FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC)

May 24, 2016

The committee will discuss the safety and efficacy of new drug application (NDA) 208583 for insulin degludec and liraglutide injection, submitted by Novo Nordisk Inc., for the proposed indication: Adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the discussion of the safety and efficacy of new drug application (NDA) 208583 insulin degludec and liraglutide injection, submitted by Novo Nordisk Inc., indicated as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1 **Division Director** Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

M E M O R A N D U M

Date:	24 April 2016
From:	Jean-Marc Guettier, MD Division Director Division of Metabolism and Endocrinology Products Office of Drug Evaluation II, Office of New Drugs, CDER
To:	The Endocrinologic and Metabolic Drug Advisory Committee
Subject:	24 May 2016 Meeting

The committee will discuss the safety and efficacy of new drug application (NDA) 208583 for insulin degludec and liraglutide injection, submitted by Novo Nordisk Inc., proposed for the treatment of adults with type 2 diabetes mellitus. This memorandum provides background information to present the issues the advisory committee was convened to discuss.

Regulatory Background

The Food and Drug Administration's policy regarding fixed combination dosage form prescription drugs for humans is defined in Section 300.50 of Title 21 of the Code of Federal Regulations (CFR) (21 CFR 300.50) as follows:

"(a) 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. Special cases of this general rule are where a component is added:

(1) To enhance the safety or effectiveness of the principal active component; and

(2) To minimize the potential for abuse of the principal active component."

The statement *"…when each component makes a contribution to the claimed effects"* is interpreted to mean that each drug product in the combination contributes to the claimed effect. For an anti-diabetic drug, the claimed effect is improvement in glucose control (i.e., a surrogate for clinical benefit). Thus, combining an effective product (i.e., one that contributes to the claimed effect) with an ineffective product (i.e., one that does not contribute to the claimed effect) would not be an acceptable combination product even though the product as a whole could be demonstrated to have the effect claimed because of one of the two components. A special case to this rule is made when one component is added for the specific purpose of enhancing the safety [e.g., combining a drug to prevent gastrointestinal ulcers with a non-steroidal anti-inflammatory drug (NSAID)] or effectiveness (e.g., combining a beta-lactamase inhibitor with an anti-bacterial drug) of the principal active component or to minimize the potential for abuse of the principal active component.

The statement *"…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"* is self-explanatory. For the majority of combination products, the safe and effective dosage of each individual component (amount, frequency, duration) is established in the development program submitted to support an application for that individual drug (e.g., generally the dose studied in phase 3 that is or will be recommended in the product label). If there is a recommended safe starting dose for one of the component in the combination for example, the combination product should include this dosage (i.e., the combination would not be "*safe and effective*" otherwise).

Combinations Indicated for the Treatment of Type 2 Diabetes Mellitus

The majority of marketed anti-diabetic combinations combine the widely used oral antidiabetic drug metformin with another oral anti-diabetic product.

Combining two products into one dosage form can reduce daily pill or injection burden (e.g., pre-mixed insulins) but the Agency does not require that potential benefits derived from enhanced convenience be demonstrated for combination product approval. The enhanced convenience that derives from combining two products into one dosage form generally comes at the cost of loss of dosing flexibility. Although individual component titration could be desired for the purpose of optimizing clinical benefit or tolerability, individual product titration is made more complex or may not be possible at all (e.g., pre-mixed insulins) with a combination product. In general, a new proposed combination product should offer doses for all the possible combinations that would be available when using individual product components so as to least burden prescribing flexibility. Absence of a specific dosage combination has to be justified based on solid grounds (e.g., generally use data showing that that specific combination would have very limited use because it addresses the need of a small minority of patients requiring the two drugs).

The approach to the development of fixed combination drug products for the treatment of type 2 diabetes, as laid out in the diabetes guidance document[1], is consistent with the above regulations and states;

> *"A fixed-dose combination of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects…and that the combination is acceptably safe."*

The development program for an antidiabetic combination product is designed to provide substantial evidence that each drug in the combination would contribute to the claimed effect of "improving glycemic control". Improvement in glycemic control, as captured by measuring the six month change in hemoglobin A1c (i.e., HbA1c) concentration from baseline, is used as a surrogate for full approval of antidiabetic products to establish the clinical benefit of antidiabetic drugs; including combination products.

It is important to emphasize that clinical studies carried out for the express purpose of establishing that each drug component in the combination contributes to improving glycemic control are not designed to provide substantial evidence to establish that use of

[1] http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf

the combination would be "clinically safer" or "better tolerated" than use of each component individually. Secondary endpoints assessing and comparing specific product related risks versus specific comparators are considered exploratory in these studies. In fact, combination products by their very nature are expected to carry two sets of product-related risks (i.e., risks associated with each one of the two components in the combination) and some risks associated with the combination product will, as result, not be associated with one or the other of the two components (e.g., compared to an insulin product used alone, a GLP-1/insulin combination product would be expected to have increased gastro-intestinal associated risks due the GLP-1 component and compared to a GLP-1 product used alone, the combination would be expected to have increased hypoglycemia risks). Interpreting the overall clinical meaningfulness of a purported safety/tolerability advantage of a combination over individual components is difficult since what may appear to be a "safer" option based on consideration of a single risk and a single comparison could be counterbalanced by other risks pertinent to the combination product that are not associated with the single component comparator and not considered. In other words, would the gains afforded by meaningful reduction in one risk be offset by the losses that arise due to the increase in another risk?

Trial Design to Demonstrate Contribution to Claimed Effect for Combinations Indicated for the Treatment of Type 2 Diabetes Mellitus

For antidiabetic products, substantial evidence that each drug in the combination contributes to improvement in glycemic control is established either, in a trial enrolling patients who are not at goal on a maximally effective fixed dose of one of the agent in the combination (i.e., a sequential "add-on" trial design) or in a factorial design study comparing various fixed doses.

The sequential "add-on" trial design more closely mimics standard clinical care where addition of a second glucose lowering agent is recommended if, after some period of time (usually 3 to 6 months), glycemia remains inadequately controlled on a maximally effective/tolerated fixed dose of the first agent.

The factorial trial design on the other hand compares the glucose lowering effect achieved by initiating two agents, at once, at a fixed dose to the glucose lowering effect achieved by initiating each agent individually at a fixed dose over some defined time period. In a full factorial design, the combination at various effective doses is compared to individual components at these same doses (e.g., low dose of the combination are compared to the low dose of the individual component etc...).

