withdrew in the placebo group due to meeting withdrawal criteria (6.8%), compared with IDegLira (0.7%). Of the subjects that withdrew due to meeting withdrawal

criteria, 6.2% of the placebo group withdrew due to continuous high SMPG, while 0.35% in the IDegLira group withdrew for this reason.

Trial 3851 - (IDegLira vs. GLP-1) - disposition
Of the 438 subjects that were randomized, 10.3% of subjects withdrew during the trial. IDegLira had a lower proportion of subjects (5.5%) than the GLP-1 group (19.9%) who withdrew. Most of the withdrawals in the IDegLira group were due to non-compliance with protocol (3.1%); whereas in the GLP-1 group, most withdrawals were due to meeting withdrawal criteria (9.6%).

When totaling the withdrawal criteria due to continuous high SMPG (GLP-1: [7.5%]; IDegLira [0.7%]) and an additional 4 subjects (1.4%) for GLP-1 identified in the "other" category which implied hyperglycemia (i.e. "unacceptable blood sugars," "hyperglycemia", and "lack of efficacy"), there was close to 9% withdrawal due to hyperglycemia in the GLP-1 arm.

Subject disposition – phase 3 trials											
	TRIAL 3697			**TRIAL 3912**		**TRIAL 3952**		**TRIAL 3951**		**TRIAL 3851**	
	IDegLira N (%)	**IDeg N (%)**	**Liraglutide N (%)**	**IDegLira N (%)**	**IDeg N (%)**	**IDegLira N (%)**	**Insulin Glargine N (%)**	**IDegLira N (%)**	**Placebo N (%)**	**IDegLira N (%)**	**GLP-1 N (%)**
Randomized	834 (100)	414 (100)	415 (100)	207 (100.0)	206 (100.0)	278 (100.0)	279 (100.0)	289 (100)	146 (100)	292 (100.0)	146 (100.0)
Withdrawn at/after randomization	98 (11.8)	48 (11.6)	73 (17.6)	32 (15.5)	35 (17.0)	28 (10.1)	14 (5.0)	38 (13.1)	35 (24.0)	16 (5.5)	29 (19.9)
Adverse event	10 (1.2)	8 (1.9)	24 (5.8)	1 (0.5)	3 (1.5)	9 (3.2)	1 (0.4)	9 (3.1)	2 (1.4)	1 (0.3)	2 (1.4)
Ineffective therapy	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)						
Non-compliance with protocol	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.7)	1 (0.4)	13 (4.5)	10 (6.8)	9 (3.1)	3 (2.1)
Withdrawal criteria	69 (8.3)	34 (8.2)	40 (9.6)	13 (6.3)	15 (7.3)	16 (5.8)	11 (3.9)	2 (0.7)	10 (6.8)	2 (0.7)	14 (9.6)
Other	16 (1.9)	5 (1.2)	9 (2.2)	17 (8.2)	13 (6.3)	1 (0.4)	1 (0.4)	14 (4.8)	13 (8.9)	4 (1.4)	10 (6.8)
Completed	736 (88.2)	366 (88.4)	342 (82.4)	175 (84.5)	171 (83.0)	250 (89.9)	265 (95.0)	251 (86.9)	111 (76.0)	276 (94.5)	117 (80.1)
Full analysis set	833 (99.9)	413 (99.8)	414 (99.8)	199 (96.1)	199 (96.6)	278 (100.0)	279 (100.0)	289 (100.0)	146 (100.0)	292 (100.0)	146 (100.0)
Safety analysis set	825 (98.9)	412 (99.5)	412 (99.3)	199 (96.1)	199 (96.6)	278 (100.0)	279 (100.0)	288 (99.7)	146 (100.0)	291 (99.7)	145 (99.3)

N= Number of subjects, %= Proportion of randomized subjects.
Source: : 2.7.3 Summary of Clinical Efficacy page 71-75, Tables: 3-4, 3-5, 3-6, 3-6, 3-7 and 3-8

Statistical Methods

The MMRM analysis of all studies applied mixed effects model to Full Analysis Set (FAS), where subjects were followed until discontinuation (dropout) or to the end of the study. All subjects were analyzed based on treatment assignment that they received at randomization. No retrieved dropout was performed. The models were similar across all Phase 3 trials and included treatment, pre-trial anti-diabetic treatment (for some trials), all stratification factors (such as pre-trial antidiabetic treatment and baseline HbA1c level; study 3697 was also stratified by sub-study participation), and country/region as fixed effects and the baseline value of the parameter as a covariate. In some of the analyses, the applicant utilized country, while using region in other analyses despite availability of information about both country and region. The results based on calculations using country in the model instead of region provided similar results.

Superiority was confirmed if the 95% confidence interval (CI) for the estimated treatment difference was entirely below 0%, equivalent to a one-sided test with significance level of 2.5%. Non-inferiority was confirmed if the 95% CI for the mean treatment difference was entirely below 0.30%.

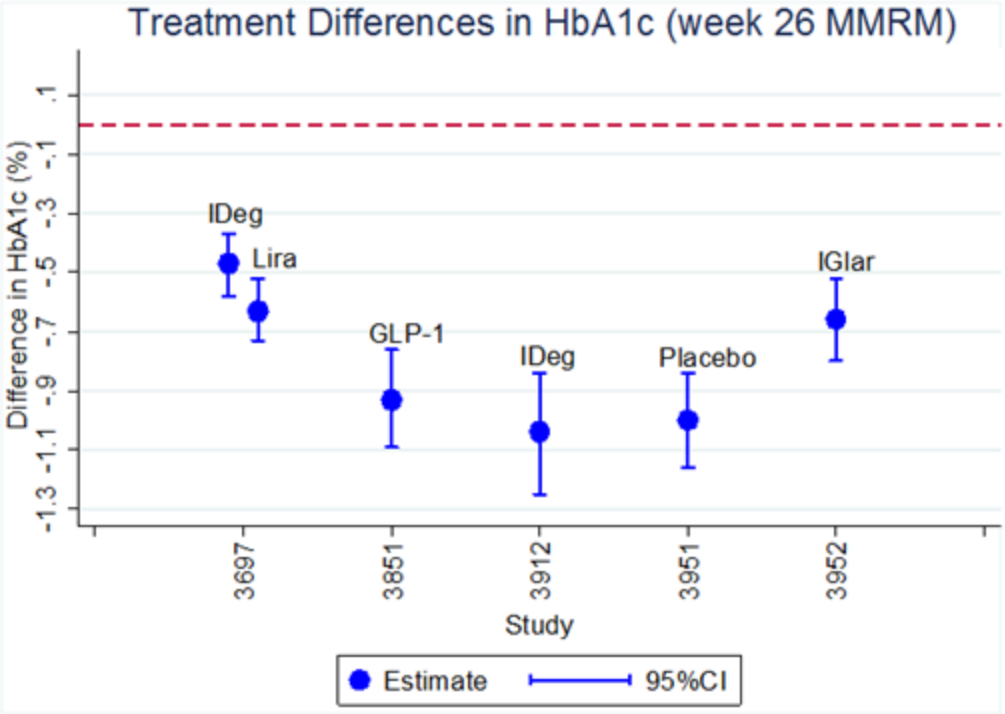
The MMRM analysis estimated the efficacy estimand, i.e., treatment differences assuming that subjects remained on trial product until week 26. This analysis relies on the assumption that the response patterns for subjects withdrawing from trial prior to completing 26 weeks of treatment are comparable to the response patterns for subjects completing 26 weeks of treatment. To appropriately account for missing data in the trial, sensitivity analyses involving multiple imputations (MI) and tipping point analyses were provided by the applicant as a part of this submission.

Analysis of the Primary Efficacy Endpoint

Overview

In all five phase 3 trials subjects in the IDegLira arm had a larger average reduction in HbA1c from baseline than subjects in the corresponding comparator arm(s) (active and placebo). Based on mixed model repeated measures (MMRM) analyses, the difference in HbA1c reduction between IDegLira and IDeg arms was 0.47% in study 3697 and 1.04% in study 3912. The difference between IDegLira and lira was 0.63% in study 3697. When IDegLira was compared to placebo (trial 3951), the average difference in reduction of HbA1c was 1%.

Graphical Summary of Efficacy Results for the IDegLira Phase 3 Clinical Program



For Study 3912 IDeg was capped at 50 units, and background therapies differed. The effect size should not be compared across studies. IGlar=insulin glargine
Source: FDA Statistical reviewer

Missing data considerations

Most of the study participants completed the 26-week study. The observed dropout rate was between 7.36% and 16.78% of all subjects among the studies. A more detailed description of dropout rates is presented below.

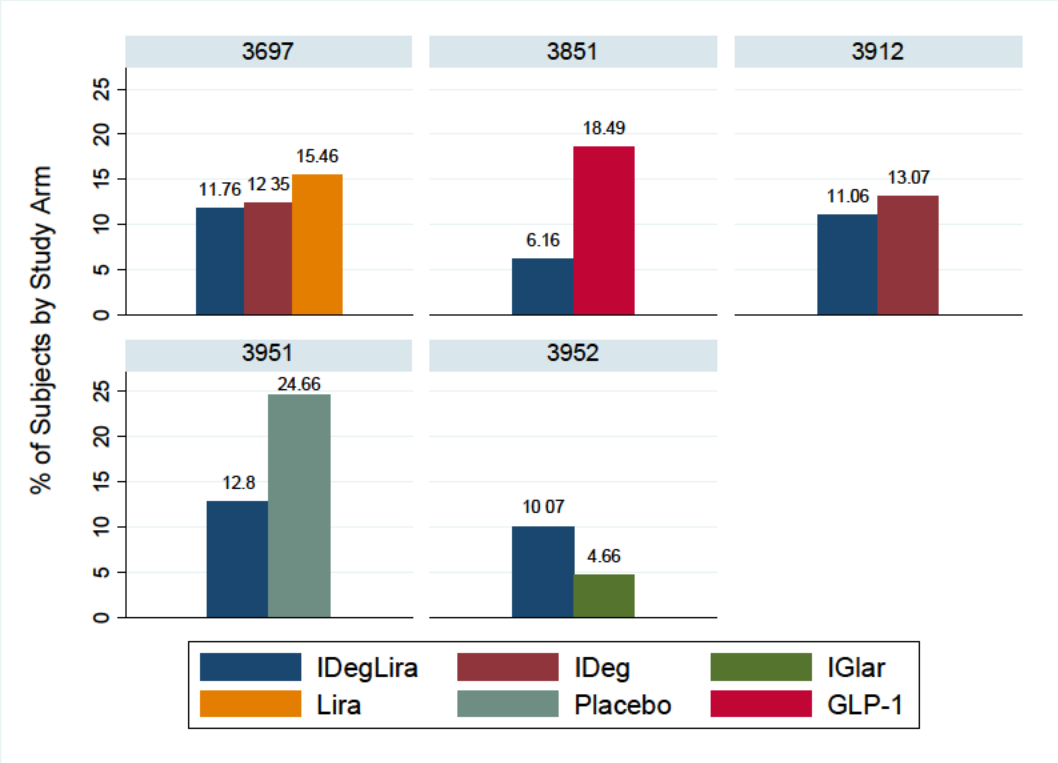
Study	% Subjects with Missing Data*	Total Number of Subjects in the study
3851	10.27	438
3952	7.36	557
3912	12.06	398
3697	12.83	1660
3951	16.78	435

*Subjects that did not have final (26-week) visit

The distribution was different among different studies and among different arms within each study. **Error! Reference source not found.** provides more detailed information on dropout rates in each arm. The overall largest dropout rate was observed in study 3951, where IDegLira was compared with Placebo. The dropout rate in IDegLira in that study (12.8%) was slightly higher, but still comparable to the dropout rate in the other studies. The dropout rate in the placebo arm was

24.66%. The second largest dropout rate was observed in the GLP-1 arm in trial 3851. The lowest dropout rates were observed in study 3952, where the dropout rate in the comparator arm was 4.66%.

Percent of subjects who did not complete 26-week study



Source: Statistical Reviewer

In addition to dropouts, missing data also resulted through exclusions. Although the percentage of those exclusions was not large, the applicant did not provide clarifications for those exclusions in the initial submission. These types of exclusions, such as multiple retests and visit reallocations altered the shape of the Hba1c history curve for individual subjects.

Number of observations excluded from analysis							
Study	**Cause for exclusion**	**IDegLira**	**IDeg**	**Lira**	**GLP-1**	**Placebo**	**Total**
3697	**All** Missing value Retest* Visit reallocation**	**63** 24 37 2	**26** 9 14 3	**31** 18 12 1			**120**
3851	**All** Missing value Retest Visit reallocation	**17** 11 4 2			**11** 7 3 1		**28**
3912	**All** Missing value Retest Visit reallocation	**18** 9 6 3	**9** 4 4 1				**27**
3951	**All** Missing value Retest Visit reallocation	**3** 1 2				**11** 5 5 1	**14**
3952	**All** Missing value Retest Visit reallocation	**23** 4 16 3	**28** 9 14 5				**51**

*Retest as defined by applicant:
"A retest could be performed due to a sample being unfit for assay (the reason could be explained in the lab comments field; however, this was not mandatory), or because an HbA1c value was considered unrealistic by the investigator." Thus, retest means the lab test was repeated and the later value used. Moreover, the later value in some cases was measured at a later date than the original test but is treated as though it were on the same date.

**Visit reallocation as defined by the applicant:
"A visit reallocation takes place when a subject withdraws or has an unscheduled visit. In these circumstances, the HbA1c value is allocated to the previous visit (using the last value)." Thus, reallocation means the visit does not fit the prescribed schedule. Either the last visit was earlier than the end of the trial or there was a visit at a different date than the standard schedule.

Sensitivity analyses methodology

To examine the impact of missing data on analysis results, the following three types of sensitivity analyses were conducted.

1. The multiple imputations used Jump to Reference (J2R) approach where subjects who dropped out from the IDegLira treatment arm were assumed to be switched to the comparator treatment after dropout, while subjects treated with the comparator were assumed to remain on their assigned treatment throughout the trial.

2. Also, the applicant conducted a more conservative Copy to Reference (CR) approach to multiple imputations. In the CR approach, the subjects who dropped out from the IDegLira treatment arm were assumed to respond as if they had been treated with the comparator for

the entire trial, while subjects treated with the comparator were assumed to remain on their assigned treatment throughout the trial.

3. Tipping point analysis was utilized to examine the robustness of the results. In this analysis, withdrawn subjects from the IDegLira arm were given a penalty, i.e., it was assumed that withdrawn subjects who were randomized to IDegLira had received a treatment that was worse than the comparator throughout the trial. The penalty was gradually increased to evaluate at which level the conclusion of the analyses in terms of statistical significance was changed. The tipping point (TP) is the penalty level, at which the magnitude of efficacy reduction in withdrawn subjects creates a shift in the treatment effect of IDegLira from being statistically significantly better than the comparator to a non-statistically significant effect. The applicant performed the tipping point analysis using imputations according to CR method.

Primary Efficacy Results by Analysis Method

Mean baseline HbA1c for subjects in the five trials was as follows: study 3697 - 8.3%, study 3951 - 7.9%, study 3912 - 8.8%, study 3952 - 8.3%, and study 3851 - 7.8%. Baseline HbA1c was balanced across trial arms within each study.

Results of MMRM analyses

The results of MMRM analyses for the primary endpoint are summarized in the table below. All results (including confidence intervals) were below zero. The superiority and noninferiority claims were supported by the fact that all of the 95% confidence intervals were below 0% and 0.3%, respectively.

The outcomes of MMRM analyses show that the performance of IDegLira is dependent on the type of patients, i.e. disease stage and background therapy. For example, in both studies 3697 and 3912, IDegLira was compared with IDeg. The main difference in those two studies was the patient population. Subjects in study 3697 were previously on OAD therapy, while subjects from study 3912 were previous basal insulin users. The 95% confidence intervals for the treatment difference from studies 3697 and 3912 do not overlap.

MMRM Analysis Results

Study	Comparator	HbA1c at week 26 IDegLira	HbA1c at week 26 Comparator	IDegLira-Comparator Estimate (95%CI)
3697	IDeg Lira	6.27	6.75 6.9	-0.47 (-0.58 , -0.37) -0.63 (-0.73 , -0.52)
3851	GLP-1	6.4	7.32	-0.93 (-1.09 , -0.76)
3912	IDeg	6.77	7.81	-1.04 (-1.25 , -0.84)
3951	Placebo	6.36	7.36	-1.00 (-1.16 , -0.84)
3952	IGlar	6.43	7.09	-0.66 (-0.80 , -0.52)

Source summary of clinical efficacy p.301-311

Multiple imputations

The results obtained using Jump to Reference and Copy Reference methods are presented in the table below. The outcomes of both sensitivity analyses were similar to the primary analyses.

Multiple Imputations Results			
Study	**Comparator**	**Jump to Reference (J2R) IDegLira-Comparator Estimate (95%CI)**	**Copy Reference (CR) IDegLira-Comparator Estimate (95%CI)**
3697	IDeg Lira	-0.42 (-0.52 , -0.31) -0.58 (-0.69, -0.47)	-0.41 (-0.52 , -0.31) -0.58 (-0.69 ; -0.47)
3851	GLP-1	-0.89 (-1.06 , -0.72)	-0.87 (-1.05 , -0.70)
3912	IDeg	-0.99 (-1.20 , -0.78)	-0.96 (-1.17 , -0.75)
3951	Placebo	-0.94 (-1.11 , -0.76)	-0.87 (-1.05 , -0.70)
3952	IGlar	-0.59 (-0.73 , -0.45)	-0.56 (-0.71 , -0.42)

Source created by reviewer

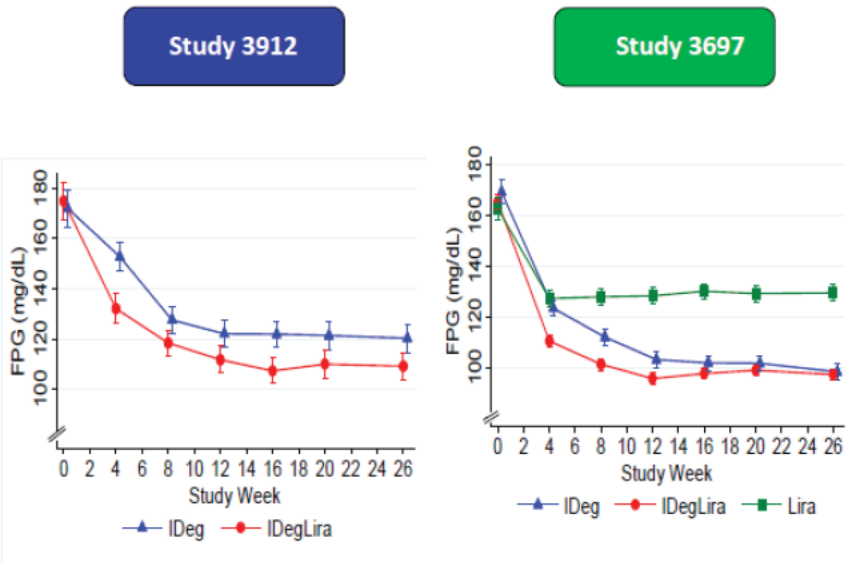
Tipping point analysis

The Applicant conducted only tipping point analysis for CR approach. FDA also examined the outcomes of tipping point examination using J2R imputation. The results obtained by those two methods were very similar. The results of tipping point analysis show that it would take impractical circumstances to tip the results from a conclusion of superiority to failing to conclude superiority.

Fasting Plasma Glucose

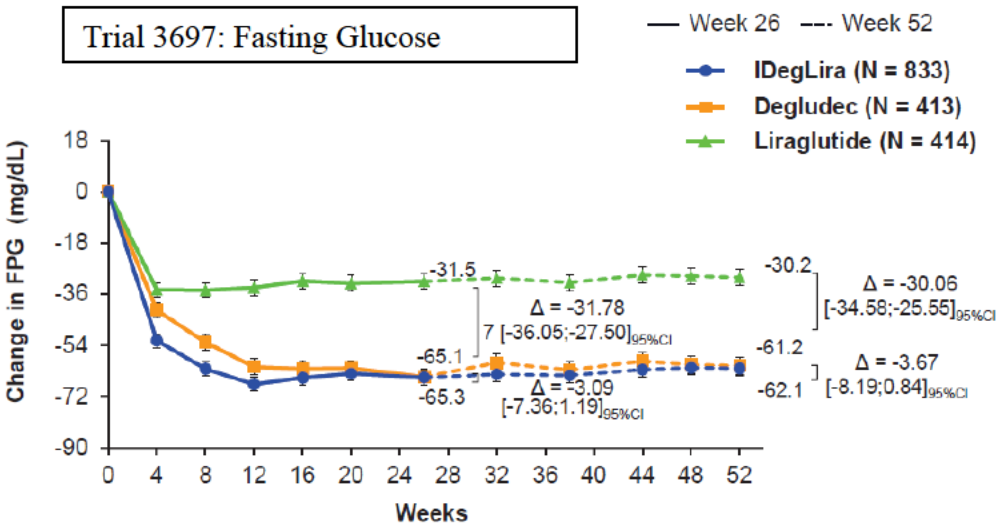
Centrally measured fasting plasma glucose (FPG) trajectories for studies 3912 and 3697 are shown below using results from the MMRM analysis.

In the graph on the left, showing the capped dose trial 3912, FPG levels stabilize in both arms around week 12 and remain parallel for the duration of the trial. This pattern is consistent with what would be expected from a trial in which the comparator dose is capped. In the graph on the right in study 3697, it is clear that FPG for subjects on IDeg was continuously dropping during the entire trial and approximated FPG for subjects on IDegLira only towards the end of the trial.



*Results from MMRM analysis

The figure above created by the FDA statistical reviewer appear slightly different than the figure (below) presented by the Applicant at the Advisory Committee meeting for trial 3697. We do not agree that the Applicant's analysis is the best approach because it uses Last Observation Carried Forward imputation.



Full analysis set. Data are mean ± SEM. Δ = Estimated treatment difference. LOCF imputation.
Week 26: p<0.0001 vs. liraglutide; p=0.1570 vs. degludec. Week 52: p<0.0001 vs. liraglutide; p=0.1107 vs. degludec.

Source: Applicant's Advisory Committee Presentation, slide CO-43

Discussion and Trial Interpretation

Trial Design and Conduct Considerations

Valid interpretation of results of the efficacy evaluation for titratable antidiabetic therapies (e.g. insulin) assumes adequate trial design and conduct, specifically how successful the trials are at

achieving titration targets so that a valid comparison of HbA1c between study arms can be made at study end. Ideally, glycemic targets should be reached 120 days before the primary efficacy endpoint measurement because HbA1c represents a weighted average of blood glucose levels for the 120 days that precede the test. The starting dose and procedures for titration of IDegLira and basal insulin comparators in the five phase 3 trials appear to affect trial interpretation are outlined below.

Because IDegLira contains two antidiabetic drugs whose individual components have proven glycemic lowering, the use of the same titration algorithm in both the IDegLira and IDeg study arms, over time, would be expected to result in a differential rate between the study arms in the time it would take to reach titration goals (i.e., a slower rate for the basal insulin comparator). Even though the titration algorithm appears the same for IDegLira and the comparator insulin, in reality the dose increase between treatment arms is different. A dose increase of '2' (dose steps or units) means a 2 unit increase for the comparator insulin and a 2 units of insulin plus 0.072 mg of liraglutide for IDegLira.

Further, the titration algorithm that was used for all phase 3 trials did not take into account the magnitude of the SMPG measurements. For example, the dose increase (dose steps for IDegLira or units for basal insulin) was always by '2' regardless of how unacceptably high the fasting plasma glucose was. Additionally, titration occurred only twice weekly. These relatively conservative aspects of the algorithm combined with the differential dose increases would be expected to bias the primary efficacy results in favor of the IDegLira arm.

An additional consideration in study 3912 is that the starting dose of IDeg was significantly reduced from the subjects' pretrial basal insulin dose. This dosing regimen would be expected to result in a longer time for subjects to return to their baseline level of glycemic control and then reach titration goals. In FDA's experience trials enrolling previous insulin users typically enroll subjects with inadequate glycemic control and then randomize them to either continue insulin therapy at their current dose or to an experimental insulin therapy at a dose expected to be similar in glycemic lowering effect (i.e. 1:1 conversion).

The aforementioned dosing procedures resulted in difficulty in trial interpretation by artificially limiting the reduction or stabilization in HbA1c in the comparator arms during the trials. Exploratory analyses showed that in all insulin-comparator trials (3697, 3912, and 3952) there was slower titration of the comparator insulin and, as would be expected based on study design, a lag in glycemic lowering in the basal insulin comparator arm (see Dr. Condarco's review for details). Further, this lag resulted in a longer time for the comparator insulin arms to achieve a stable insulin dose, or they were continuing to be titrated at the end of the trial. Data specific to each trial are discussed below.

Trial 3697- Subjects were started on 10 units of IDeg or 10 dose steps of IDegLira at randomization. The Clinical reviewer performed analyses of insulin dose patterns in subjects who met titration targets (**Error! Reference source not found.**). During the up-titration of IDegLira the proportion of patients who met titration targets was higher for IDegLira than IDeg. As the dose of IDeg increased (i.e. continued titration throughout the study) the trend reversed—a higher proportion of patients in the IDeg arm reached targets, than those on IDegLira. However, at week 26 the dose of IDeg was continuing to be titrated in the IDeg arm, i.e. the comparator insulin had not reached a stable dose. The FDA Statistical reviewer conducted analyses of insulin dose patterns

over time (**Error! Reference source not found.**). The corresponding Kaplan-Meier plots provide illustration to the length of dose escalation periods by arm. Only half of the subjects in the IDeg arm reached their insulin target dose. **Error! Reference source not found.** presents the average time to dose stabilization. It is uncertain whether IDegLira would be superior to IDeg if maximally titrated. The data also do not suggest that the proportion of subjects who reached titration targets had reached maximum (i.e. 'maxed-out') due to some dose limiting adverse effect such as hypoglycemia.

As noted previously, HbA1c represents glycemic control over the preceding 3 months. In trial 3697, mean fasting plasma glucose was similar between the IDegLira and IDeg study arms at 26 weeks (97.02 mg/dL and 98.1 mg/dL, respectively) in the FDA analysis which used Last Observation Carried Forward imputation. While FPG and HbA1c measure different aspects of glycemic control (i.e. fasting vs. average glucose), HbA1c is also different in that it represents glycemic control over the previous 3 months. It is possible that the similar FPG is a more proximal measure of the success of titration that was not yet fully reflected in the HbA1c measurement.

3912- Patients previously on 20 to 40 units of basal insulin were started on 16 units of IDeg or 16 dose steps of IDegLira at randomization, had discontinuation of their pre-trial OADs (with the exception of metformin) and capped at either 50 units of IDeg or 50 dose steps of IDegLira. Throughout the duration of the study, the proportion of patients meeting targets, randomized to IDegLira were always higher than those randomized to IDeg (**Error! Reference source not found.Error! Reference source not found.**). Dose stabilization in the IDeg arm was achieved relatively early compared to the other insulin comparator trials (median 10 weeks and mean 12 weeks) because maximum dose of IDeg was artificially limited by the study design (**Error! Reference source not found.** and **Error! Reference source not found.**).

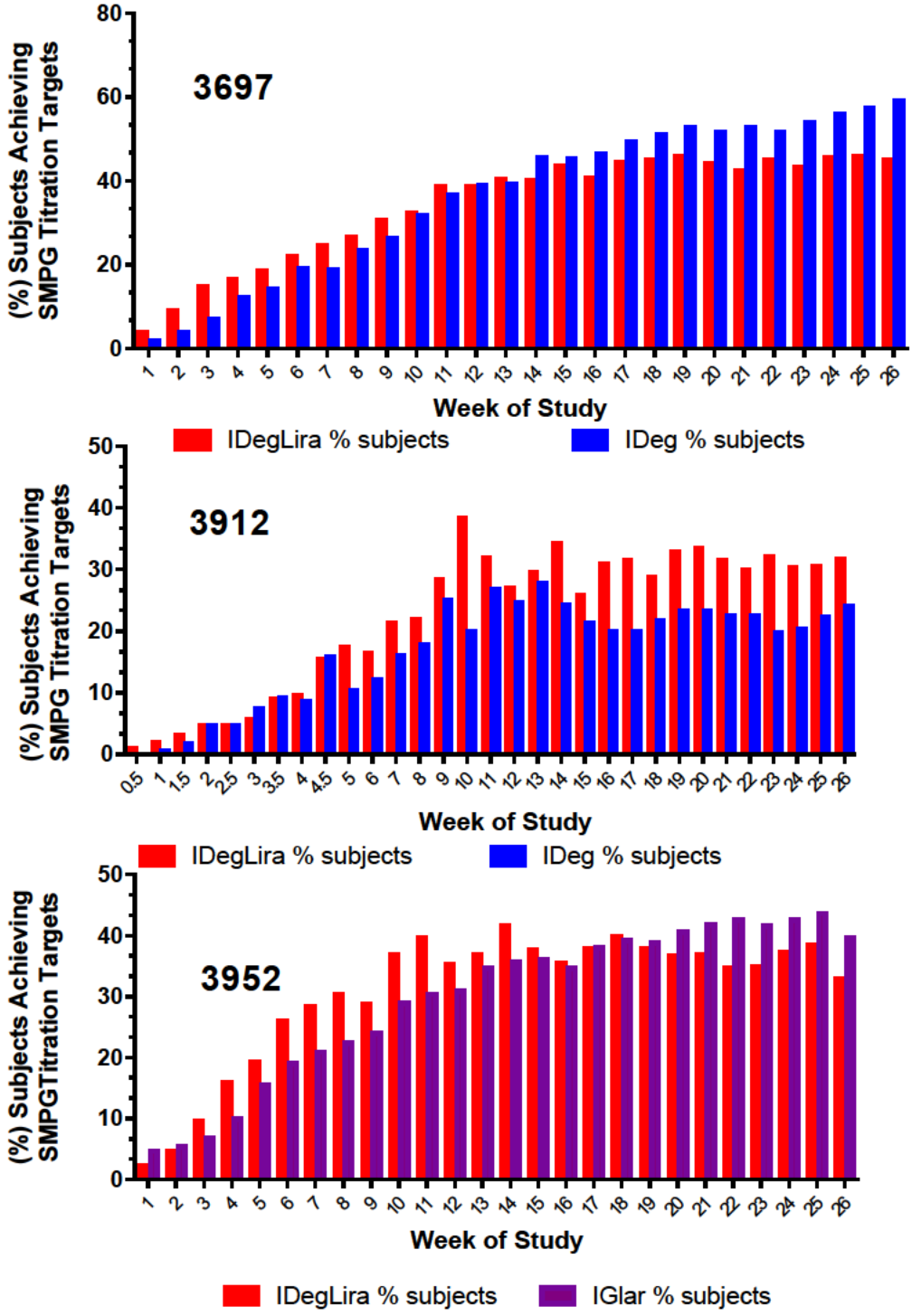
3952- Patients previously on 20-50 units of insulin glargine were continued on the same insulin at the same insulin dose or converted to 16 dose steps of IDegLira at randomization. During the up-titration of IDegLira the proportion of patients who met titration targets was higher for IDegLira than for insulin glargine. As the dose of IDeg increased through continued titration throughout the study the trend reverse; a higher proportion of patients on insulin glargine reached targets than those on IDegLira. However, only half of subjects achieved a stable insulin dose prior to week 19, i.e. seven weeks before the conclusion of the study.

In trial 3952 the mean fasting plasma glucose was similar between IDegLira and IDeg at 26 weeks (104.94 mg/dL and 108 mg/dL, respectively). As noted above, it is not possible to determine whether the similar FPG at 26 weeks, concurrent with a lower HbA1c for IDegLira, reflects a difference in fasting compared to average (or postprandial) glucose control or the fact that FPG decreases more rapidly as compared to HbA1c with improved glycemic control.

The trial does not provide compelling evidence that IDeg is clinically superior to insulin glargine at improving glycemic control in adults with type 2 diabetes mellitus because a different outcome may have been observed had a less conservative insulin glargine dosing algorithm been utilized, the dosing algorithm had reflected the liraglutide component of IDegLira, or a different assessment time point been used (e.g., a year).

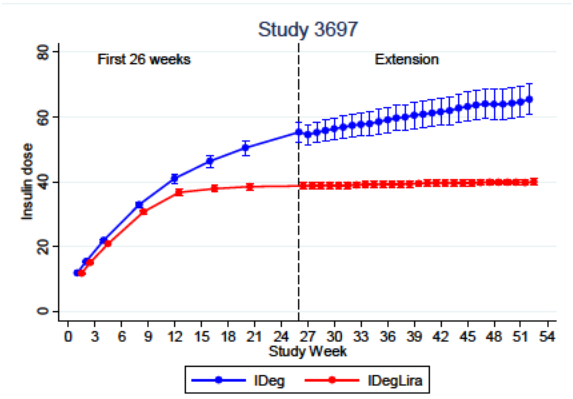
Finally, while this discussion has focused on comparisons between groups regarding the rate of titration, it is important to note that for both groups, the success rate of subjects achieving FPG targets was poor overall in the trials.