Although a factorial study design allows one to establish that initiating two agents at once will result, on average, in greater glucose lowering than initiating each agent separately, the factorial trial design does not address more fundamental clinical questions such as:

Does a strategy that relies on initiating two drugs at once (dual therapy) confer an advantage in the long-run over a strategy that relies on sequential addition of drugs (sequential add-on)? Do the long-term benefits gained by more rapid achievement of glucose control outweigh the potential added risks that come with being exposed to two drugs compared to one? Put in another way, if a patient is able to get to the desired therapeutic goal with a single agent (an unknown when deciding to initiate dual therapy), are risks associated with a second agent justified?

Therapeutic guidelines issued by professional societies recommend "considering" initiating dual therapy in patients with particularly poor control at baseline (i.e., HbA1c > 9%). The arguments used to justify a role for initiating dual, or even initial triple therapy, are usually based on pathophysiology (i.e., it is better to address multiple metabolic abnormalities at once, two drugs are usually needed to get to goal when the disease is poorly controlled) or logic [i.e., additional glucose lowering gained by starting two agents at once will translate to better long term outcomes, more rapid glucose lowering is better because it results in increased adherence, fewer office visits (e.g., "therapeutic inertia") etc.]. While some of these arguments may be on their face valid, there are really no robust empiric data to inform the question of whether a strategy that consists of starting multiple products at once will offer clinically meaningful long-term benefits to patients compare to a strategy that relies on a sequential add-on paradigm.

While these uncertainties remain, the indication that has been granted to currently marketed combination products that demonstrate a "contribution to the claimed effect" through a factorial study has been; "*to improve glycemic control in adults with type 2 diabetes mellitus when both drugs are indicated*". The currently marketed combination products themselves are amenable to be used in either a sequential add-on paradigm or a dual therapy paradigm and the indication does not expressly prohibit initiating the two agents at once in patients who have not been previously treated with either. The Agency's approach is internally consistent with our current policy of considering glycemic reduction a valid surrogate for clinical benefit.

Specific Issues with the Proposed Combination Product

The combination proposed in this application combines a product that, when administered alone, is a fixed dose product (the GLP-1 agonist) with another product that is a titratable product dosed on a close to continuous scale (the insulin). All antidiabetic combinations approved and marketed to date have combined either two individual fixed dose products (.e.g., two oral anti-diabetics) or two individual titratable products (e.g., mixed insulin products).

In the proposed combination, the GLP-1 component is in essence "transformed" into a titratable product. To establish that the ***insulin component*** in the combination product contributes to the claimed effect (i.e., improvement in glycemic control), the applicant compared the combination product titrated to a target fasting glucose goal to the fixed dose of the GLP-1 marketed or recommended as the safe and effective dose. To establish that the ***GLP-1 component*** in the combination product contributes to the claimed effect, the applicant compared the combination product titrated to a target fasting glucose goal to doses of the insulin in the combination also titrated to a target fasting glucose goal. Most trials relied on a single algorithm to dose both the insulin and the combination product and in many trials the dose in the insulin arm was capped so as not to exceed the highest insulin dose of insulin that can be delivered in the combination. This is different from the care setting as insulin dose increase is not constrained by an algorithm, the maximum insulin dose is not capped and the time to achieve glycemic control goal is not limited to six months.

Issues that relate to the interpretability of the study findings and practical utility of the combination are listed below.

1. The proposed dosage for the GLP-1 component in the combination (a variable close to continuous dose range) is not the dosage recommended and established as effective when the GLP-1 product is used alone (i.e., a discrete fixed dose range). In fact, the dose range proposed for the GLP-1 component in the combination product includes doses that were not effective when used alone. Although these low doses may be useful to ensure safe titration of one or both of the components, it is possible that specific patient populations (i.e., insulin sensitive individuals who require low doses of the combination for control) could be exposed to one component that provides no therapeutic benefit and causes specific adverse reactions. Making a determination of *contribution to the claimed effects* in the low-dose part of the range based on a retrospective analysis of a post-randomization event (i.e., subgroups of patients who ended up on a specific dose of insulin) is subject to the limitations of such analyses and provides only limited useful information to address the question.

2. Interpreting the clinical meaningfulness of the results of a study designed to demonstrate *"contribution to the claimed effects"* when one of the comparator is a titratable product is problematic. Factorial studies generally compare fixed doses and some comparisons generally include the maximally effective doses of all products. In this application one of the comparators (i.e., the insulin) has no maximally effective dose and insulin dosing in the trial is artificially constrained compared to the clinical care setting (i.e., starting dose of the insulin is

standardized to that the combination product, the dose adjustment for the insulin is fixed and standardized to that of the combination, the maximum allowable dose of the insulin is capped in some studies and the final determination of benefit is fixed and made at 6 months). While the study can address a within trial question of *"contribution to claimed effect"*, use of insulin in these studies bears little resemblance to the clinical care setting where dosing of insulin use is not artificially constrained. In the clinical care setting insulin dose can continue to be titrated beyond 6 months, there is no "one-size fits all" cap for allowable insulin dose increment, and there is no cap on overall insulin dose.

3. Dosing algorithms for the titratable products in the trial were utilized to ensure adequate dosing of each product. Actual dosing adequacy can only be examined retrospectively (i.e., after the trial is completed by reviewing the proportion of individuals who reached the intended goal fasting glucose targeted by the algorithm). The majority of participants in studies never reached the intended plasma glucose target (for reasons that were not captured) suggesting product dosing may have been inadequate. Inadequate dosing of the insulin in the studies could have biased the estimate of efficacy in favor of the combination product. This would further confound interpretability of a clinical superiority claim for the combination against the insulin comparator.

4. With regards to practical utility, patients currently treated with one of the two products in the proposed combination cannot be easily switched to the combination product without a significant reduction in dose of the component they were previously on. This is a unique problem inherent to this specific antidiabetic combination. For other marketed fixed dose combinations, no dose reduction in either component is needed when making the switch. In the combination proposed in this application, a patient who is inadequately controlled on a maximally effective dose of the GLP-1 agonist, for example, would be receiving a substantially lower dose of the GLP-1 agonist (perhaps an ineffective dose) when initiating use of the combination because of the risk of hypoglycemia associated with starting insulin at a high dose. A reduction in the dose of the GLP-1 agonist is generally not required when initiating insulin in a patient not optimally controlled on this therapy. Similarly, a patient who is inadequately controlled on basal insulin would have to reduce the dose of the basal insulin to start the combination. Again this is not currently recommended when using the products independently. As a result of this inflexibility in dosing, switching to the combination product may translate to a loss of glycemic control compared to addition of the second component administered independently.

5. For patients not using either components (i.e., patients naïve to insulin and GLP-1), initiating the combination product commits patient to two products, each associated with independent product-related adverse reactions when at least some of the patients initiated on the drug could have been controlled on a single agent (an unknown when the decision is taken to initiate the combination product).

6. Medication errors in the clinical care setting may result due to the complex nature of the proposed combination. The two active components in the combination do not share a common measure term for dosing. The measure term for insulin is units and the measure term for the GLP-1 is milligrams or micrograms. A dose of the combination is neither an accurate representation of an insulin unit nor an accurate representation of a weight based measure term but a combination of the two. This may not be obvious or readily apparent to prescribers and may lead to confusion and medication errors in the clinical care setting [e.g., prescribing a GLP-1 twice "medication duplication", or overdosing on the GLP-1 component by using the combination product as they would a titratable product with no upper dose limit (i.e., an insulin)]. Recognition that the combination contains two components will also be needed to prevent medication errors and to safely transition patients to alternative products between the home care and institutionalized care setting.

2 Draft Points to Consider

1. Discuss the role for use of a basal insulin with a GLP-1 agonist in the overall approach to the treatment of patients with type 2 diabetes mellitus (i.e., population, disease stage etc.)
2. Discuss the role for simultaneous initiation of dual therapy with a basal insulin and a GLP-1 agonist in the treatment of patients with type 2 diabetes mellitus previously naïve to these therapies (i.e., population, disease stage etc.).
3. Discuss the benefits of the combination product.
4. Discuss the risks of the combination product.
5. Discuss your level of concern with limitations of the product presentation (a pen device) in light of the issues discussed in draft points 1-4.

Clinical Table of Contents

Clinical Table of Tables

Clinical Table of Figures

Statistics Table of Contents

Statistics Table of Tables

Statistics Table of Figures

Clinical Pharmacology Table of Contents

Clinical Pharmacology Table of Figures

Clinical Pharmacology Table of Tables

DMEPA Table of Contents

DEPI Table of Contents

DEPI Table of Tables

Abbreviations

AACE	American Association of Clinical Endocrinologists
AC	advisory committee
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
ALAT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTR	clinical trial report
DMC	data monitoring committee
DPP4	Dipeptidyl peptidase 4
EAC	event adjudication committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETS	Extension Trial Set
-ext	52 weeks of trial 3697 (main + extension part)
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1 analogs
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	Hemoglobin A1C
HDL	high density lipoprotein
HLGT	high level group term
HLT	high level term
IDeg	Insulin degludec
IDegLira	Insulin degludec and liraglutide
IGlar	insulin glargine
IMP	investigational medicinal product
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL	low density lipoprotein
lira	liraglutide
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
Met	metformin
NDA	new drug application
NME	new molecular entity
OAD	oral antidiabetic drug
OD	daily
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
pio	pioglitazone
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PPI	subject package insert
PT	preferred term
PYE	subject year exposure
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SMPG	self-monitored plasma glucose
SMQ	standardized MedDRA query
SOC	standard of care
SU	sulfonylureas
TEAE	treatment emergent adverse event
TID	three times a day
TZD	thiazolidinedione
ULN	upper limit of normal

3 Clinical Introduction and Executive Summary

1.1 Introduction

This document provides the briefing material for the May 24, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) to discuss the findings in new drug application (NDA) 208583 for an insulin degludec and liraglutide combination product.

1.2 Executive Summary

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. The proposed indication is 'as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Insulin degludec and liraglutide are both approved and marketed products. As such the clinical development program for IDegLira was primarily designed to meet the requirements of 21 CFR 300.50, the Agency's 'combination drug rule'. In support of the NDA the Applicant submitted five phase 3 trials that evaluated the safety and the glucose lowering effect of IDegLira. Two of the trials specifically addressed the combination drug rule and 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.

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. This product is clearly intended for patients to initiate both GLP-1 therapy and basal insulin at once. Note that the labeled limitation of use that liraglutide is not recommended for first-line therapy (due to concerns over thyroid C-cell tumors) would necessitate IDegLira be used as add-on to some other agent.

Efficacy

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. However, the interpretation of the efficacy findings in the basal insulin comparator trials 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 we are not able to conclude that IDegLira is superior to IDeg,

as the Applicant has concluded. 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.

Safety

Overall, there were no new safety issues identified for IDegLira that were not already known for IDeg and liraglutide. However, it is important to note that use of IDegLira would expose patients to safety risks associated with both products. As was seen in the IDegLira program, subjects randomized to IDegLira experienced adverse events caused by both of its components, namely subjects experienced gastrointestinal adverse events (liraglutide) and hypoglycemia (insulin degludec). Further, the use of IDegLira allows for doses of liraglutide lower that that approved for glycemic lowering (i.e. doses less than 1.2 mg), and a patient may be exposed to a dose of liraglutide that has not been studied in phase 3 trials and determined to be efficacious while incurring safety risks associated with liraglutide use.

Discussion of Type 2 Diabetes Management and the Role of IDegLira in the Armamentarium of Antidiabetic Therapies

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) [2] and ADA (American Diabetes Association)[3] publish recommended guidelines for the approach to glycemic lowering based on data available at the time of publication. Most relevant for this Advisory Committee meeting are recommendations regarding when and in whom to start dual (or triple) anti-diabetic therapy at once (Table 1). 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.

[2] 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.

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

Table 1- 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.

The inability to titrate insulin separately from liraglutide in the IDegLira product results in an inflexible approach to the clinical management of diabetes, and it is not clear that the development program for IDegLira has demonstrated any unique benefit to this approach that would outweigh this inflexibility. Safety findings were as expected, i.e. that IDegLira is associated with the safety risks known for both products such that use of IDegLira would not be expected to result in fewer adverse reactions than using the individual components separately at reduced doses. We note that 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 benefit. In addition, comparative safety assessments may be confounded by the trial design issues outlined above.

Points for Consideration

We request that the committee discuss how the approval of IDegLira would contribute to the available treatment options for patients with type 2 diabetes, considering, in part, the glycemic management consensus approaches to glycemic management published by the professional societies described above (or to other reasonable approaches). FDA would also appreciate the committee's opinion regarding the patient population(s) for whom IDegLira may be useful and a discussion of the risks and benefits of starting basal insulin and liraglutide in combination. The committee should also evaluate whether the data provided by the Applicant is adequate to support the proposed indication.

4 Background

2.1 Product Introduction and Regulatory History

Insulin degludec and liraglutide (IDegLira), is a drug device combination product that is composed of a fixed ratio of two drug products: a long acting human insulin analog (insulin

degludec) and a glucagon-like-peptide-1 receptor agonist (liraglutide) administered subcutaneously *via* a pre-filled pen injector.

2.1.1 Insulin Degludec

Insulin degludec injection (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 insulin degludec is individualized based on the subjects metabolic needs, blood glucose monitoring results and glycemic goal[4].

2.1.2 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).