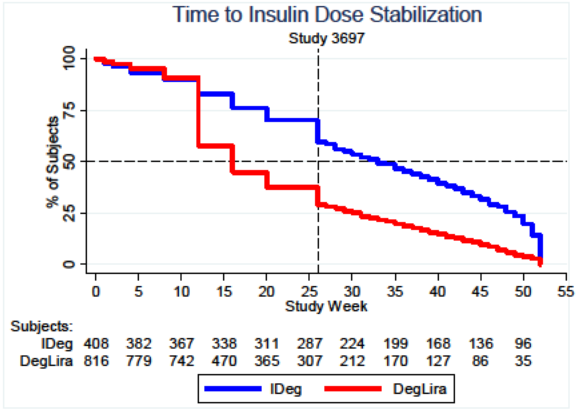
Proportion of patients in insulin trials achieving goal SMPG per visit

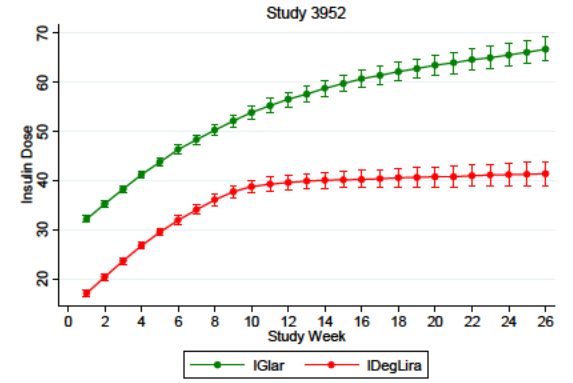


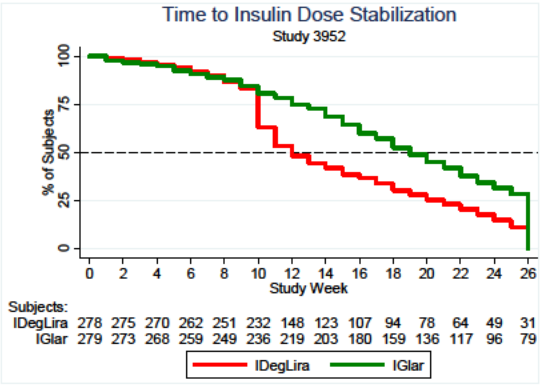
Source: % patients achieving SMPG titration targets requested by FDA on 1/8/16, received 1/15/16: \\cdsesub1\evsprod\NDA208583\0016\m1\us\111-info-amendment\re-fda-req-20160108.pdf

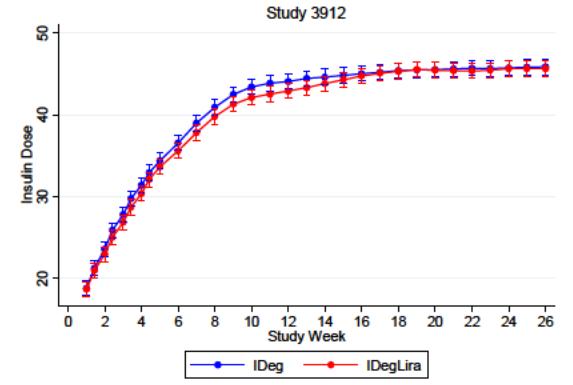
Insulin dose over time and time to insulin dose stabilization

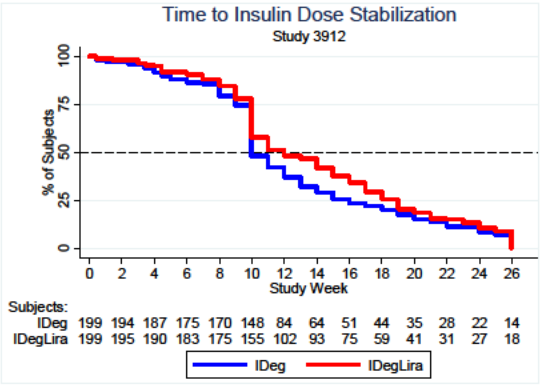












Source: Created by FDA Statistical reviewer

Similar to body weight, the analysis of change in insulin dose was conducted using MMRM approach, i.e. utilizing the same model and replacing body weight with insulin dose.

Time to dose stabilization (weeks)					
Study	**Treatment Arm**	**Median**	**Minimum**	**Maximum**	**Mean**
3697	IDeg	26.0	1.0	26.0	19.5
	IDegLira	16.0	1.0	26.0	15.8
3952	IGlar	19.0	1.0	26.0	18.1

Time to dose stabilization (weeks)					
Study	**Treatment Arm**	**Median**	**Minimum**	**Maximum**	**Mean**
	IDegLira	12.0	1.0	26.0	14.7
3912	IDeg	10	0.4	26	12.6
	IDegLira	12	0.4	26	13.9

Source: Created by FDA Statistical reviewer, see also Statistical Summary

Contribution of Liraglutide Component at Lower Doses

Victoza is approved at a dose of 1.2 mg or 1.8 mg once daily; liraglutide was not studied as a titratable antidiabetic therapy in its single-agent development program. While the labeled starting dose of Victoza is 0.6 mg once daily, this dose is recommended to improve GI tolerability and alone is not effective for glycemic lowering.

The proposed dosing regimen for IDegLira allows for titration of the liraglutide component without specification of a minimum required dose. In the pre-NDA meeting the Division emphasized that it would be important to evaluate subjects in phase 3 trials who received less than the approved (and possibly minimally effective) doses of liraglutide after the titration period.

Exploratory analyses of the doses achieved of the liraglutide component of IDegLira showed that the dose was on average greater than 1.2 mg**Error! Reference source not found.**, ranging from a mean of 1.0 mg (in 3951) to 1.6 mg (in 3912 and 3851).

An evaluation of the proportion of patients reaching dose step tertiles is shown below.

IDegLira subjects [n (%)] by 'dose step' tertile at the end of the trials (observed values), safety analysis set							
Dose steps	**Liraglutide dose range (mg)**	**Trial 3697 (26 weeks)**	**Trial 3697 (52 weeks)**	**Trial 3912**	**Trial 3851**	**Trial 3951**	**Trial 3952**
			N (safety analysis set)				
		825	825	199	291	288	278
			N (end of trial)				
		757	623	187	281	267	264
≤ 16	**≤ 0.58**	61(8.1)	37(5.9)	2(1.1)	7(2.5)	72(27.0)	2(0.8)
17 to ≤ 32	**0.61 to 1.16**	173(22.9)	135(21.7)	17(9.1)	33(11.7)	102(38.2)	56(21.2)
33 to 50, inclusively	**1.19 to 1.8**	522(69.0)	451(72.4)	168(89.8)	241(85.8)	93(34.8)	206(78.0)
Source: Information request received on January 15, 2016 \\cdsesub1\evsprod\NDA208583\0006\m1\us\111-info-amendment\re-fda-20151203.pdf							

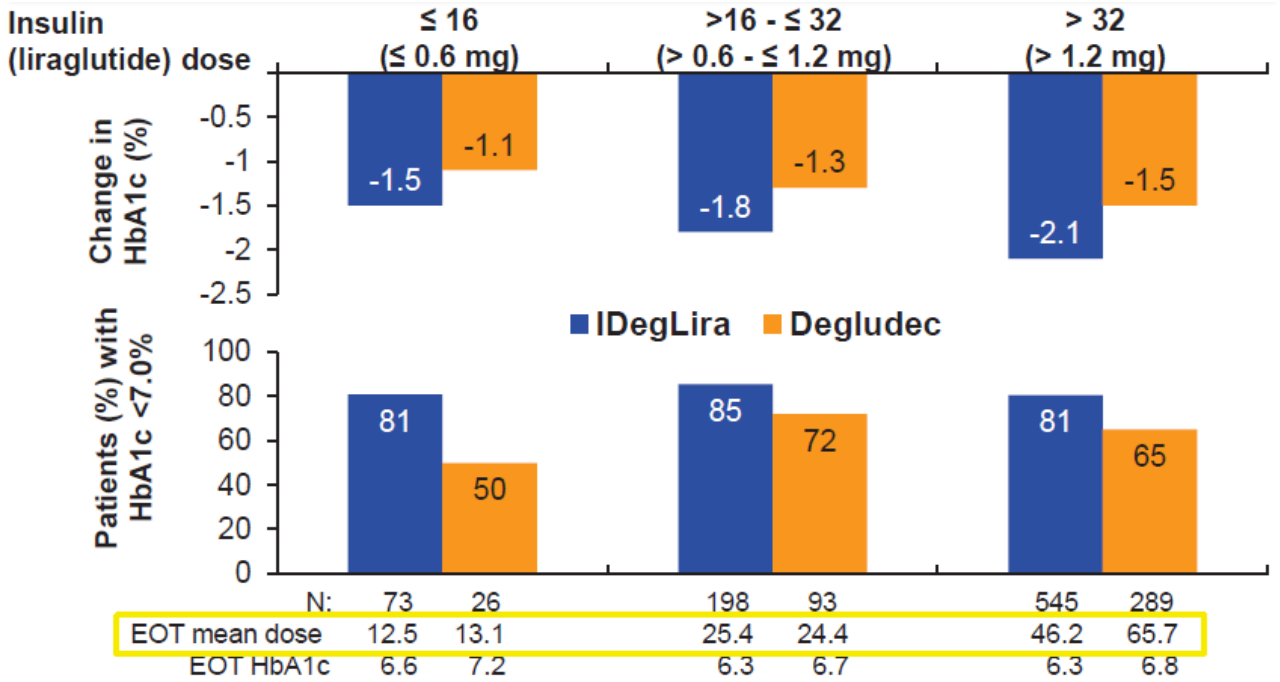
Recall that 33 'dose steps' contains just about 1.2 mg of liraglutide which is the lowest approved dose of liraglutide. Therefore, an exploratory analysis was performed to examine the percentage of subjects who reached 32 dose steps or fewer in the phase 3 trials**Error! Reference source not found.**. The percentage ranged from 10% to 65%. The lowest percentage of subjects was seen in 3912 which was made up by subjects who were previously on basal insulin. The highest proportion

of subjects with doses less than 1.2 mg were seen in the insulin and GLP-1 naïve group (3697 and 3951), followed by subjects previously on GLP-1 (3851).

IDegLira subjects [n (%)] with 'dose step' ≤32 at the end of the trials (observed values), safety analysis set							
Dose steps	**Liraglutide dose range (mg)**	**Trial 3697 (26 weeks)**	**Trial 3697 (52 weeks)**	**Trial 3912**	**Trial 3851**	**Trial 3951**	**Trial 3952**
			N (safety analysis set)				
		825	825	199	291	288	278
			N (end of trial)				
		757	623	187	281	267	264
≤32	**≤1.16**	234(31)	172(27.6)	19(10.2)	40(14.2)	174(65.2)	58(22)

The percentage of subjects using at least 33 dose steps (and hence 1.2 mg of liraglutide) at the end of the trials was influenced by the relatively low FPG targets in the trials (72-90 mg/dL for most trials). Because for an individual patient, more antidiabetic drug is necessary to achieve tighter glycemic control subjects who did reach or came close to reaching these goals received higher doses of liraglutide than these subjects might have received if more typical FPG goals were used. Therefore, the clinical development program for IDegLira probably overestimates the number of subjects who would be receiving at least 1.2 mg of liraglutide in a real world setting.

The slide below was presented by the Applicant at the Advisory Committee meeting for this product held on 24 May 2015 (see Advisory Committee section 9 of this review). The slide is titled by the Applicant 'liraglutide component contributed to HbA1c reduction at all doses' and intends to show that contribution to claimed effect of the liraglutide component can be assured throughout the dosing range, even at 10 to 16 units per day. I do not agree that it can be reliably concluded from these data that liraglutide contributes at all dosing ranges. In the 'treat-to-target' design the final IDegLira dose reflects patient characteristics such as insulin sensitivity that can bias analysis results. FDA did not do a similar analysis because of the statistical validity issues inherent in such a post-hoc analysis where subgroups are examined based on a post-randomization variable.



Full analysis set (efficacy), Safety analysis set (dose); Mean at end of trial for continuous endpoints; LOCF imputation. EOT: end of trial

Source: Slide presentation by Applicant EMDAC Meeting 24 May 2016

Secondary endpoints

Secondary endpoints of hypoglycemia and body weight are discussed in the safety section below. Consideration of these variables in light of the efficacy findings is discussed in the overall risk/benefit assessment.

8. Safety

Data from all five phase 3 trials were pooled for the evaluation of safety. Subjects receiving each of the four treatments studied among the five trials [i.e. IDegLira, basal insulin (IDeg or IGlar), GLP-1 (lira or exenatide), and placebo] were pooled to create 4 groups for safety comparisons. Exposure among the 4 pooled groups varied greatly and exposure adjusted event rates are shown for most of the safety analyses. This approach was agreed upon at pre-submission meetings.

Pooling strategy for phase 3 completed trials	
Group	**Source of data**
IDegLira	IDegLira arm from all 5 completed trials
Basal Insulin	Combined data for IDeg arm of Trials 3697-ext and 3912, and IGlar arm of Trial 3952
GLP-1	Combined data for liraglutide arm in Trial 3697-ext and liraglutide/exenatide arm in Trial 3851
Placebo	placebo arm from Trial 3951
Source: Applicant; IGlar=insulin glargine	

Overall Exposure and Demographics of the Safety Population

For the combined phase 3 trials, 1881 subjects were exposed to IDegLira for a total of 1200.8 patient-year exposure (PYE). The largest exposure to IDegLira was seen in the insulin/GLP-1 naïve trial, 3697, with 705 PYE, while the lowest IDegLira exposure was seen in previous insulin users (trials 3912 and 3952 with 91.9 PYE and 129.6 PYE, respectively. The table below shows exposure of IDegLira by demographic characteristic for all five phase 3 trials pooled.

Exposure was evenly distributed between sexes. When exposure was evaluated by age, most of the exposure was in the group ≥18 - <65 years with 19% of the exposure in subjects aged ≥65 years. When comparing across racial groups, the smallest exposure occurred across all non-White subjects, with 28% of the total exposure. The exposure by region was largest for Europe followed by an exposure of 33% from North America with 29% of the total exposure coming from the US. The exposure of subjects with duration of diabetes of ≥10 years was approximately half of the exposure of subjects with duration of longer than 10 years.

IDegLira Exposure by demographics - completed phase 3 trials, safety analysis set	
	IDEGLIRA
	N (PYE)
Safety analysis set	1881 (1200.8)
Sex	
Male	990 (624.9)
Female	891 (576.0)
Age group (years)	
≥18-<65 years	1506 (976.2)
≥65 years	375 (224.7)
≥65-<75 years	323 (198.3)
≥75 years	52 (26.3)
Race	
White	1411 (865.2)
Asian	327 (243.2)
Black or African American	116 (72.0)
Other	24 (17.9)
American Indian or Alaska Native	3 (2.5)
Ethnicity	
Not Hispanic or Latino	1582 (1022.1)
Hispanic or Latino	299 (178.8)
Region (continent)	
Europe	733 (467.9)
North America	661 (396.4)
Asia	248 (187.9)
South America	99 (53.6)
Africa	88 (60.0)
Australia	52 (34.9)
Region (US/non-US)	
non-US	1284 (848.7)
US	597 (352.1)
Duration of diabetes	
<10 years	1196 (806.3)
≥10 years	685 (394.5)
BMI group (kg/m^2)	
30;35	652 (406.6)
25;30	551 (356.3)
35;	518 (327.8)
0;25	160 (110.2)
Renal function	
Normal	944 (610.3)
Mild impairment	820 (522.3)
Moderate impairment	116 (68.2)
Severe impairment	1 (0.0)

Data are based on trials NN9068-3697 (including extension part), NN9068-3912, NN9068-3851, NN9068-3951 and NN9068-3952.
N: number of subjects; PYE: patient years of exposure (1 PYE = 365.25 days).
Renal function is classified using creatine clearance estimated using the CKD-EPI equation: Normal eGFR: ≥90 mL/min/1.73m^2; Mild impairment: eGFR 60−89 mL/min/1.73m^2; Moderate impairment: eGFR 30−59 mL/min/1.73m^2; Severe impairment: eGFR 15−29 mL/min/1.73m^2.

Source: ISS, Table 1-8, page 42-43, modified to show the IDegLira arm only

General Safety Results

Adjusted Pooling
Because naïve pooling of AE data from trials with different treatments and/or different randomization ratios may introduce bias when comparing treatments (i.e., due to Simpson's paradox), the Applicant was asked to provide adjusted pooled rates and frequencies for adverse events. A method was used that 1) adjusted the AE incidences in each trial based on the pooled AE incidence for IDegLira, and, 2) weighted the trials according to the number of subjects in the IDegLira group. The same method was also applied to AE rates. Presentation of the Applicant's adjusted pooled data will be specified in this review by the terms "adjusted rate" or "adjusted frequency." The FDA statisticians reviewed the adjustment strategy and found it acceptable. The FDA clinical reviewer reviewed the unadjusted safety analyses and there were no important differences; therefore, the adjusted analyses are shown in this section. To be clear, these adjusted rates address differences among trials, e.g. randomization ratio, and as stated above *exposure* adjusted event rates are also provided in summary tables in Dr. Condarco's review.

Event Adjudication Committee
The Applicant selected deaths, thyroid neoplasms and pancreatitis or suspicion of pancreatitis (among other events) as adverse events of interest that were adjudicated by a blinded event adjudication committee (EAC). The Adjudication process is shown in the Appendix, and appears similar to what has been done previously. The FDA did not identify any concerns with the adjudication process used.

Deaths

All fatal events were adjudicated and classified as cardiovascular or non-cardiovascular death. If the cause of death was 'unknown" the Applicant classified the cause as cardiovascular cause.

Five deaths were reported in the completed Phase 3 trials (four of which occurred during the treatment emergent period and 1 death which occurred after the treatment emergent period). Four of the 5 deaths were due to cardiovascular causes (with 3 of these deaths adjudicated as CV death). The adjusted death rates reported by the Applicant were 0.3 and 0.2 events per 100 PYE for IDegLira and IDeg respectively.

Serious Adverse Events

The overall incidence of SAEs in the adjusted pooled analysis of IDegLira vs. basal insulin or vs. GLP-1 was similar. No pattern emerged of a single type of serious adverse event, or grouping of serious adverse events, that occurred with greater frequency among IDegLira subjects than among its mono-component comparators (in the pivotal trials) or when compared to basal insulins or GLP-1 analogs.

Notable SOCs present in the IDegLira pool only included: General disorders and administration site conditions (which included PTs: fever, death and non-cardiac chest pain); Reproductive system and breast disorders (which included PTs: benign prostatic hyperplasia, postmenopausal hemorrhage and dysfunctional uterine bleeding); Vascular disorders (which included PTs: peripheral artery

stenosis, peripheral artery thrombosis and hypotension); investigations (which included PTs amylase increased and lipase increased); blood and lymphatic system disorders (which included PT: iron deficiency anemia). Review of narratives for these events did not suggest a causal relationship between the events and IDegLira use.

Overall, the incidence and pattern of serious adverse events do not suggest a new or worsening safety signal for IDegLira compared to what is known about the individual components (see table below).

Table of Serious Adverse Events Observed in the IDegLira Program – Phase 3 trials												
	IDegLira			Basal insulin			GLP-1			Placebo		
System organ class (SOC)	N (adj. pct)	E	Adj. rate	N (adj. pct)	E	Adj. rate	N (adj. pct)	E	Adj. rate	N (adj. pct)	E	Adj. rate
Safety analysis set	1881			890			557			146		
Total exposure (yrs)	1200.8			575.2			400.2			62.1		
Serious adverse events	73 (3.9)	102	8.5	42 (5.3)	53	11.9	27 (4.3)	34	9.9	5 (2.7)	5	3.4
Cardiac disorders	15 (0.8)	17	1.4	8 (0.8)	8	1.4	3 (0.5)	4	1.1	1 (0.4)	1	0.8
Infections and infestations	9 (0.5)	12	1	5 (0.5)	5	0.9	2 (0.3)	4	1	2 (0.9)	2	1.1
Nervous system disorders	10 (0.5)	10	0.8	6 (0.6)	6	1	1 (0.1)	1	0.2			
Neoplasms benign, malignant and unspecified (include cysts and polyps)	9 (0.5)	9	0.7	3 (0.3)	3	0.6	2 (0.3)	2	0.5			
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	1	<0.1	5 (0.7)	8	1.4						
Injury, poisoning and procedural complications	7 (0.4)	8	0.7	5 (0.6)	6	1.4	2 (0.4)	2	0.7	1 (0.2)	1	0.4
Gastrointestinal disorders	5 (0.3)	5	0.4				5 (0.5)	6	1.0	1 (0.5)	1	0.9
Hepatobiliary disorders	5 (0.3)	5	0.4	5 (0.6)	6	1.2	2 (0.3)	2	0.6			
Musculoskeletal and connective tissue disorders	5 (0.3)	5	0.4	2 (0.2)	2	0.3	4 (0.4)	4	0.6			
Surgical and medical procedures	5 (0.3)	5	0.4	3 (0.3)	3	0.5	1 (0.1)	2	0.4			
General disorders and administration site conditions	4 (0.2)	4	0.3									
Metabolism and nutrition disorders	4 (0.2)	4	0.3	1 (<0.1)	1	0.2						
Reproductive system and breast disorders	3 (0.2)	3	0.2									
Vascular disorders	3 (0.2)	3	0.2									
Renal and urinary disorders	3 (0.2)	3	0.2	3 (0.5)	3	0.5	2 (0.4)	2	0.4			
Investigations	1 (<0.1)	2	0.2									
Eye disorders	2 (0.1)	2	0.2	1 (0.1)	1	0.2	1 (0.2)	2	0.5			

Ear and labyrinth disorders	1 (<0.1)	1	<0.1	1 (<0.1)	1	0.2						
Skin and subcutaneous tissue disorders							1 (0.2)	1	0.2			
Blood and lymphatic system disorders	1 (<0.1)	1	<0.1									
Endocrine disorders	1 (<0.1)	1	<0.1				1 (0.2)	1	0.2			
Psychiatric disorders	1 (<0.1)	1	<0.1				1 (0.2)	1	0.2			

N: number of subjects, E: number of adverse events. Adj. Pct: adjusted percent; Adj. rate: adjusted rate per 100 exposure years. Information request on October 22, 2015: table

Explanation of data columns:

IDegLira Combines data from all 5 completed trials

Basal insulin Combines data for IDeg and IGlar from Trials 3697-ext and 3912 and Trial 3952, respectively

GLP-1 RA Combines data for liraglutide (Trial 3697-ext) and liraglutide/exenatide (Trial 3851)

Placebo Data from the placebo arm of Trial 3951

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Dropouts and/or Discontinuations Due to Adverse Events

The adjusted incidence of dropouts due to adverse events was 1.7%, 2.2%, 6.5%, and 0.7% in the IDegLira, basal insulin, GLP-1, and placebo groups, respectively. The exposure adjusted event rate of dropouts due to adverse events was 3.5, 5.1, 15.8 and 1.2 events per 100 PYE in the IDegLira, basal insulin, GLP-1, and placebo groups, respectively. Most of the AEs resulting in withdrawal occurred in the 'gastrointestinal disorders' SOC with adjusted rates of 0.9 and 7.5 events per 100 PYE for IDegLira and GLP-1, respectively.

Withdrawals due to adverse events were also evaluated by trial, since baseline characteristics could result in differences in dropout rates (i.e. patients randomized to GLP-1 who were previously using and tolerating GLP-1 therapy may be less likely to drop out due to GI intolerability). When evaluating withdrawals due to adverse event by trial:

In trial 3697, 42 subjects withdrew due to adverse events (1.2% for IDegLira, 1.9% for IDeg and 5.8% for liraglutide). The adverse events leading to withdrawal for IDegLira were distributed across different SOCs, except for 'injection site rash' which was reported in 2 subjects. Most adverse events leading to withdrawal with liraglutide were due to GI events (i.e. more than one subject had the following PTs: nausea, vomiting, diarrhea and gastritis). Withdrawals due to IDeg were distributed across different SOCs except for 'weight increased' which was reported in 2 subjects.

In trial 3912, four subjects withdrew due to adverse events (0.5% for IDegLira and 1.5% for IDeg). One subject, randomized to IDegLira was withdrawn due to 'major depression' and 'acute renal failure.' The adverse event PTs that resulted in withdrawal for IDeg were varied and included: acute myocardial infarction, cholelithiasis and ischemic stroke.

In trial 3851, three subjects withdrew due to adverse events. One subject (0.3%) in the IDegLira group withdrew due to 'drug hypersensitivity'; the two other subjects randomized to GLP-1 withdrew due to either 'abdominal discomfort' or 'foot fracture.' Note that trial 3851 included previous GLP-1 users.

In trial 3951 there were 11 subjects (2.5%) who had adverse events leading to withdrawal: 9 subjects (3.1%) in the IDegLira group and 2 subjects (1.4%) in the placebo group. Of the subjects who withdrew in the IDegLira group: 4 subjects (0.9%) withdrew due to amylase/ lipase increase; 2 subjects (0.45%) withdrew due to recurrent hypoglycemia, while the remaining subjects withdrew due to distinct PT terms (pyelonephritis, anxiety, injection site pain, or congestive heart failure).

In trial 3952, there were 10 subjects (1.8%) who had adverse events leading to withdrawal: 9 subjects (3.2%) in the IDegLira group and 1 subject (0.4%) in the IGlar group. The IDegLira withdrawals included: 1 subject withdrawing due to increased lipase, 4 subjects withdrawing due to nausea/dyspepsia abdominal pain/distention, 1 subject withdrawing due to pancreatic carcinoma, 1 subject withdrawing due to blood creatinine increased, 1 subject withdrawing due to respiratory tract infection, and 1 subject withdrawing due to nephropathy. The one withdrawal in the IGlar group was due to fatal hemorrhagic stroke.

Overall, the incidence and pattern of dropouts due to adverse events do not suggest a new or worsening safety signal for IDegLira compared to what is known about the individual components.

APPEARS THIS WAY ON ORIGINAL

Known safety issues with insulin degludec

Hypoglycemia

Methodology for defining, capturing, and reporting of hypoglycemia events.

Definitions of hypoglycemia

Hypoglycemia events were defined in multiple ways in the IDegLira development program. These definitions are described below. Some definitions are sensitive but not specific and some definitions are specific but not sensitive. The FDA relies on multiple definitions to get an appreciation for overall sense of risk. In a population of patients at low risk of developing hypoglycemia such as the population in the IDeg/Lira program most of the data to inform risk will be derived from a non-specific definition. Events captured with this definition may or may not capture clinically meaningful events. Of all these definitions of hypoglycemia, severe hypoglycemia is considered the most specific definition and the most clinically face-valid and meaningful definition.

External review of severe hypoglycemia

Episodes of severe hypoglycemia were reviewed by an external clinician (endocrinologist) blinded to treatment allocation.

The American Diabetes Association's definitions of hypoglycemia

- **Severe hypoglycemia:** an episode requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
- **Documented symptomatic hypoglycemia:** an episode during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL)
- **Asymptomatic hypoglycemia:** an episode not accompanied by typical symptoms of hypoglycemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL)
- **Probable symptomatic hypoglycemia:** an episode during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L [70 mg/dL])
- **Relative hypoglycemia:** an episode during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia but with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL)

'Novo Nordisk confirmed hypoglycemia'

A **Novo Nordisk's confirmed episode of hypoglycemia** - was composed of the pool of ADA **severe** (as described above) and **minor hypoglycemic** episodes. Minor hypoglycemic episodes were defined as an episode with symptoms consistent with hypoglycemia with a plasma glucose < 3.1 mmol/L (56 mg/dL) and which was handled by the subject himself/herself or any asymptomatic plasma glucose value < 3.1 mmol/L (56 mg/dL) or full blood glucose value < 2.8 mmol/L (50 mg/dL).

Capture of hypoglycemia events:

Hypoglycemia is a self-reported event and is based on subject's SMPG recordings. All SMPG values (if above or below 70 mg/dL) were to be recorded in a subject diary and the information from the diary was to be transferred to a hypoglycemia episode form in the eCRF by the investigator if the SMPG value or the characteristics of the episode met the definition. For all trials, subjects were instructed to measure SMPG upon suspicion of hypoglycemia using a glucose meter calibrated to plasma values. Any SMPG value meeting the threshold (regardless of whether it was measured for cause) could be considered a hypoglycemia event. Episodes of severe hypoglycemia were recorded by the investigator.

Glucose meters used:
The Applicant stated that glucometers used were compliant with ISO standards 2003:15917 and 2013:15197 were used with test strips that had to be calibrated to plasma values by then end user and had to be used in accordance with the manufacturer's instructions. No specific glucose meter was required.

Analysis Methods
An analysis of 'Novo Nordisk confirmed hypoglycemia' was a pre-specified secondary analysis in trials 3697 and 3952. The FDA statistician confirmed that overall, the pre-specified confirmatory statistical testing strategy controlled the type I error rate at a 2.5% level with respect to testing both the primary hypothesis and the secondary hypotheses. Hypoglycemic episodes were analyzed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycemic episode is considered treatment emergent as offset. The model included treatment, previous anti-diabetic treatment, baseline HbA1c stratum, substudy participation and country as fixed factors. Other definitions of hypoglycemia were not included in pre-specified hypothesis testing, but are considered relevant to this review. We also looked at AE reports of hypoglycemia and dropouts due to hypoglycemia.

Results of hypoglycemia analyses in phase 3 trials
The summary table below shows the results provided by the Applicant for hypoglycemia across the 5 phase 3 trials in the IDegLira program for three definitions (ADA severe, ADA documented symptomatic, and Novo Nordisk confirmed).

ADA Severe hypoglycemia
A total of 12 events of severe hypoglycemia were identified by the investigators in the IDegLira program, when also considering the 52 week period of 3697. Of the 12 cases, 10 cases were identified by the blinded reviewer as meeting criteria for severe hypoglycemia: 5 in the IDegLira pool, 3 in the basal insulin pool, and 2 in the GLP-1 analog pool (see Dr. Condarco's review for narratives).

Overall the event rate of severe hypoglycemia was higher for IDegLira compared to placebo or GLP-1 analogs. There were too few cases of severe hypoglycemia to differentiate any clear difference between IDegLira and basal insulin.

There were a total of 5 serious[2] hypoglycemic events (4 events in IDegLira and 1 event for insulin glargine) all serious hypoglycemia events were captured as severe episodes, except for one evet).

The analysis conducted by the FDA statistical reviewer of severe hypoglycemia included data from the 26 week treatment periods of each trial for a total of 9 cases of severe hypoglycemia.

Other less specific hypoglycemia definitions

The pattern of treatment differences for the ADA documented symptomatic and Novo Nordisk confirmed hypoglycemia definitions were similar across the phase 3 trials. In trial 3851 the direction of the findings not favoring IDegLira was consistent across all definitions. Similar findings were seen when comparing IDegLira to liraglutide in 3697 or when comparing IDegLira to placebo in trial 3951. For insulin comparator trials (i.e. trials 3697, 3912, 3952) the event rate per 100 patient years of documented symptomatic hypoglycemia or Novo Nordisk confirmed hypoglycemia was higher for the comparator insulin than IDegLira.

Withdrawals due to hypoglycemia were captured in both categories 'withdrawals of adverse events' and withdrawals due to 'other.' When combining these two categories, there were a total of 5 subjects for IDegLira and 2 subjects for basal insulin who withdrew due to hypoglycemia.

Overall, the data do not clearly demonstrate a hypoglycemia advantage for IDegLira vs. basal insulin for severe hypoglycemia although numbers of events were few and it is difficult to draw any meaningful conclusion. Less specific definitions of hypoglycemia such as documented symptomatic and Novo Nordisk confirmed appeared to trend towards what would be expected for each product with the most hypoglycemia generally observed in insulin only arms and the least in GLP-1 only arms with IDegLira falling somewhere in the middle. However, analyses of hypoglycemia should be interpreted in light of the dosing and titration concerns discussed previously. Further, a comparison of hypoglycemia between GLP-1 at maximal dose with basal insulin added vs. IDegLira is not available because a trial of this design was not conducted.

Therefore, it remains unclear with regard to hypoglycemia, for a patient who is tolerating liraglutide at the maximally approved dose for diabetes of 1.8 mg, if there is any benefit beyond the convenience of one injection per day, of changing to IDegLira therapy instead of adding basal insulin.