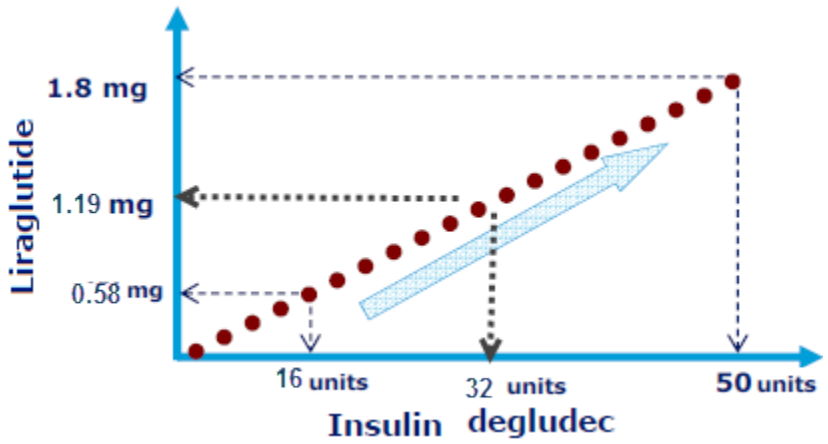
2.1.3 IDegLira

The liraglutide and the insulin degludec 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

[4] Tresiba [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; September 2015.

change (Figure 1). Another consequence of this fixed ratio formulation is that one drug cannot be titrated without titration of the other drug.

Figure 1 - Principle of adjustment of the IDeg and liraglutide dose levels in the IDegLira fixed ratio product



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

During the development of IDegLira the FDA expressed concerns to the Applicant regarding its development program. In a pre-submission discussion, there were differing opinions regarding who would be the patient population that would benefit from IDegLira. The Applicant stated that IDegLira is intended for patients who are naïve to both insulin and GLP-1 analogs. The FDA stated that IDegLira would be an attractive option for patients treated with either basal insulin or a GLP-1 analog and who required intensification of anti-diabetic therapy or patients seeking the convenience of one daily injection (with IDegLira instead of two/three daily injections with a co-administered basal insulin and a GLP-1 analog).

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'[5] 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.

[5] 21 CFR 300.50, "fixed-combination prescription drugs for humans".

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.

5 Overview of Clinical Trials Used to Support Efficacy and Safety

The clinical trials conducted during the development program of IDegLira are identified by the project number NN9068 followed by a unique four-digit trial ID. In this document, the clinical trials will be referred to by their unique ID.

Throughout the IDegLira development program, the Applicant refers to the IDegLira dosing unit as a "dose step." Although this terminology does not reflect established regulatory terminology, it is used in this document in order to ensure consistency across documents.

3.1 Study Design of Phase 3 clinical trials

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).

3.1.1 Phase 3 trial design overview

The designs of the five trials are summarized in Table 2 and
Figure 2. The individual trial designs are also discussed in the Statistical Summary.

Table 2- 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

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 presented in the Appendix.

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) -

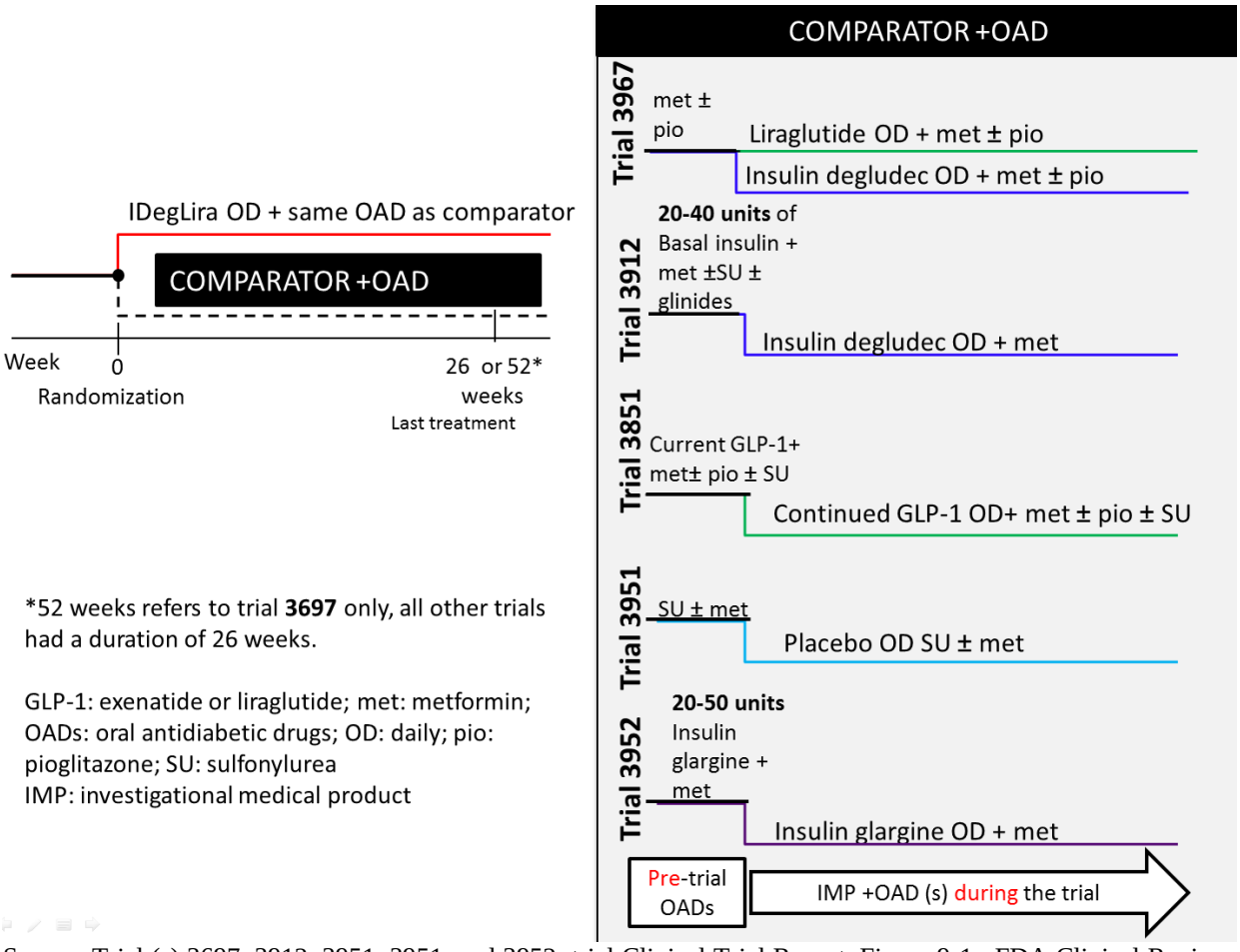
thus *non*-insulin naïve; two trials were add on to OADs, other than metformin (3697 and 3951) in insulin naïve subjects, and one trial was a conversion from GLP-1 analog (3851).