Summary of Hypoglycemia, IDegLira program, across definitions												
	IDegLira			**Basal Insulin**			**GLP-1**			**Placebo**		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Trial 3697												
ADA Severe	2(0.2) 3(0.4)*	2 3*	0.5 0.4*	2(0.5) 2(0.5) *	2 2*	1.0 0.6*	--- 2(0.5)	--- 2*	--- 0.6*			
ADA Documented symptomatic	300(36.4) 360(43.6)*	1601 2961*	412.7 419.7*	188(45.6) 233(56.6)*	1112 2237*	575.4 639.0*	36(8.7) 48(11.7)*	65 123*	34.9 36.8*			
Novo Nordisk confirmed	263(31.9) 327(39.6)*	699 1247*	180.2 176.7*	159(38.6) 203(49.3)*	496 977*	256.7 279.1*	28(6.8) 44(10.7)*	41 64*	22.0 19.1*			
Trial 3912												
ADA Severe	1 (0.5)	1	1.1	---	---	---						
ADA Documented symptomatic	71(35.7)	402	437.3	62(31.2)	470	522.2						
Novo Nordisk confirmed	48(24.1)	141	153.4	49(24.6)	237	263.3						
Trial 3851												
ADA Severe	1 (0.3)	1	0.7				---	---	---			
ADA Documented symptomatic	112(38.5)	974	691.1				12(8.3)	33	50.1			
Novo Nordisk confirmed	93(32.0)	397	281.7				4(2.8)	8	12.1			
Trial 3951												
ADA Severe	2 (0.7)	2	1.5							---	---	---
ADA Documented symptomatic	147(51.0)	994	748.6							31(21.2)	164	264.0
Novo Nordisk confirmed	120(41.7)	467	351.7							25(17.1)	84	135.2
Trial 3952												
ADA Severe	---	---	---	1 (0.4)	1	0.7						
ADA Documented symptomatic	137(49.3)	1041	803.2	182(65.2)	2113	1563.5						
Novo Nordisk confirmed	79(28.4)	289	223.0	137(49.1)	683	505.4						

*refers to the 52 week data for study 3697
Source: ISS; page 289 table 2-89; page 323 table 2-91; severe hypoglycemia- 3697: CSR page 1228, table 14.3.1.45; 3912: CSR page 705, table 14.3.1.46; 3851 CSR: page 680, table 14.3.1.47; 3951 CSR: page 610, table 14.3.1.46; 3952 CSR: page 678, table 14.3.1.47.
N: Number of Subjects; %: Percentage of Subjects with the Event; E: Number of Events; R: Event Rate per 100 Patient Year(s) of Exposure

Weight gain

Weight gain can occur with insulin therapy, including insulin degludec. The Applicant examined body weight changes as a pre-specified secondary hypothesis in trials 3697 (factorial study) and 3952 (vs. IGlar) to compare body weight change for IDegLira vs. insulin active comparator. The FDA statistician confirmed that overall, the pre-specified confirmatory statistical testing strategy controlled the type I error rate at a 2.5% level with respect to testing both the primary hypothesis and the secondary hypotheses. (b) (4)

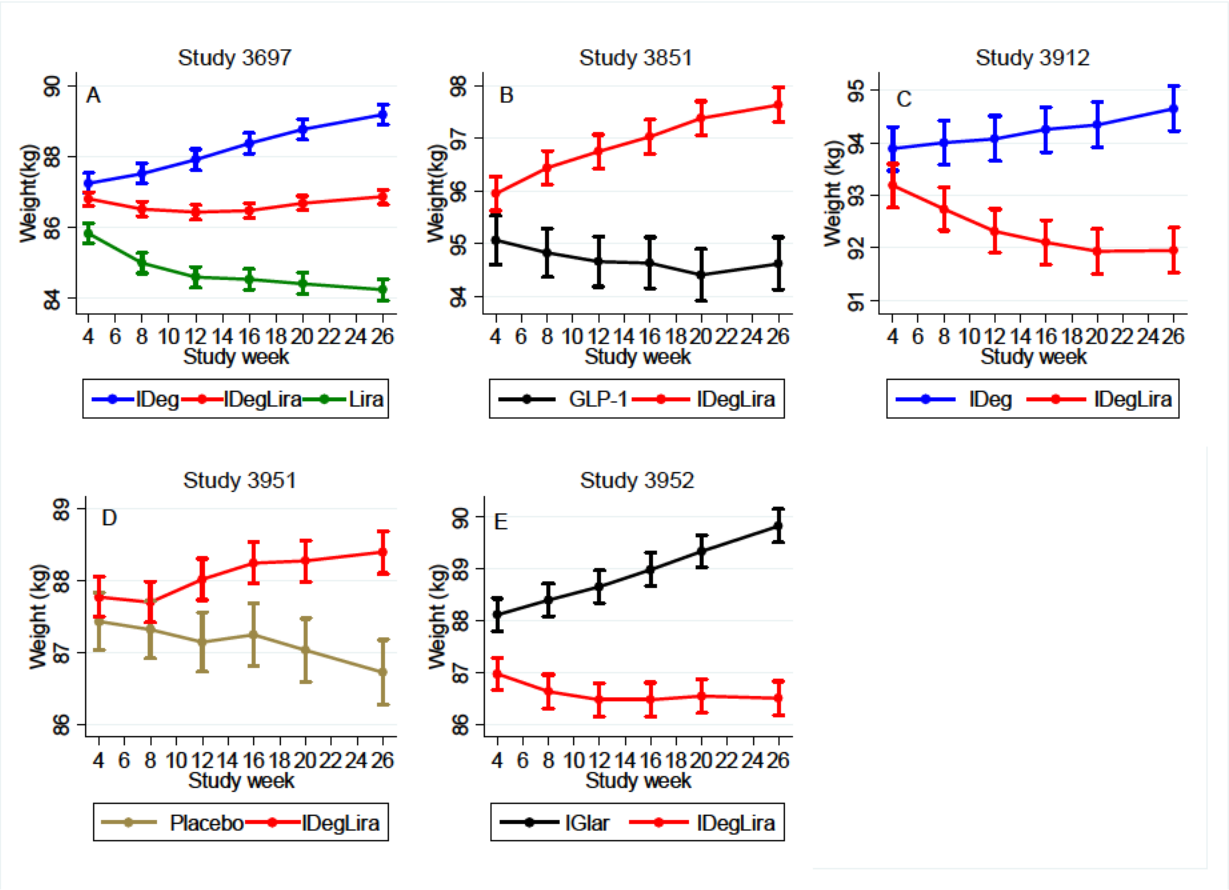
(b) (4)

The estimated differences in weight between arms are presented in the table below based on an MMRM analysis (with a similar method as that used for the primary endpoint, i.e. the mixed effects model included treatment, pre-trial anti-diabetic treatment (for some trials), all stratification factors (such as pre-trial antidiabetic treatment and baseline HbA1c level, study 3697 was also stratified by sub-study participation), and country/region as fixed effects and the baseline value of the parameter as a covariate). Generally, IDegLira caused weight gain when it was compared to a GLP-1 (3697 or 3851) or placebo (3951), IDegLira caused numerically less weight gain when it was compared to insulin (3697, 3912, 3952).

Estimated differences in body weight (kg) across phase 3 trials - FAS				
Study	**Treatment arm**	**Comparator arm**	**Estimate**	**95% CI**
3697	IDegLira	IDeg	-2.3	(-2.7, -2)
	IDegLira	Lira	2.6	(2.3, 3)
	IDeg		89.2	(88.9, 89.5)
	IDegLira		86.9	(86.7, 87.1)
	Lira		84.2	(83.9, 84.5)
3952	IDegLira	IGlar	-3.3	(-3.8, -2.9)
	IDegLira		86.5	(86.2, 86.8)
	IGlar		89.8	(89.5, 90.2)
3912	IDegLira	IDeg	-2.7	(-3.3, -2.1)
	IDegLira		91.6	(91.5,92.4)
	IDeg		94.7	(94.2,95.1)
3851	IDegLira	GLP-1	3.0	(2.4, 3.6)
	GLP-1		94.6	(94.1,95.1)
	IDegLira		97.6	(97.3, 98)
3951	IDegLira	Placebo	1.7	(1.1, 2.2)
	Placebo		86.7	(86.3,87.2)
	IDegLira		88.4	(88.1, 88.7)

Source: created by FDA statistical reviewer

Longitudinal changes in body weight are also what would be expected from these products (see figure below). In study 3697, body weight changes favored IDegLira over IDeg. At the same time, body weight changes were more favorable with lira when compared to IDegLira. In study 3851, body weight changes favored GLP-1 over IDegLira, and in study 3951, body weight changes favored placebo over IDegLira.



Source: created by statistical reviewer

Known safety issues with both insulin degludec and liraglutide

This section discusses the known safety issues associated with both insulin degludec and liraglutide use. Aside from the dose-dependent safety concerns such as GI tolerability, weight gain and hypoglycemia, I agree with Dr. Condarco's conclusions that overall, the use of liraglutide in combination with insulin degludec does not appear to significantly change the known safety profile of these two drugs relative to use of the individual components alone. No *new* safety concerns when combining the two drugs were identified. (Safety concerns related to the product presentation are discussed elsewhere in this review).

Immunogenicity

IDeg and liraglutide are both protein-based drugs that individually have a risk of causing immunogenicity related adverse events. Antibody development was assessed in one single dose-clinical pharmacology trial 3632 and 2 phase 3 trials: 3697 and 3912. For both phase 3 studies, the Applicant carried out multiple analyses to evaluate the relationship of antibody levels to adverse events and HbA1c. For both phase 3 studies, the Applicant carried out multiple analyses to evaluate the relationship of antibody levels to adverse events and HbA1c, across multiple studies there were no clinically meaningful differences noted.

Injection site reactions

Injection site reactions are labeled for both insulin degludec and for liraglutide. The Applicant's predefined MedDRA search for injection site reactions, across the pooled adjusted phase 3 trials revealed that the rate of adverse events for IDegLira were similar to placebo. When compared to active comparator, IDegLira had lower adjusted rates than basal insulin, but higher adjusted rates than GLP-1. For all treatment groups, the highest PT was injection site bruising.

Injection site reactions (predefined MedDRA search) by SOC and PT- treatment-emergent - completed phase 3 trials, adjusted frequencies and rates

	IDegLira			Basal insulin			GLP-1			Placebo		
System organ class (SOC) Preferred term (PT)	N (adj. pct)	E	Adj. rate	N (adj. pct)	E	Adj. rate	N (adj. pct)	E	Adj. rate	N (adj. pct)	E	Adj. rate
Safety analysis set	1881			890			557			146		
Total exposure (yrs)	1200.8			575.2			400.2			62 1		
Adverse events	49(2.6)	115	9.6	20(4.6)	28	18.3	20(2.7)	27	6 5	4 2.1)	13	9.5
General disorders and administration site conditions	49(2.6)	115	9.6	20(4.6)	28	18.3	20(2.7)	27	6 5	4 2.1)	13	9.5
Injection site bruising	29(1.5)	76	6.3	9(1)	10	1.9	9(1.2)	13	3	2 1)	11	6.5
Injection site pain	9(0.5)	13	1.1	4(0.3)	5	0.8	2(0.3)	2	0 4	1 0.9)	1	2.3
Injection site reaction	8(0.4)	9	0.7	3(0.3)	3	0.5	3(0.5)	5	1 2	1 0.4)	1	0.8
Injection site urticarial	1(<0.1)	5	0.4	1(<0.1)	1	0.2						
Injection site pruritus				4(0.5)	4	0.7	1(0.2)	1	0 2			
Injection site rash	2(0.1)	2	0.2									
Injection site mass	2(0.1)	2	0.2				1(<0.1)	1	0 1			
Infusion site pain				1(<0.1)	2	0.3						
Injection site hemorrhage	1(<0.1)	1	<0.1	1(<0.1)	1	0.2						
Injection site hematoma							1(0.2)	1	0 2			
Injection site nodule	1(<0.1)	1	<0.1				1(0.2)	1	0 2			
Injection site extravasation				1(<0.1)	1	0.2						
Vessel puncture site hematoma							1(0.2)	1	0 4			
Vessel puncture site bruise	1(<0.1)	1	<0.1									
Injection site inflammation	1(<0.1)	1	<0.1									
Application site reaction	1(<0.1)	1	<0.1									
Injection site swelling	1(<0.1)	1	<0.1	1(0.2)	1	0.2						
Injection site erythema	1(<0.1)	1	<0.1				1(<0.1)	1	0 1			
Injection site induration	1(<0.1)	1	<0.1									

Data are based on trials NN9068-3697 (including extension part), NN9068-3912, NN9068-3851, NN9068-3951 and NN9068-3952. N: number of subjects with adverse events; E: number of adverse events. Adj. pct: Adjusted percent; Adj. rate: Adjusted rate per 100 exposure years; Adjusted: Trial specific percentages (rates) are adjusted based on the relative risk vs. IDegLira and the naive IDegLira percentage (rate). Adjusted percentages (rates) are then weighted according to the number of subjects exposed to IDegLira for each trial. MedDRA version 17.0. Adverse events are summarized by SOC and PT and sorted by descending frequency.
Source: Applicant-adjusted rates for injection site reactions, table 14, submitted in information request 22 October 2015: \\cdsesub1\evsprod\NDA208583\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\integrated-summary-of-safety\adjusted-rates-meddra-hier.pdf

Known safety issues with liraglutide

This section discusses the safety issues associated with liraglutide use. Overall, the use of liraglutide in combination with insulin degludec does not appear to change the known safety issues relative to liraglutide use alone.

Gastrointestinal events

Gastrointestinal (GI) adverse reactions (e.g. nausea and vomiting) are common adverse reactions that are more frequently reported with liraglutide than with placebo. In the IDegLira program the incidence of adverse events in the Gastrointestinal Disorders SOC were higher in the IDegLira pool than in the basal insulin pool. The adjusted event rate of GI adverse events was 80.3, 33.4, 124.4 and 70.8 events per 100 PYE for IDegLira, IDeg, liraglutide and placebo respectively. PT terms present in more than 5% of the IDegLira subjects included diarrhea and nausea. Overall, GI adverse events were more common for the GLP-1 and IDegLira pool than for basal insulin or placebo pools.

When evaluating withdrawals due to adverse events in the Gastrointestinal Disorders SOC 0.4% of subjects withdrew in the IDegLira pool) while there were no withdrawals in the in the basal insulin or placebo pools for this SOC. Further, the rate of SAEs coded to the Gastrointestinal Disorders SOC was 0.4 per 100 PYE for IDegLira with no SAEs in this SOC in the basal insulin pool. The preferred terms in the IDegLira arm included: pancreatitis acute, colitis ischemic, small intestinal obstruction, gastrointestinal hemorrhage and gastritis (see Dr. Condarco's review for selected case narratives).

Many of the GI adverse events in the table below are not likely related to liraglutide use (e.g. toothache). However, it is clear from these data that patients treated with IDegLira will be expected to experience GI tolerability related adverse reactions that they would not otherwise experience if being treated with basal insulin without the GLP-1 analog component. The incidence of GI adverse events in the IDegLira group was not meaningfully different than placebo, but it is notable that the incidence of GI events in the basal insulin group was about half of those in the IDegLira and placebo groups, suggesting an unexpectedly high incidence in the placebo group.

Gastrointestinal events by SOC 'Gastrointestinal disorders' and PT- completed phase 3 trials with adjusted frequencies and rates												
	IDegLira			**Basal insulin**			**GLP-1**			**Placebo**		
System organ class (SOC)	N (adj.	E	Adj.	N (adj.	E	Adj.	N (adj.	E	Adj.	N (adj.	E	Adj.
Preferred term (PT)	pct)		rate	pct)		rate	pct)		rate	pct)		rate
Safety analysis set	1881			890			557			146		
Total exposure (yrs)	1200.8			575.2			400.2			62.1		
Gastrointestinal disorders	**470(25.0)**	**964**	**80.3**	**131(13.8)**	**213**	**33.4**	**217(33.5)**	**493**	**124.4**	**22(23.1)**	**33**	**70.8**
Diarrhea	141(7.5)	203	16.9	42(4.4)	51	8.1	75(11.4)	103	24.2	7(8.6)	8	20.6
Nausea	146(7.8)	182	15.2	26(2.7)	31	5.1	98(15.1)	125	32.7	5(5.9)	5	10.8
Vomiting	73(3.9)	104	8.7	15(1.5)	15	2.2	42(7.4)	61	19.2	4(4.4)	4	10.6
Dyspepsia	57(3.0)	67	5.6	7(0.8)	7	1.2	22(3.5)	28	7	1(0.7)	1	1.5
Constipation	46(2.4)	54	4.5	7(0.7)	7	1.1	21(2.9)	23	4.7	1(0.8)	1	1.6
Toothache	38(2.0)	52	4.3	13(1.4)	15	2.6	11(1.7)	11	3.1	2(8.0)	2	18.5
Gastritis	36(1.9)	46	3.8	8(0.8)	9	1.4	11(2.6)	13	4.7			
Abdominal pain	33(1.8)	36	3	11(1.5)	13	2.5	13(4.5)	13	7.8			
Abdominal distention	26(1.4)	28	2.3	9(1.0)	10	1.8	11(2.3)	12	4.4	1(0.9)	1	1.7
Abdominal pain upper	23(1.2)	24	2	12(1.5)	13	2.3	10(1.9)	12	3.9	1(0.6)	2	2.1
Abdominal discomfort	19(1.0)	21	1.7	6(0.7)	6	1.2	13(2.5)	15	5.5	1(0.7)	1	1.6
Gastroesophageal reflux disease	18(1.0)	18	1.5	4(0.4)	5	0.8	14(2.0)	18	4.1			
Flatulence	15(0.8)	15	1.2				5(0.5)	6	1.1			
Hyperchlorhydria	9(0.5)	10	0.8	1(0.1)	1	0.2	9(1.4)	9	2.5			
Eructation	9(0.5)	9	0.7				3(0.4)	3	0.7			
Dental caries	9(0.5)	9	0.7	1(0.1)	1	0.2	2(0.2)	2	0.4			
Colitis	5(0.3)	7	0.6	2(<0.1)	2	<0.1		2(0.8)	2	1.8		
Food poisoning	6(0.3)	7	0.6	4(0.3)	4	0.5	1(<0.1)	1	0.2			
Dry mouth	7(0.4)	7	0.6	3(0.3)	4	0.7	5(0.7)	5	1.1	1(0.4)	1	0.6
Abdominal pain lower	4(0.2)	6	0.5				1(0.2)	1	0.4			
Enteritis	4(0.2)	4	0.3	1(<0.1)	1	<0.1						
Hiatus hernia	4(0.2)	4	0.3				1(0.1)	1	0.2			
Abdominal tenderness	2(0.1)	2	0.2				1(<0.1)	1	0.1			
Irritable bowel syndrome	2(0.1)	2	0.2	1(0.1)	1	0.2	2(0.3)	2	0.5			
Esophagitis	3(0.2)	3	0.2									
Apthous stomatitis	2(0.1)	2	0.2	1(<0.1)	1	0.2						
Mouth ulceration	2(0.1)	2	0.2									
Hematochezia	3(0.2)	3	0.2	1(0.2)	1	0.3	1(0.2)	1	0.4			
Gastrointestinal hemorrhage	2(0.1)	2	0.2				1(<0.1)	1	0.1			
Hemorrhoids	3(0.2)	3	0.2	1(0.2)	1	0.3	2(0.5)	2	0.8	1(0.7)	1	1.6
Diverticulum	2(0.1)	2	0.2									