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

Figure 2 – Schematic of IDegLira phase 3 studies



Source: Trial (s) 3697, 3912, 3951, 3951, and 3952: trial Clinical Trial Report, Figure 9-1. FDA Clinical Reviewer generated figure

3.1.2 Dosing and titration of investigational drugs

Starting Dose
The starting dose of IDegLira varied in each trial reflecting the population enrolled (Table 3).

Table 3– 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		

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 (Table 3) 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 (Table 3). 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.

Table 3 – 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.

3.1.3 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.

6 Review of Efficacy

4.1 Subject demographics and disease characteristics

4.1.1 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 in Table 4. 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 $mL/min/1.73m^2$.

Table 4 – 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 2 OADs >2 OADs	693 (83.2%) 140 (16.8%) 0 (0.0%)	684 (82.7%) 143 (17.3%) 0 (0.0%)
3912	1 OAD 2 OADs >2 OADs Total insulin dose (u/kg): Total insulin dose (u):	95 (47.7%) 104 (52.3%) 0 (0.0%) 0.3 (0.1%) 29.0 (7.7%)	98 (49.2%) 101 (50.8%) 0 (0.0%) 0.3 (0.1%) 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 (%)		1858 (98.3%)	1578 (98.8%)

	IDegLira (N=1891) N(%) or mean SD	Comparator [a](N=1597) N(%) or mean SD
Mean (SD) daily dosing in mg	1954.1 (469.0)	1943.0 (447.7)
Glinide n (%)		
Repaglinide n (%)	4 (0.2%)	2 (0.1%)
Mean (SD) daily dosing in mg	9.8 (2.9)	9.0 (4.2)
Sulfonylurea n(%)		
Glibenclamide n (%)	87 (4.6%)	47 (2.9%)
Mean (SD) daily dosing in mg	13.5 (4.5)	13.2 (4.5)
Gliclazide n (%)	104 (5.5%)	59 (3.7%)
Mean (SD) daily dosing in mg	105.6 (61.7)	117.1 (65.3)
Glimepiride n (%)	188 (9.9%)	114 (7.1%)
Mean (SD) daily dosing in mg	5.0 (4.4)	4.6 (1.9)
Glipizide n (%)	76 (4.0%)	56 (3.5%)
Mean (SD) daily dosing in mg	18.0 (6.7)	18.1 (7.7)
Glyburide n (%)	1 (0.1%)	0 (0.0%)
Mean (SD) daily dosing in mg	10.0 (−)	0
Gliquidone n (%)	0 (0.0%)	2 (0.1%)
Mean (SD) daily dosing in mg	0	120.0 (0.0)
Thiazolidinedione n(%)		
Pioglitazone n (%)	154 (8.1%)	148 (9.3%)
Mean (SD) daily dosing in mg	32.1 (6.8)	32.9 (6.2)
Insulin used at baseline [f]		
Insulin glargine n (%)	363 (19.2%)	367 (23.0%)
Mean (SD) daily dosing in units	30.6 (9.7)	31.3 (9.8)
Insulin detemir n (%)	32 (1.7%)	35 (2.2%)
Mean (SD) daily dosing in units	32.5 (7.2)	31.3 (7.2)
Insulin neutral protamine Hagedorn n (%)	79 (4.2%)	71 (4.4%)
Mean (SD) daily dosing in units	28.1 (7.2)	28.2 (7.8)
Biosynthetic human insulin (BHI) n (%)	0 (0.0%)	1 (0.1%)
Mean (SD) daily dosing in units	0	30.0 (−)
Human insulin (HI) n (%)	0 (0.0%)	2 (0.1%)
Mean (SD) daily dosing in units	0	20.0 (0.0)
Insulin aspart (IAsp) n (%)	0 (0.0%)	1 (0.1%)[g]
Mean (SD) daily dosing in units	0	20.0 (−)
Mean eGFR (mL/min/1.73 m2)		
% 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

4.1.2 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 Table 5. 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.

Table 5 – 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

4.2 Subject Disposition

Table 6 summarizes subject disposition for the 5 phase 3 trials. 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.

Table 6 – Subject disposition – phase 3 trials

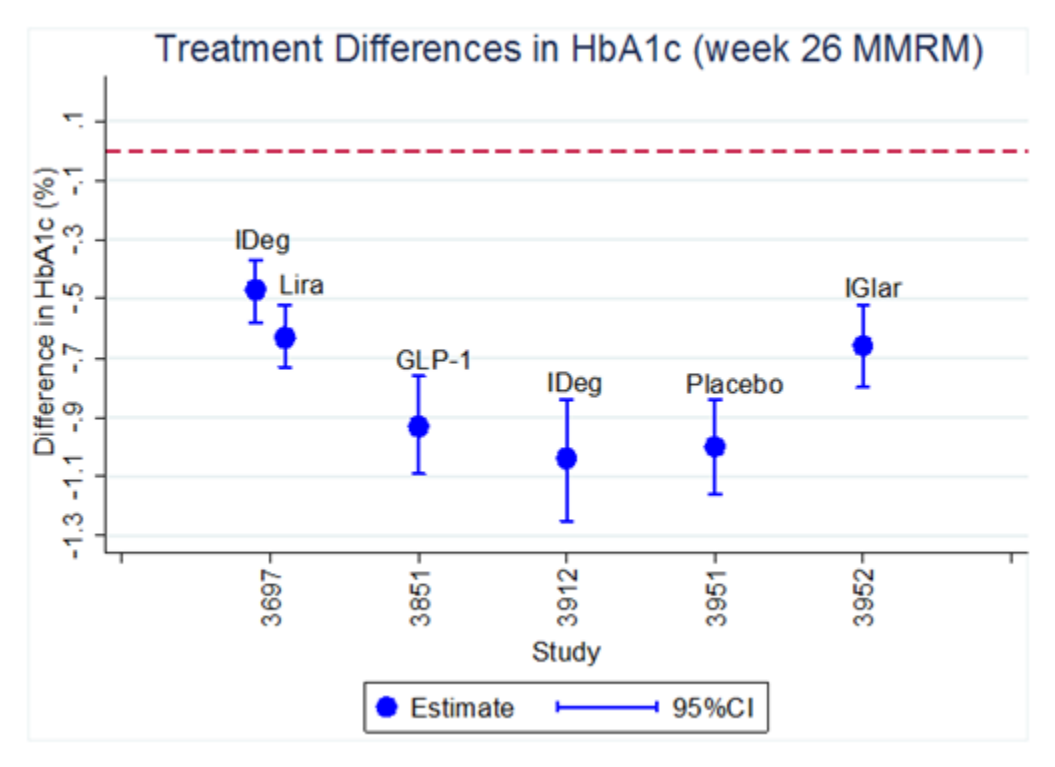
	TRIAL 3697			TRIAL 3912		TRIAL 3952		TRIAL 3951		TRIAL 3851	
	IDegLira N (%)	**IDeg N (%)**	**Liraglutide N (%)**	**IDegLira N (%)**	**IDeg N (%)**	**IDegLira N (%)**	**Insulin Glargine N (%)**	**IDegLira N (%)**	**Placebo N (%)**	**IDegLira N (%)**	**GLP-1 N (%)**
Randomized	834 (100)	414 (100)	415 (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

4.3 Analysis of the Primary Efficacy Endpoint

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%.

Figure 3– Summary of Efficacy Results for the IDegLira Phase 3 Clinical Program



Source: Created by FDA Statistical reviewer

The reader is referred to the Statistical Summary for a complete review of FDA's analyses of the primary efficacy endpoint.

4.4 Secondary Efficacy Endpoints

The reader is referred to the Statistical Summary for a discussion of secondary efficacy endpoints. In the Clinical summary body weight changes and hypoglycemia are discussed in the Review of Safety.

4.5 Trial Interpretation and Clinical Considerations

4.5.1 Dosing of IDegLira and basal insulin comparators in the phase 3 trials

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 were described in section 3.1.2 of this document. Several aspects of this design element that 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. 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 (Figure 4). 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 (Figure 5). 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. Table 7 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). 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.

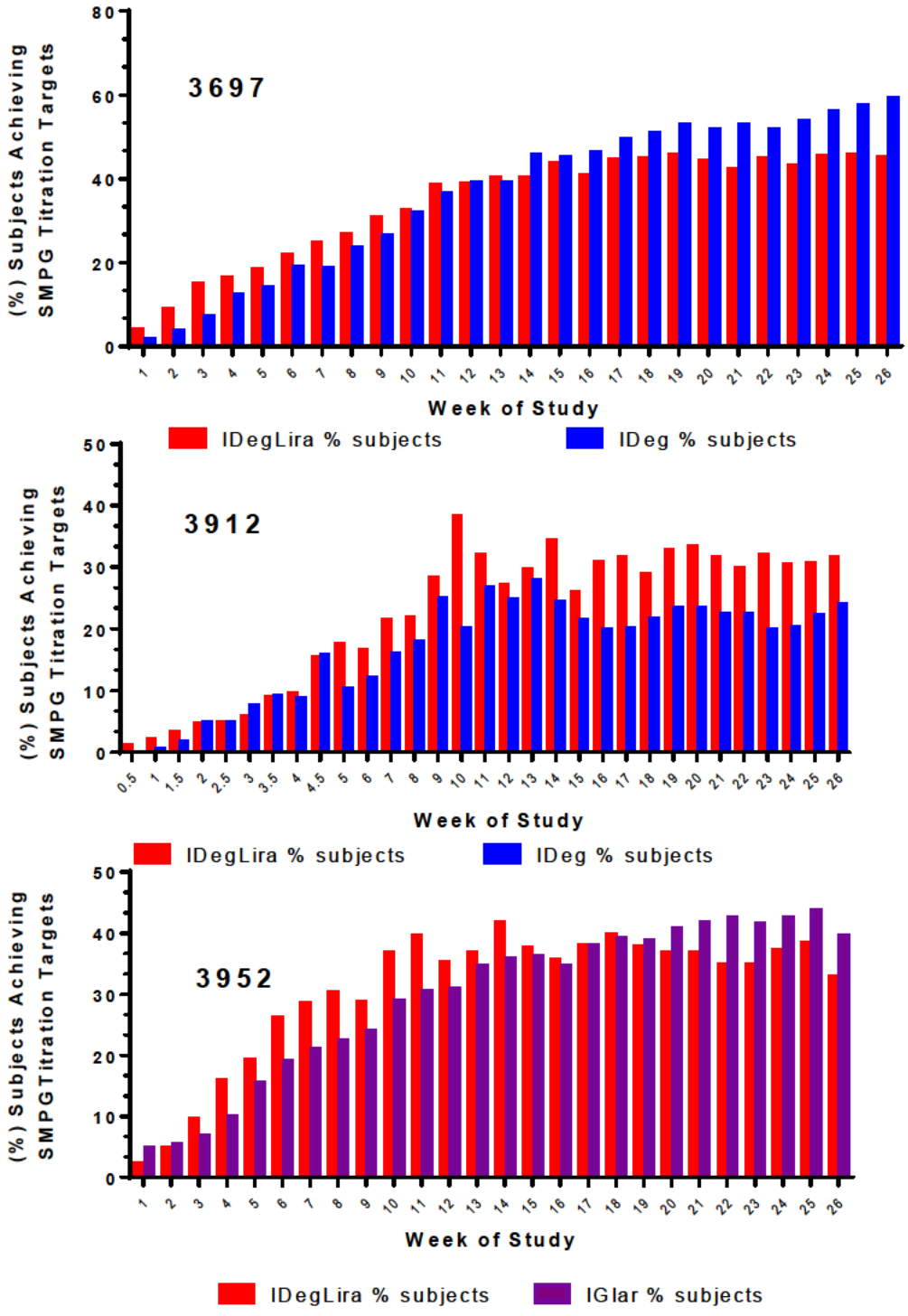
3912- Patients previously on 20 to 40 units of basal insulin were started on 16 units of IDeg or 16 dose steps of IDegLira at randomization, had discontinuation of their pre-trial OADs (with the exception of metformin) and capped at either 50 units of IDeg or 50 dose steps of IDegLira. Throughout the duration of the study, the proportion of patients meeting targets, randomized to IDegLira were always higher than those randomized to IDeg (Figure 4). 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 (Figure 5 and Table 7).

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 (Figure 4). However, only half of subjects achieved a stable insulin dose prior to week 19, i.e. seven weeks before the conclusion of the study (Figure 5 and Table 7).

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.