Large intestine polyp	2(0.1)	2	0.2	1(<0.1)	1	0.1				1(0.7)	2	3.2
Peptic ulcer	2(0.1)	2	0.2	1(<0.1)	1	<0.1	1(0.2)	1	0.3			
Gastrointestinal pain	1(<0.1)	1	<0.1				2(0.4)	2	0.4			
Feces soft	1(<0.1)	1	<0.1									
Aerophagia	1(<0.1)	1	<0.1									
Dysphagia	1(<0.1)	1	<0.1				1(<0.1)	1	0.1			
Abnormal feces	1(<0.1)	1	<0.1									
Frequent bowel movements	1(<0.1)	1	<0.1									
Diarrhea hemorrhagic	1(<0.1)	1	<0.1									
Gingival pain	1(<0.1)	1	<0.1									
Tooth impacted	1(<0.1)	1	<0.1									
Tooth disorder	1(<0.1)	1	<0.1	1(<0.1)	1	0.2						
Poor dental condition	1(<0.1)	1	<0.1									
Enterocolitis	1(<0.1)	1	<0.1	2(0.1)	2	0.2	1(<0.1)	1	0.1			
Gastrointestinal inflammation	1(<0.1)	1	<0.1									
Colitis ischemic	1(<0.1)	1	<0.1									
Duodenitis	1(<0.1)	1	<0.1									
Esophageal disorder	1(<0.1)	1	<0.1									
Oral pain	1(<0.1)	1	<0.1	1(<0.1)	1	0.1	2(0.2)	2	0.3			
Paraesthesia oral	1(<0.1)	1	<0.1									
Odynophagia	1(<0.1)	1	<0.1	1(<0.1)	1	<0.1						
Melena	1(<0.1)	1	<0.1									
Diverticulum intestinal	1(<0.1)	1	<0.1							1(0.7)	1	1.6
Anal fissure	1(<0.1)	1	<0.1	1(<0.1)	1	0.1	1(<0.1)	2	0.3			
Pancreatitis acute	1(<0.1)	1	<0.1									
Pancreatitis chronic	1(<0.1)	1	<0.1									
Tongue discoloration	1(<0.1)	1	<0.1									
Small intestine obstruction	1(<0.1)	1	<0.1									
Feces discolored							1(0.2)	1	0.4			
Impaired gastric emptying										1(0.7)	1	1.6
Change of bowel habit							1(0.2)	1	0.2			
Gingival bleeding							1(0.2)	1	0.2	1(0.7)	1	1.6
Tooth loss				1(<0.1)	1	0.2						
Tooth deposit							1(0.2)	1	0.2			
Gastric disorder				1(<0.1)	2	0.3						
Gastrointestinal disorder							1(0.2)	1	0.2			
Salivary gland calculus				1(0.2)	1	0.2						
Lip dry							1(0.2)	1	0.2			
Stomatitis				1(0.2)	1	0.2						
Mouth hemorrhage				1(0.2)	1	0.2						

Cheilitis							1(0.2)	1	0.2			
Hemorrhoidal hemorrhage							1(0.2)	2	0.4			
Umbilical hernia							2(0.4)	2	0.4			
Abdominal hernia							1(0.2)	1	0.2			
Gastric polyps							1(0.2)	1	0.2			
Gastritis erosive										1(0.7)	1	1.6

Data are based on trials NN9068-3697 (including extension part), NN9068-3912, NN9068-3851, NN9068-3951 and NN9068-3952. N: number of subjects with adverse events; E: number of adverse events. Adj. pct: Adjusted percent; Adj. rate: Adjusted rate per 100 exposure years; Adjusted: Trial specific percentages (rates) are adjusted based on the relative risk vs. IDegLira and the naive IDegLira percentage (rate). Adjusted percentages (rates) are then weighted according to the number of subjects exposed to IDegLira for each trial. MedDRA version 17.0.
Adverse events are summarized by PT and sorted by descending frequency. Source: : Applicant-adjusted rates for injection site reactions, table 16, submitted in information request 22 October 2015: \\cdsesub1\evsprod\NDA208583\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5353-rep-analys-data-more-one-stud\integrated-summary-of-safety\adjusted-rates-meddra-hier.pdf

Thyroid neoplasms

Currently all approved long acting GLP-1 analogs, including Victoza, have a boxed warning for related to findings of thyroid c-cell tumors in rats and mice. At this time, the relevance of this finding to humans is uncertain but medullary thyroid carcinoma is a potential safety risk for long acting GLP-1 analogs. Further evaluation of this potential safety concern is ongoing, through postmarketing requirements invoked with the approval of Victoza as well as other GLPL-1 analog programs. It is perhaps important to note that unlike GI adverse reactions which appear to be dose dependent, the relationship between dose and thyroid c-cell tumors (if any) in humans is unknown.

The clinical development program for IDegLira is too small and short-term to reasonably expect to see any cases of MTC; nevertheless, this safety issue was an area of special interest in the IDegLira development program. An external blinded event adjudication committee adjudicated thyroid disease events as those requiring thyroidectomy and/or a thyroid neoplasm. For events classified as a neoplasm, the type of neoplasm and malignancy status was noted. A total of **one** event was adjudicated as "confirmed" by the EAC. The EAC classified the event as "non-neoplasm." This event occurred in a 72 year old woman randomized to liraglutide with pre-existing history of a multinodular goiter.

Results of laboratory measures of calcitonin
Calcitonin concentrations were measured at baseline, week 12, 26 (and 38 and 52 for 3697) and results reported separately for males and females. Evaluations of shifts from baseline to end-of-trial in pivotal trials or pooled phase 3 studies were unremarkable. The proportion of subjects in the pooled phase 3 studies that shifted from normal to a high calcitonin level were 2.5%, 3.7%, 3.2% and 0.9% for IDegLira, basal insulin, GLP-1 analog, and placebo, respectively. 1.3%, 2.4%, 1.3% and 1.4 % of subjects randomized to IDegLira, basal insulin, GLP-1 analog and placebo, respectively, had an increase in calcitonin ≥20 ng/dL. Only one subject, randomized to IDegLira had an increase in calcitonin ≥50 ng/L.

Overall, there are no additional data derived from the IDegLira program that change the known safety profile of liraglutide with regard to thyroid neoplasms.

Pancreatitis

Pancreatitis has been reported with use of incretin-based therapies; all GLP-1 based therapies, including Victoza, have labeled warnings concerning the risk of pancreatitis. In the IDegLira development program, pancreatitis was evaluated by adverse event reports adjudicated by an external blinded committee and by examination of routine laboratory monitoring of serum amylase and lipase concentrations which was specified for collection a minimum of 3 times during the trial (including at the beginning and at trial end). Adverse event reports of 'lipase increased' or 'amylase increase' were also examined. However, these were not adjudicated.

Of the five events reported as 'pancreatitis' by the investigator, that were sent for adjudication, only 2 events were adjudicated as acute pancreatitis (1 event for liraglutide and 1 event for IDeg).

In the pooled analysis of unadjudicated adverse event reports of 'lipase increased' event rates were similar among the IDegLira, GLP-1, and placebo arms and lower in the basal insulin arm. Adverse event reports of 'amylase increased' were similar among groups.

When evaluating by trial, IDegLira had a higher event rate per 100 PYE than comparators in all trials (with the exception of trial 3697-ext, where liraglutide had a higher rate than IDegLira). In trial 3851, subjects in the IDegLira arm had a higher incidence of 'lipase increased' than those in the GLP-1 arm. The event rates per 100 PYE of IDegLira for 'amylase increased' were higher than comparator for trials 3912 and 3951; otherwise findings were similar between treatment groups.

Rates of MedDRA PTs of 'lipase increased' and 'amylase increased'- phase 3 trials

Trial ID	IDegLira	Basal insulin	GLP-1	Placebo	IDegLira	Basal insulin	GLP-1	Placebo
	Lipase increased (events per 100 PYE)				**Amylase** increased (events per 100 PYE)			
Pivotal trials								
3697-ext	7.8	5.7	12.0		2.8	2.3	2.7	
3912	13.1	7.8			5.4	2.2		
Other phase 3 trials								
3851	22.0		12.1		1.4		1.5	
3951[a]	22.6			12.9	8.3			4 8
3952	6.9	3.0			1.5	1.5		
Pooled	11.4	5.4	12.0	12.9	3.3	2.1	2.5	4 8

a: Note: in addition, 1 event of 'hyperlipasaemia' was reported in the IDegLira group (rate: 0.8 events per 100 PYE) Source: ISS, page 197, table 2-39.

Labeling for liraglutide containing products already include a Warning and Precaution for pancreatitis and describe increased lipase in the laboratory values section. There are no new findings in the IDegLira program that would change this approach to labeling these safety concerns, and IDegLira should include the same language in its Prescribing Information.

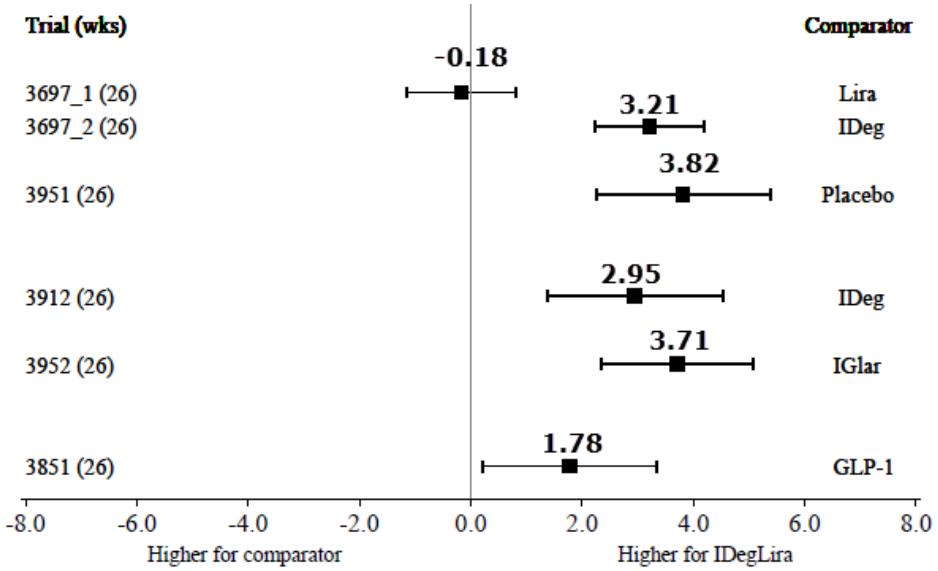
Heart rate increase

Liraglutide is associated with a 2-3 beat per minute heart rate increase. The clinical significance of this finding is unknown and will be evaluated during review of the cardiovascular outcomes trial for Victoza (the LEADER trial). Labeling for liraglutide containing products already contain information about increased heart rate and the data from the IDegLira program are consistent with current labeling for liraglutide products. In the

IDegLira clinical development program, the IDegLira arm in phase 3 trials generally had an increase in mean heart rate of 2-3 beats per minute from baseline (with the exception of 3851, where there was no increase in mean heart rate). Similar heart rate changes were seen in the liraglutide arm of 3697.

Pre-specified statistical analyses conducted by the Applicant showed that the change in mean resting heart rate from baseline to week 26 was statistically significantly greater when comparing IDegLira to IDeg, placebo or insulin glargine (IGlar). In trial 3851 the IDegLira arm had a stable mean resting heart rate during the study while the GLP-1 arm showed a mean decrease in resting heart rate, resulting in a statistically significant difference between groups.

Mean change in heart rate from baseline to 26 weeks- completed phase 3 trials - plot of treatment contrasts - FAS



wks: weeks. Estimates with 95% confidence interval. Last observation carry forward imputed data.

Source: ISS, Figure 4-1, page 405. Mean treatment difference between IDegLira and comparator was added by FDA reviewer from ISS, table 4-5, page 408.

Safety concerns related to the product presentation

Overdose

The Applicant carried out a pre-defined MedDRA[3] search for overdose and found a total of 13 events in the pooled safety dataset: 6 in the IDegLira group, 1 in the basal insulin group, 2 in the GLP-1 agonist group, and 4 in the placebo group, corresponding to adjusted event rates of 0.5, <0.1, 0.4 and 6.4 per 100 PYE, respectively. Therefore, this analysis does not suggest a risk of overdose in the clinical development program. However, discussions with DMEPA have raised the point that Phase 3 clinical trials, due to their duration, size, and oversight, are

[3] The MedDRA search was for the following PT terms: Accidental overdose, Completed suicide, Intentional overdose, Overdose, Prescribed overdose, Suicide attempt

very unlikely to identify potential medication errors, such as overdose, that may occur in the care setting. Further, the MedDRA search for overdose performed by the Applicant was primarily focused on 'intentional' overdose, and does not help to elucidate risk due to accidental error.

To more broadly evaluate the risk of overdose and the associated AEs, Dr. Condarco queried the Applicant about the proportion of subjects who overdosed (at some point took >50 dose steps of IDegLira). The Applicant reported that 74 of 1881 (3.9%) subjects randomized to IDegLira exceeded the maximum permitted dose of 50 dose steps. Of note, the pen used in the clinical trials could exceed the 50 dose step dose, unlike the to-be-marketed pen, which can only be dialed up to a maximum of 50 dose steps.

Of these 74 subjects, 20 AEs in 16 subjects were identified[4] From the PT terms in these subjects, most (5) had "accidental overdose." One subject injected 50 dose steps twice on one occasion because he forgot he had taken a dose. There were no adverse events associated with hypoglycemia with any of these overdoses.

Medication error

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to review the prescribing information (PI), Medication Guide, Instructions for Use (IFU), carton labeling, and the proposed pen dial design and re-design for Xultophy (Appendix A) and to evaluate the human factors (HF) validation study report, labeling comprehension study and the Applicant's proposed Tradename. While it is understood that DMEPA routinely provides consultative review to the Division for proposed new products, for IDegLira there were a number of medication error safety concerns identified in the submission for which DMEP sought expert advice.

As noted previously in this review, IDegLira is a multi-ingredient product that combines an insulin with a GLP-1 agonist in a single container closure system. The introduction of a non-insulin component to what has traditionally been only insulin-based combination products presents a challenge with respect to the product's labeling in order to ensure that the pen injector is likely to be used appropriately.

Term of Measure

Unlike insulin-insulin combination products, the two active ingredients in this proposed product are dosed using different terms of measure (units vs. mg). Additionally, unlike the other insulin-insulin combination products, the components of this product are not conventionally dosed in the same manner. Insulin is dosed on a continuous scale; doses can be adjusted unit-by-unit depending on the patient's clinical need. In contrast, the currently approved GLP-1 agonists are dosed at fixed increments that provide the range of dosing intended to meet clinical needs, but not on a continuous scale. For example, liraglutide dosing is initiated at 0.6 mg, increased to a dose of 1.2 mg, and then, as needed, increased 1.8 mg.

[4] AEs were identified from the first day the first day of the overdose and up to 7 days following the last dose of >50 dose steps \\cdsesub1\evsprod\NDA208583\0006\m1\us\111-info-amendment\re-fda-20151203.pdf

The pen device cannot deliver doses that fall intermediate to these increments; doses such as 0.7 mg or 1.5 mg cannot be achieved using the currently approved products. As such, this proposed combination product would differ from other injectable combinations of insulins. Insulin combinations that contain two active ingredients share a common measure (units) term and the components are each amenable to dosing in a continuous fashion.