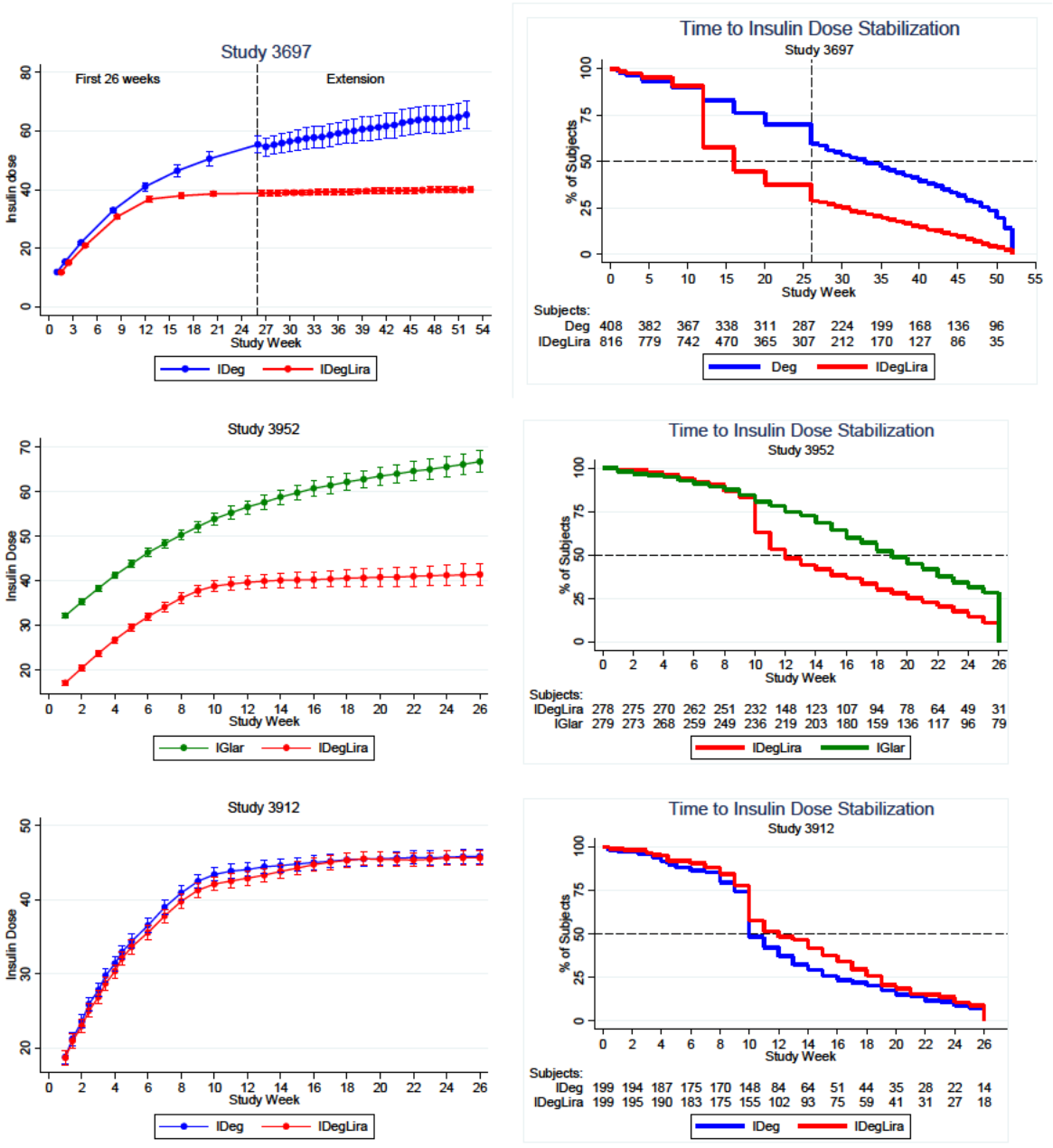
Finally, while this discussion has focused on comparisons between groups regarding the rate of titration, it is important to note that for both groups, the success rate of subjects achieving FPG targets was poor overall in the trials.

Figure 4- 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

Figure 5 - Insulin dose over time and time to insulin dose stabilization



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

Table 7 - 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
	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

4.5.2.1 Dosing of liraglutide

Liraglutide (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, 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 in Table 8.

Table 8 - 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 Table 9. 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).

Table 9 - 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.

4.5.3 Clinical relevance of the capped dose insulin trial - 3912

During pre-submission correspondence with the Applicant, the FDA recommended that the primary objective of the pivotal trials should demonstrate superiority on HbA1c for IDegLira over each of the individual components (as described in section 2.1.3). 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 FDA 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.

5 Review of Safety

5.1 Safety Review Approach

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.

Table 10 – 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[a] and 3912, and IGlar arm of Trial 3952
GLP-1	Combined data for liraglutide arm in Trial 3697-ext[a] and liraglutide/exenatide arm in Trial 3851
Placebo	placebo arm from Trial 3951

5.2 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).

Table 11 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 a duration of longer than 10 years.

Table 11 – 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

5.3 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 here. 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.

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 could not identify any concerns with the adjudication process used. An overview of these results is found in the appendix, Figure 7.

5.3.1 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, see Table 21 in Appendix). The adjusted death rates reported by the Applicant were 0.3 and 0.2 events per 100 PYE for IDegLira and IDeg respectively.

5.3.2 Serious Adverse Events

Table 12 shows incidence and exposure-adjusted and pooled-adjusted incidence rates of serious adverse events (SAEs) by system organ class (SOC). A similar table showing SAEs by Preferred Term is in the Appendix of the Clinical Summary. 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.

Table 12 - Serious adverse events by system organ class (SOC) - completed 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		
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 4 \\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

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

5.3.3 Dropouts and/or Discontinuations Due to Adverse Events

The pooled adjusted incidence and exposure adjusted event rates for AEs resulting in dropout due to adverse events in each of the 4 prespecified safety pools are shown in Table 13. 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.

Table 13- Adjusted pooled analysis of dropouts due to adverse events - phase 3 trials - SOC and PT terms												
	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	32(1.7)	42	3.5	13(2.2)	16	5.1	28(6.5)	37	15.8	2(0.7)	2	1.2
Gastrointestinal disorders	8(0.4)	11	0.9				17(2.7)	21	7.5			
Nausea	2(0.1)	2	0.2				9(1.4)	9	2.3			
Dyspepsia	2(0.1)	3	0.2									
Vomiting	1(<0.1)	1	<0.1				3(0.2)	3	0.4			
Abdominal pain	2(0.1)	2	0.2									
Abdominal discomfort	1(<0.1)	1	<0.1				2(0.3)	2	0.5			
Abdominal distention	1(<0.1)	1	<0.1				1(0.2)	1	0.2			
Gastroesophageal reflux disease							1(0.2)	1	0.2			
Constipation							1(0.2)	1	0.2			
Diarrhea	1(<0.1)	1	<0.1				1(<0.1)	1	0.1			
Gastritis							2(0.4)	2	0.4			
Peptic ulcer							1(0.2)	1	0.2			
Investigations	8(0.4)	10	0.8	3(0.8)	4	1.4	5(1.6)	6	2.6			
Lipase increased	6(0.3)	6	0.5				2(0.9)	2	1.6			
Amylase increased	2(0.1)	2	0.2				2(0.3)	2	0.5			
Weight increased	1(<0.1)	1	<0.1	3(0.2)	4	0.4						
Weight decreased							2(0.4)	2	0.4			
Blood creatinine increased	1(<0.1)	1	<0.1									
General disorders and administration site conditions	6(0.3)	6	0.5	1(0.1)	1	0.2						
Injection site rash	2(0.1)	2	0.2									
Injection site pain	1(<0.1)	1	<0.1									
Death	1(<0.1)	1	<0.1									
Hunger				1(0.2)	1	0.2						
Malaise	1(<0.1)	1	<0.1									
Pyrexia	1(<0.1)	1	<0.1									