In the IDegLira clinical development program the term "dose step" was used as the term of measure. Subsequently, the Sponsor proposed to remove the term of measure altogether. Neither of these approaches were considered acceptable by DMEPA because most electronic medical systems require the specification of a unit of measure before a drug can be prescribed; a drug with a novel term of measure such as 'dose steps' would not be able to be entered into an electronic system, and the lack of any unit of measure could result in confusion and potential errors in the postmarketing period. Also, neither approach would convey what is contained in the product. The use of both dosage units ("units" and "mg") was also considered, but this approach, was felt, would create more confusion (for patients and prescribers) even if the pen device was re-designed to show both drug components.

(b) (4)

If the dosing in the PI and on the pen device were to express both active ingredients, it may be cumbersome in labeling and practice. On the other hand, focusing on the insulin component alone may introduce a risk of medication error if prescribers neglect to take into account the GLP-1 component when dosing the product.

Since the product dosing is centered upon the insulin component, practitioners may be inclined to express the dose using the unit terminology. The labeling comprehension study for IDegLira (see Dr. Conrad's review in DARRTS 13 Jul 2016) conducted by the Applicant indicated that the majority of the errors occurred when the prescribers did not use the PI and relied on their own experience with dosing insulin products. However, several prescribers that did use the PI for dosing information chose to deviate from the PI as well because they incorporated their clinical experience into their decisions. This could result in dosing the liraglutide component too high when initiating therapy with IDegLira with resultant GI intolerability. In the labeling comprehension study DMEPA noted that 17 of the 20 prescriber participants referred to the IDegLira dose using the term "units" at least once when completing the written prescribing tasks during the study. In addition, multiple participants expressed uncertainty about how to refer to the dose and asked for assistance to determine if the dose would be considered units.

DMEPA noted that experience with other multi-ingredient products was not able to inform this issue. In the examples identified where the products contained two or more active ingredients with different unit of measure, dosing of the product could be conveyed using the presentation[5] or the dosage form[6] to be administered. In these instances, the dose of each single ingredient

[5] For example, a multi-ingredient contains 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g citric acid is supplied as a powder in a packet has dosing that is consistent with the entire contents of the package, which allows the dose to be reduced to "1 packet" on prescriptions.

[6] Consider, for example, a product like Neosporin which contains neomycin 3.5 mg, polymyxin B 10,000 units,

would generally not be specified on the prescription order since there are other more simple terms available to accurately and efficiently describe the dose.

DMEPA stated that considering the current design of the pen injector and user familiarity with the term for insulin products, "units" may be the least problematic strategy for the IDegLira labels and labeling.

Proprietary name

In part, because if approved, IDegLira would have the term of measure of 'units', DMEPA agreed with DMEP that a modifier to the proprietary name could be helpful in reminding prescribers that there are two drug components in the product. The name 'Xultophy 100/3.6' was recommended based on the concentration of each component in the final formulation. Another term considered was (b) (4) However, DMEPA noted that this approach would deviate from precedent and may introduce additional medication error risk by confusing patients that they must give themselves that specific dose. Since 100/3.6 will not be an approved dose for IDegLira, this mix-up is less likely to occur. I agree with the recommendation of DMEPA that 'Xultophy 100/3.6' is the most reasonable proprietary name that incorporates a numerical modifier to indicate that there are two drugs in the product. This nomenclature is similar to that currently used for marketed insulin/insulin mixtures, where the numerical modifier conveys the percentage of each insulin in the mixture.

Potential overdose of liraglutide component

DMEPA also identified a potential medication error concern related to the potential for overdose of liraglutide with multiple injections, particularly for patients that may need doses of insulin degludec greater than 50 units. Although the proposed labeling may provide statements that advise clinicians of the maximal dose, prescribers may inadvertently prescribe doses larger than 50 units given their familiarity with the practice for prescribing long-acting insulin products, including IDeg, which do not have maximum doses. As a result, if this product is prescribed for doses that are higher than 50 units, the liraglutide component that could be delivered would be higher than the maximum labeled dose recommended for that component (i.e., 1.8 mg), which could lead to an increased likelihood of certain adverse events such as severe nausea and vomiting. Prominent labeling warnings that indicate IDegLira should not be dosed more than 50 units daily and should not be administered with other GLP-1 analogs is recommended.

Human factors evaluation

Separately, the Applicant has completed validation studies that assess whether users can operate the pen as intended to administer the drug. Human Factors (HF) study for insulin degludec and liraglutide was conducted with 174 representative users (16 physicians/physician assistants/nurse practitioners, 15 pharmacists, 15 nurses, and 64 adult diabetes patients, and 64

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and bacitracin 400 units per gram, is supplied as an ointment and is usually prescribed with instructions such as "apply as directed" or "apply the ointment ...".

elderly diabetes patients). The study was designed to simulate use tasks and provide data to support that intended users can dispense, differentiate, prepare, and administer doses. The study evaluated all the tasks necessary for the injection process (e.g., dialing and administering a dose). Although some errors occurred in the HF study, the use errors noted in the HF study occur with this device platform and can be adequately addressed with routine labeling.

9. Advisory Committee Meeting

An Advisory Committee meeting was held on May 24, 2016 to discuss the IDegLira application.

The committee members were first asked to discuss whether they would start IDegLira in patients with type 2 diabetes who had not been exposed to either of the two components (lixisenatide and glargine) and to explain why they would or would not use the combination in these patients. Many of the endocrinologists (Burman, Wilson, and Smith) did not see a benefit of the combination in patients naïve to either product and could not identify a patient population of naïve patients for whom this combination would be useful. Dr. Gelato stated that giving a lower dose of two drugs may help patients reach glycemic targets while mitigating other effects such as weight gain. Dr. Kewalramani and Neaton both suggested using the HbA1c enrollment criteria to guide for whom the drug may be beneficial.

Dr. Berman: What I'm having trouble with is the issue of who exactly this medication be used on in an insulin-naïve patient. So for example, if a patient has a hemoglobin A1c of, let's say, 7 to 9 percent, why not just start with a single agent? Because if you start double agents, you may be giving them a medication that they don't need. And it costs money, and time, et cetera. And I realize the convenience of one injection however. On the one hand, if the hemoglobin\ A1c is 9, or 10, or 11, I realize there are glucose toxicity issues. But most people are going to start as much insulin as they need and move up very rapidly with long-acting insulin probably with short-acting pre-meal insulin at the same time. So I recognize the need in the physician armamentarium for this medication, but I don't have it clear in my own mind which group of patients it would be most useful for. We don't have a study 1 comparing the combination therapy versus individual independent agents to see which ones were more effective and got to the glycemic control quicker.

Dr. Smith: I've struggled with the same issue. Typically, in patient care, with concerns about side effects of drugs, which are often difficult to anticipate, it's wanting to expose patients to the minimum number of agents, i.e. one at a time, as one advances. I understand that -- or I believe that there certainly are patients who benefit from both of these drugs. It's a question – given simultaneously, the question is how to get there. And I had the same difficulty recognizing some of the advantages of using the drugs in combination such as potential effects in decreasing the weight gain that often occurs with insulin. But I, again, feel confronted with the problem in anticipating how to start these on the background of neither which is the variability in patient responses in terms of something such as weight gain. So certainly, for some patients, that's a major problem. It's difficult to predict that. There are patients who are very resistant to taking insulin either because they have heard from various sources that

weight gain is a problem -- and it can be very difficult to convince them otherwise -- or because perhaps they previously had a period of insulin treatment and they experienced weight gain. So that might be a group of patients, perhaps not a very large one, where it really could make the difference in terms of persuading them to start insulin. That's the same group of patients, however, that one could alternatively potentially start on a GLP-1 receptor agonist. …if I had a patient who had pretty markedly elevated glucose levels, where I was anticipating that insulin would most likely be something that they would require very strong probability, and I was in this situation of resistance, I can see situations where I might be able to convince that patient. That patient might be comfortable accepting insulin knowing that they are getting a drug that will address a concern that -- that really for some patients, they simply won't take insulin no matter how terrible those blood glucose levels -- of course, I'm speaking from direct anecdotal personal experience. So I guess that's one set of patients I can see where, perhaps not supported adequately by data, in terms of the anticipated response in that patient, in real life, it might make a difference in their willingness to accept insulin.

Dr. Wilson: …This is the algorithm that's set forward by the American Diabetes Association and it's the starting point for those of us who are endocrinologists. A tremendous 1 amount of work has gone in to develop this over the last 20 years or more. And it's really targeted towards adults with type 2 diabetes…. So the question is, where would this new formulation fit? And for sure, one of the places it would fit is as a person who is a little lower (than 10), in the 7 to 8 range and would get a GLP-1 receptor antagonist, and if they do not get a good response right away, potentially you would get the combination therapy, because then, as you move to the triple therapy, you would go from an insulin to an insulin plus a GLP-1 drug.

Dr. Gelato: I agree with Dr. Wilson that I think one of the places where this could fit is in people who have A1cs that are somewhere in that 7-9 range. I agree that, when you get to 10, you're really looking at having to treat the patient in a different way and I'm not sure this is the drug for that….So I think that even though it is two drugs, if you're giving lesser of both, then it looks like hopefully you might get them to their target and minimize any other effects. And if you mitigate the weight gain, which I agree with you is a real problem for patients, then to me, there's a place for this drug to fit in, in that category.

Dr. Smith wondered how the use of IDegLira in patients naïve to either component would be different than starting metformin and insulin at the same time, which is done frequently in clinical practice. Dr. Budnitz pointed out that with metformin the effective dose is known and prescribed upfront, whereas with the product presentation of IDegLira *it's not clear to me that the GLP-1 agonist here is effective at the dose that we would start independently.*

The committee members were then asked to discuss the benefits of using the fixed-combination drug product containing lixisenatide and insulin glargine in patients with type 2 diabetes previously treated with either a basal insulin or a GLP-1 agonist i.e. adding a single new drug by using this combination to an existing regimen. The endocrinologists on the panel seemed more open to this approach.

Dr. Burman: I think the advantages of the combination are obvious with regard to cost, and single injection, and patient compliance. I, personally, as I have indicated before, would

prefer this approach of adding one agent on to another first to see whether the initial agent is effective over a period of 4 to 8 weeks or whatever and then add on the second agent…patients who would prefer this approach, given that you always want patient interaction and discussion about what you're doing and the management, and especially if the A1c was minimally elevated in the 7 to 9 range, and you wanted to start this combination, individually, I think that would be fine.

Committee members felt that for a patient already on insulin, adding a GLP-1 without increasing the number of daily injections was a benefit.

With regard to the fact that when changing from one of the individual components to the combination the dose of the individual component would have to be decreased, panel members stated the following:

Dr. Smith: that presents a challenge and it's not ideal. But I do think we heard some about it from the open public hearing today, but certainly, from my practice experience as well, one injection versus two injections is a major issue…if one experiences a little bump in glycemia as a consequence of that switch, I would anticipate that to be a modest impact.

Dr. Burman: I still would consider it, but would monitor the patient closely.

The committee members requested additional analyses from the Applicant which showed that initiating IDegLira in a patient already using either component, despite the dose reduction, did not experience glycemic escape in the early period and no subject had to withdraw from the trial for hyperglycemia in the early weeks.

Dr. Smith summarized this part of the discussion as follows: *it would be nice to give a more directive clear summary and advice to the FDA than we're giving on this one, but I don't think we can. There is generally more acceptance of the notion that there may be significant patient populations among individuals who are on either insulin, and not a GLP-1 agonist or a GLP-1 agonist, and not insulin in whom a transition to this combination might be acceptable. But it would perhaps be most comfortable in the case of patients who are on a GLP-1 agonist who then may transition to the combination recognizing that it would mean initially a lowering of their dose of the GLP-1. For patients who are on insulin…there may be a significant population in which this would apply…although data presented showing that patients on as much as 40 units of insulin at the time that they undergo a step down and a transition to the combination by fasting glucose appeared not to have severe adverse effects of that transition…with the data available, it's difficult to define level of insulin, a dosage of insulin that is where we would start it and a dose where we would not.*

With regard to the product presentation, Dr. Meisel, an expert in Medication Error stated: *so you're going to enter an order into a computer. I want to give 16. Well, 16 what? Every computer will require a unit of measure, right? I'm not sure if the computer companies are going to be happy about coming up with a new one called "dose steps" or something. We need to come up with something that's different. I could also see that the fact that this is a combination of two different drugs being real apparent to an endocrinologist, but really lost*

on an orthopedic surgeon who's admitting somebody for a broken leg at 9:00 on a Friday night and wanting to continue home medications. And then there's calls of blood sugars high and they're doing all sorts of things that they shouldn't be doing. So I think we need to get into the real world of practicality of how a product like this will end up getting used in a large population and make it real clear that this is not just insulin, but this is two medicines with unique profiles. You don't go and add Victoza to this. And then if patient reaches 50, you can easily see a person who doesn't know what they're doing saying, well, add 10 more, and so then they're getting two shots. And whether they go and add Lantus to this and that, you know, all sorts of things will end up causing all sorts of -- I can see the med-error reports flying in to my desk today…the prescribers in this 1 case will be very broad because we've got to be thinking beyond the endocrinologist and even the internist who's prescribing it de novo. It's the people who are continuing it, the hospitalists, the orthopedic surgeons, the whoevers, the nursing-home doctors, whoever they may be that would be continuing therapy, started by somebody else. But they're still put in the business of prescribing it, and monitoring, and doing all the other kind of work.

At the end of the meeting the Advisors were asked if they recommended approval of the fixed combination drug product delivered using the proposed pen device for the treatment of adult patients with type 2 diabetes. The vote was unanimously for approval: Vote: Yes: 16; No: 0; Abstain: 0. Please see Dr. Condarco's review for the rational explained by each committee member for their vote. In general, the votes were explained by the reasoning articulated during the discussion section of the meeting which is outlined above. The majority of panel members either did not comment on the appropriate patient population or stated that they felt most comfortable with use of this product for patients already using one of the components who required additional glycemic control.

10. Pediatrics

For this application, we are waiving the pediatric study requirement in patients aged 0 to < 10 years old for this application because necessary studies are impossible or highly impracticable. We are waiving the pediatric study requirement in patients aged 10 years to <18 years old for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age range and is not likely to be used in a substantial number of pediatric patients in this age range. This determination was made based on the following:

> Appropriate studies to support the safety and effectiveness of this fixed dose combination product would require enrollment of patients for who require treatment with three or more antidiabetic agents. The population of patients appropriate for such a study are small (estimated to be 1% of the pediatric type 2 diabetes mellitus population) and are impractical. Additionally, the fixed dose combination product does not provide any meaningful therapeutic benefit over the use of the separate individual products.

The Pediatric Review Committee has agreed with the above plan.

11. Other Relevant Regulatory Issues

Regulatory Briefing

A closed (to the public) discussion occurred for this product on 29 Jul 2016 to discuss issues related to IDegLira and the similar product Soliqua that still remained after the Advisory Committee meetings for these products. The questions posed to the panel included:

1. *Discuss the specific limitations of the proposed fixed combination drug product. Specifically discuss issues related to the following:*
    a. *A dose range that includes a potentially ineffective dose of one of the components*
    b. *Lack of flexibility and the ability of the proposed drug product to address the needs of a significant patient population requiring concurrent therapy*
    c. *The potential for medication errors due to the product design (e.g., strengths, device, naming, expression of dosing, etc.)*

Based on the discussion to question 1, do you feel that the drug product as currently designed would be safe and effective for patients with diabetes?

The Panel agreed that both products met the regulatory statute of the combination rule; however there was still residual concern over medication errors and the appropriate population for whom these products would be useful. In particular, there was concern over loss of glycemic control when converting from maximally dosed GLP-1 analog to the combination product. Panel members felt that converting a patient on a maximally effective dose of a GLP-1 analog to a combination of GLP-1 and insulin with a consequent reduction of the GLP-1 dose was of questionable clinical sense. However, the availability of one injection instead of two injections in patients who required both products was considered a clinical benefit.

Despite the agreement that the programs had satisfied the combination drug rule, there was still concern about the questionable efficacy of the GLP-1 component, at the lower dose range. It did not appear that the concern was an approvability issue, but again, was a question of what patient population would benefit from this product. Patients using low doses of this product would be receiving low doses of the GLP-1 component for which there was not specific data to justify (as discussed previously, effectiveness was established as a whole across the entire dose range).

Data Quality/Integrity

The Office of Scientific Investigations, Good Clinical Practice Assessment Branch was consulted for inspection of clinical sites for this NDA. Six clinical investigator sites were inspected. These inspections did not reveal significant regulatory violations and no Form FDA 483s were issued. These inspections have been classified as No Action Indicated (NAI).
I agree with the conclusion of the OSI consultants that based on results of these clinical investigator inspections, the data submitted by the sponsor in support of this NDA are acceptable and the studies appear to have been conducted adequately. Details of the inspections are included in the reviews by Dr. Alfaro from OSI, and Dr. Condarco.

12. Labeling

1. The proposed indication is 'as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The revised indication will include that patients should be inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily) to ensure safe and effective use of the product.

2. The recommended proprietary name is Xultophy 100/3.6. The modifier reflects that there are two drugs in the product. See 'Medication Error' discussion above. The indication section of labeling should also state that 'Xultophy 100/3.6 is a combination of insulin degludec and liraglutide.'

3. A limitation of use (LOU) is recommended to ensure prescribers avoid duplication of therapy with existing GLP-1 receptor agonist products as follows: XULTOPHY 100/3.6 is not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist.

4. For the purposes of labeling the phase 3 trial findings in Section 14 of the PI, we want to show the analysis that best represents the 'true' treatment effect of the drug. The statistical review team recommended a multiple imputation approach. Specifically, a return to baseline was assumed for subjects who dropped out, i.e. missing values at end of trial were imputed from the baseline value adding a random error. The random error was normally distributed with a mean of zero and a standard deviation equal to the residual standard deviation. For each complete dataset, the change from baseline to week 26 was analyzed using an ANCOVA model with pre-specified covariates explanatory variables (treatment, baseline HbA1c stratum, sub-study, concomitant diabetes treatment, and country).The estimates then were pooled using Rubin's rule. The Applicant confirmed the analysis results using this approach and these will be included in agreed upon labeling.

5. During pre-submission correspondence with the Applicant, the Division recommended that the primary objective of the pivotal trials should demonstrate superiority on HbA1c for IDegLira over each of the individual components. Because IDegLira has a maximum dose of 50 dose steps, while IDeg has no upper limit, the Division agreed that it would be acceptable for the pivotal trial to limit the maximal degludec dose to 50 units in order to evaluate if the product met the combination rule regulatory requirement. The Division recognizes that this regulatory requirement does not reflect clinical practice. In clinical practice, insulin would not be "capped" at a specific maximum dose. Insulin, in clinical practice, is titrated to the maximally effective clinical dose that results in adequate glycemic lowering while maintaining a tolerable adverse event profile. Therefore, the design of trial 3912 limits its clinical applicability in a real world setting, including a conclusion of clinical superiority of IDegLira vs. IDeg. Labeling should include disclaimers that convey these ideas.

6. DMEPA conducted a labeling review and found that the carton and container labeling, PI, IFU, and professional sample labeling were overall acceptable from a medication error perspective after several recommended modifications (see multiple reviews in DARRTS).

7. The Office of Prescription Drug Promotion (OPDP) provided a consultative review for recommendations on the proposed drug labeling (version dated 18 Aug 2016). In addition, OPDP provided later advice regarding the disclaimers in the PI intended to inform that the difference in effect between IDegLira and comparator in the two basal insulin active comparator trials may be due to trial design and would not necessarily be similar to what would be observed in the clinical care setting. OPDP advised to include the disclaimer in both the text and footnotes of tables in Section 14 of labeling to be clear that it must be included in any promotional material that describes the effect size of IDegLira vs. a basal insulin alone.

8. Patient labeling review was conducted by the Division of Medical Policy Programs (DMPP) (see DARRTS 29 Aug 2016). Recommendations were incorporated into the Medication Guide and Instructions for Use.

9. The Division of Pediatric and Maternal Health (DPMH) provided a consultative review for recommendations for labeling language to satisfy the Pregnancy and Lactation Labeling Rule (PLLR). See review in DARRTS dated 28 Sep 2016. Dr. Lee Elmore, Pharm Tox Supervisor from DMEP also contributed to the crafting of the PLLR language and agreed with not using the term 'teratogenic' (see Pharm Tox section of this memo).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval with modified indication as follows:
Indicated to improve glycemic control in adults with diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).

While the overall recommendation is approval, there are several concerns with this product (and similar fixed- ratio insulin/GLP-1 analog products) that necessitate changes to the proposed indication and labeling to ensure safe and effective use. Currently under review by the Agency are the IDegLira NDA and a similar NDA submitted by another Sponsor that combines insulin glargine (a basal insulin) and lixisenatide (a GLP-1 analog) into a single dosage form. The applications for these two products were submitted to the Agency around the same time, and both were discussed at (separate) Advisory Committee meetings. Much of the concepts discussed here in this review apply to both products. For parity, the Agency has attempted to take a similar approach for these two products, recognizing some inherent differences in the development programs. Please refer to Dr. Guettier's Division Director

Memorandum regarding the insulin glargine/lixisenatide product for further discussion of the Division's thinking on fixed- ratio insulin/GLP-1 analog products.

- Risk Benefit Assessment

The Applicant is seeking approval of an NDA for insulin degludec and liraglutide (IDegLira), a fixed-ratio combination of a glucagon-like peptide 1 receptor agonist and a basal insulin into a single solution for injection. The solution contains a fixed amount of insulin degludec and liraglutide per unit volume (100 units of insulin degludec and 3.6 mg of liraglutide per mL). The rationale for this product design is not clear; insulin degludec (and all insulins) is a 'titratable' product in that dosage is individualized based on a glycemic target. In contrast, dosage of liraglutide (and all currently approved GLP-1 analogs) is based on discrete doses. In the IDegLira product design, dose adjustment for the individual drug components is not possible which deviates from the way the drugs would be used individually. If the rationale for the product were to combine two injectable drugs into a single injection for patient convenience, this would make sense; but in that case the product would have been designed to administer titratable doses of insulin with the discrete, approved doses of liraglutide. Therefore, even in the conceptual phase, the Division grappled with the rationale for the IDegLira product and for whom it would be beneficial.

Efficacy

In support of the NDA the Applicant submitted five adequate and well-controlled phase 3 trials that evaluated the glucose lowering effect of IDegLira. Two of the trials tested for superiority of IDegLira over IDeg (in a trial with a dose cap for the IDeg arm) and IDegLira over GLP-1 therapy alone. Three other trials, a factorial study with three arms comparing IDegLira to each of the individual components, a placebo controlled trial, and an active comparator trial against insulin glargine were also submitted.

I conclude that the clinical development program for IDegLira has met the requirements of 21 CFR 300.50, the Agency's 'combination drug rule'. All phase 3 trials met their pre-specified primary endpoint, in fact, all trials showed superiority of IDegLira to comparator, even when non-inferiority was pre-specified. Efficacy conclusions were not altered by missing data or by analysis method.

However, the interpretation of the efficacy findings in the basal insulin comparator trials with regard to conclusions of superiority was complicated by the protocol specified starting dose and titration algorithm used for the studies. Evaluations of the proportion of subjects who reached titration targets and the relative time needed to reach dose stabilization demonstrated that the titration algorithm resulted in a lag in both the proportion of subjects reaching glycemic targets and the time to reach dose stabilization in the comparator insulin arms of the trials, such that the HbA1c comparison between study arms was biased. Further, 26-week comparator HbA1c did not reflect a period of preceding glycemic stability.

Due to these trial design concerns it is not possible to conclude that IDegLira is superior to IDeg. To reach such a conclusion, a trial in which both arms were dosed and titrated in a

maximally effective and balanced manner would be needed. Note, however, that in pre-submission meetings the Agency agreed that an 'artificial' trial design limiting the maximal insulin degludec dose to 50 units once daily so that the superiority of IDegLira over IDeg could be tested would be acceptable. Demonstration of superiority of IDegLira over IDeg in a trial that studied the products the way that they would be used in clinical practice, i.e. with no dose cap, was not a requirement. (b) (4)

Another concern is that insulin degludec and liraglutide are optimally dosed very differently. Insulin degludec, like all insulins, are dosed to effect; whereas liraglutide for the treatment of type 2 diabetes is available at two discrete doses: 1.2 mg and 1.8 mg. The 0.6 mg dose is intended for titration to mitigate GI adverse reactions and is not an approved efficacious dose. Using IDegLira forces the patient and prescriber to modify dosing of one component based on the other and may result in less than optimal dosing of both drugs. The Phase 3 program has met the objective of demonstrating contribution to claimed effect of both components of IDegLira based on an average dose achieved after titration. As it is not feasible to conduct a clinical trial evaluating every possible dose of IDegLira, establishment of efficacy is based on *average* HbA1c reduction for the study population vs. comparator. While this approach was agreed upon pre-submission and has been deemed acceptable to satisfy the combination drug rule, clinical concerns are raised regarding the overall benefit/risk consideration for patients who would be expected to require low doses of IDegLira, such as those who are not already using basal insulin or liraglutide.

Safety

The clinical safety assessment for IDegLira was based on the same five adequate and well-controlled Phase 3 trials submitted to support efficacy. Overall, there were no new safety issues identified for IDegLira that were not already known for IDeg and liraglutide. However, it is clear from the data that use of IDegLira will expose patients to drug-related risks associated with both products, namely risks attributable to IDeg (hypoglycemia) and liraglutide components (gastrointestinal adverse reactions) or both (allergic reactions, injection site reactions and immunogenicity related risks).

The estimates for these drug-related risks were found to be additive and not synergistic, and the incidence of some adverse reactions caused by IDeg and lira when administered as IDegLira (such as gastrointestinal adverse reactions) appear to be attenuated with the lower doses of each product administered when both are combined. While, some may perceive this as a benefit, whether or not the approach of 'two sets' of safety risks, albeit at lower rates, is better or worse than 'one set' of risks from one drug is unknown and may come down to patient preference. Further, conclusions regarding safety issues associated with antidiabetes therapies such as body weight gain and hypoglycemia should be limited because phase 3 trials

were not designed to assess these endpoints in a way that can provide robust evidence to establish a clinically meaningful difference for one approach over another. In addition, comparative safety assessments may be confounded by the trial design concerns. Nevertheless, decisions regarding risk benefit of the one or two drug approach can be reasonably made by the prescriber on a patient-by-patient basis.

Potential medication error due to the product presentation was a large concern for this application. These concerns included lack of an appropriate term of measure and potential confusion over the fact that the product contains two drugs and the amount of each drug per dose increment. Ultimately, in concert with DMEPA we have determined these concerns can be acceptably addressed through labeling. First, a modifier will be added to the tradename to indicate the presence of two components. This numerical modifier shows the concentration of the two drug components, i.e. Xultophy 100/3.6 represents that there are 100 units of insulin degludec and 3.6 units of liraglutide in each mL of the solution. Second, a change to the pen dial was incorporated so the pen will only dial doses for which the product is recommended with the goal of reducing risk of subtherapeutic doses of the liraglutide component. Other strategies to reduce the risk of medication error include a clear table in the PI which shows the dose of each component individually for each unit of IDegLira, a Limitation of Use that IDegLira should not be used with any other GLP-1 analog containing drug, a Warning and Precaution that the product contains two drugs, and clear and concise Dosing and Administration instructions that include a statement that the maximum dose of the product is 50 units per day (which contains 50 units of insulin degludec and 1.8 mg of liraglutide).

Clinical Utility and Indication

The principles of management of type 2 diabetes stem from the concept that lowering HbA1c can reduce microvascular complications of diabetes. Professional societies including AACE (American Association of Clinical Endocrinologists)[7] and ADA (American Diabetes Association)[8] publish recommended guidelines for the approach to glycemic lowering based on data available at the time of publication. Especially relevant for this Application are recommendations regarding when and in whom to start dual (or triple) anti-diabetic therapy at once. Note that these recommendations vary somewhat, in part, because the basis for many of the recommendations is derived from expert consensus, since clinical trials evaluating the merit of different treatment approaches are lacking. The guidelines suggest that dual combination or triple combination therapy should be considered when HbA1c is relatively high to more expeditiously achieve the target HbA1c level. However, the clinical implications of the rapidity in achievement of the target HbA1c level remains an area of uncertainty in diabetes management, and the clinical benefit of sequential vs. initial dual/triple therapy is unclear. Combination antidiabetic products are therefore viewed as convenience products

[7] Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2016 Executive Summary. Endocr Pract 2016;22:84-113.

[8] Professional Practice Committee for the Standards of Medical Care in Diabetes-2016. Diabetes Care 2016;39 Suppl 1:S107-8.

whose main role in the therapeutic armamentarium is to reduce daily pill or injection burden in patients requiring two agents.

Summary of commonly used clinical guideline recommendations regarding initial dual or triple antidiabetes therapy	
Guideline	**Recommendation**
American Diabetes Association	Consider dual initial therapy with metformin plus another antidiabetic agent when HbA1c is ≥ 9%. Consider combination injectable therapy (metformin + basal insulin + mealtime insulin or GLP-1 receptor agonist) if HbA1c if ≥ 10-12% and/or blood glucose is ≥ 300-350 mg/dL, especially if symptomatic or catabolic features are present. If symptomatic or catabolic features are present, basal insulin + mealtime insulin is the preferred regimen.
American Association of Clinical Endocrinologists	Consider dual initial therapy if HbA1c is ≥ 7.5%. Consider triple initial therapy if HbA1c is ≥ 9% and asymptomatic. Use insulin +/- other agents if HbA1c ≥ 9% and symptomatic.

For IDegLira, however, the Applicant has developed a product that doesn't simply combine the two drugs into a single dosage form, as the dosing regimen for liraglutide has changed from a discrete dose to a titrated dose. The inability to titrate insulin separately from liraglutide in the IDegLira product results in an inflexible approach to the clinical management of diabetes, and the development program for IDegLira has not demonstrated any unique benefit to this approach that would outweigh this inflexibility. The Advisory Committee panel members raised the point that this product might be appropriate patients for whom more than one injection daily would be objectionable. For these patients IDegLira may allow dosing of both insulin degludec and liraglutide, but the compromise to their clinical care of the lack of dosing flexibility in terms of glucose lowering (vs. using the two drugs individually) is unknown.

In the IDegLira clinical development program, treatment scenarios studied included add-on to metformin (±pioglitazone and/or sulfonylurea), add-on to metformin (±pioglitazone and/or sulfonylurea) and GLP-1 (IDegLira replacing the GLP-1 agonist), and add-on to metformin and basal insulin (IDegLira replacing basal insulin) in patients needing additional glycemic control. The product was not studied to assess the benefits of adding the combination to patients already on a GLP-1 and insulin as there were no trials that converted patients already using both a GLP-1 analog and a basal insulin to IDegLira. The various patient populations studied, then, did include patients naïve to both GLP-1 analogs and insulin and the Applicant proposed to indicate IDegLira for this patient group. However, the Division has concerns about recommending use of IDegLira in patients who are 'naïve' to either component. For these patients, glycemic control may be achieved with GLP-1 analog or insulin alone and the risks incurred by unnecessarily administering two drugs may not be justified. Also, these

patients are more likely to require lower doses of IDegLira for which the benefit of the liraglutide component is unclear.

During internal discussion, the point was raised that it doesn't make clinical sense to indicate the product for patients already using a GLP-1 analog because changing to IDegLira would necessitate dose reduction of the GLP-1 component (that was already not providing enough glucose control). My recommendation is to grant an indication for this patient population because here are no available data to suggest that using a maximal dose of liraglutide is clinically better or worse than a lower but efficacious dose of liraglutide plus insulin degludec. In this clinical scenario, patients are likely to require both drugs, and low doses of liraglutide for which the benefit of this component is unclear is less of a concern.

In light of these considerations, the indication that will be granted will be: Xultophy 100/3.6 is a combination of insulin degludec and liraglutide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or on liraglutide. The verbiage that patients should be inadequately controlled on *liraglutide* in the indication reflects the differing potencies of the various approved GLP-1 analogs.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Approval of this product will require a REMS (Communication Plan (CP) only REMS).

DRISK provided a consultative review (see DARRTS 28 Jul 2016); DRISK agrees with DMEP that the totality of the risks associated with IDegLira is serious and it is necessary for prescribers to understand these risks and the importance of monitoring for them and agree that requiring a REMS consisting of a CP and a timetable for submission of REMS assessments is necessary to ensure that the benefits of IDegLira outweigh its risk of thyroid C-cell tumors.

Both liraglutide-containing products approved by FDA, i.e. Victoza and Saxenda, have a boxed warning for the risk of thyroid C-cell tumor and a CP REMS to mitigate this risk and the risk of pancreatitis. Other FDA-approved products in the GLP-1 analog class (i.e., exenatide ER, albiglutide, and dulaglutide) currently have, or have had at some point in their lifecycle, a CP REMS to mitigate the risk of thyroid C-cell tumor but also communicate the risk of pancreatitis associated with these products.

REMS for IDegLira should be consistent with REMS for Victoza and Saxenda and must include a communication plan targeted to healthcare providers who are likely to prescribe IDegLira.

Please see review from DRISK for further details.

- Recommendation for other Postmarketing Requirements and Commitments

none

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

/s/

LISA B YANOFF
11/21/2016

JEAN-MARC P GUETTIER
11/21/2016

Dr. Yanoff's review serves as the decisional memorandum for this application. I concur with her recommendation to approve this product. This application raised a number of new regulatory and clinical issues which are reviewed in this document and in my summary memorandum of NDA#208673, an application for a similar product reviewed concurrently.