Nervous system disorders	1(<0.1)	1	<0.1	4(0.5)	4	0.7	2(0.4)	2	0.4			
Hemorrhagic stroke				1(<0.1)	1	0.2						
Ischemic stroke				1(<0.1)	1	0.2						
Headache				1(0.2)	1	0.2						
Dementia Alzheimer's type							1(0.2)	1	0.2			
Dysgeusia							1(0.2)	1	0.2			
Hypoglycemic unconsciousness	1(<0.1)	1	<0.1									
Guillan-Barre syndrome				1(0.2)	1	0.2						
Musculoskeletal connective tissue disorders	2(0.1)	3	0.2	2(0.1)	2	0.2	1(<0.1)	1	0.1			
Intervertebral disc protrusion	1(<0.1)	1	<0.1									
Intervertebral disk disorder				1(0.2)	1	0.2						
Osteoarthritis							1(0.2)	1	0.2			
Arthralgia	1(<0.1)	1	<0.1									
Back pain	1(<0.1)	1	<0.1	1(<0.1)	1	0.1						
Psychiatric disorders	2(0.1)	2	0.2									
Major depression	1(<0.1)	1	<0.1									
Anxiety	1(<0.1)	1	<0.1									
Infection and infestations	2(0.1)	2	0.2				1(0.2)	1	0.3			
Pyelonephritis chronic	1(<0.1)	1	<0.1									
Gastroenteritis							1(0.2)	1	0.2			
Septic shock	1(<0.1)	1	<0.1									
Renal and urinary disorders	2(0.1)	2	0.2				1(0.2)	1	0.2			
Nephropathy	1(<0.1)	1	<0.1									
Renal failure acute	1(<0.1)	1	<0.1									
Renal failure							1(<0.1)	1	<0.1			
Cardiac disorders	2(0.1)	2	0.2	2(0.2)	2	0.4	1(0.2)	1	0.3			
Angina pectoris							1(0.2)	1	0.2			
Acute myocardial infarction	1(<0.1)	1	<0.1	1(<0.1)	1	0.2						
Acute coronary syndrome				1(0.2)	1	0.2						
Cardiac failure congestive	1(<0.1)	1	<0.1									
Immune system disorders	1(<0.1)	1	<0.1									

Drug hypersensitivity	1(<0.1)	1	<0.1									
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)							1(0.2)	1	0.2			
Pancreatic carcinoma stage IV							1(0.2)	1	0.2			
Hepatobiliary disorders				1(<0.1)	1	0.2						
Cholelithiasis				1(<0.1)	1	0.2						
Metabolism and nutrition disorders							1(0.2)	1	0.2	1(0.7)	1	1.6
Hyperglycemia										1(0.7)	1	1.6
Decreased appetite							1(0.2)	1	0.2			
Vascular disorders	1(<0.1)	1	<0.1									
Hypotension	1(<0.1)	1	<0.1									
Eye disorders	1(<0.1)	1	<0.1									
Necrotizing retinitis	1(<0.1)	1	<0.1									
Skin and subcutaneous tissue disorders							1(0.2)	1	0.2	1(0.7)	1	1.6
Rash							1(0.2)	1	0.2			
Pruritus generalized										1(0.7)	1	1.6
Injury, poisoning and procedural complications				1(0.2)	1	0.2	1(0.2)	1	0.4			
Humerus fracture				1(0.2)	1	0.2						
Foot fracture							1(0.2)	1	0.4			
Respiratory, thoracic and mediastinal disorders				1(0.2)	1	0.2						
Chronic obstructive pulmonary disease				1(0.2)	1	0.2						

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
Source: FDA IR via teleconference on 10/14/ 2015. IR receipt on 10/22/15., table 2 \\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

6 Known safety issues with insulin degludec

6.1 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:
In an information request sent on November 18, 2015, the reviewer asked the Applicant to specify the glucometers used during the trials. No specific meter was identified by the Applicant. 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.

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
Table 14 summarizes 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 (Table 14). 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 Table 24 in the Appendix for narratives).

Analysis of severe hypoglycemia by trial is shown in Table 14. 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[6] hypoglycemic events (4 events in IDegLira and 1 event for insulin glargine) all serious hypoglycemia events were captured as severe episodes, except for one event, the narrative of which is in the appendix, Table 25).

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. For details, refer to the Statistical Summary and to Table 14.

Other 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 totality of the data does not clearly demonstrate a hypoglycemia advantage for IDegLira vs. basal insulin. Additionally, analyses of hypoglycemia should be interpreted in light of the dosing and titration concerns discussed previously.

[6] Serious adverse event is an event that results in death, is life-threatening, results in permanent damage or disability, results in congenital anomaly or requires medical/surgical intervention to prevent permanent impairment.[7] The MedDRA search was for the following PT terms: Accidental overdose, Completed suicide,

Table 14 – 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

6.2 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). 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.

The Applicant conducted body weight change analyses using the LOCF approach. FDA disagrees with this approach and these analyses are not shown here. An MMRM analysis with a similar method as that used for the primary endpoint was also provided, 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.

The estimated differences in weight between arms are presented in Table 15. 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 treatment differences between study arms were small and the clinical relevance of these changes are unclear.

Table 15 – 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

7 Known safety issues with insulin degludec and liraglutide

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

7.1 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.

7.2 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 (Table 16). For all treatment groups, the highest PT was injection site bruising.

Table 16 - 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

8 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.

8.1 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.

All preferred terms in the Gastrointestinal Disorders SOC were included in the following analysis (shown in Table 17 and Table 26). 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 (refer to Table 13 shown previously), 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, as previously shown in Table 12 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 Appendix 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.

Table 17 – 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

8.2 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.

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. The narrative for this subject is in the Appendix, Table 23.

8.3 Pancreatitis or suspicion of 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.

The event adjudication committee adjudicated potential pancreatitis adverse events through two approaches (see Table 20 in Appendix). Each approach underwent independent adjudication, thus each approach is shown in Figure 7 by a different color (red or orange).

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.

Table 18 – 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)

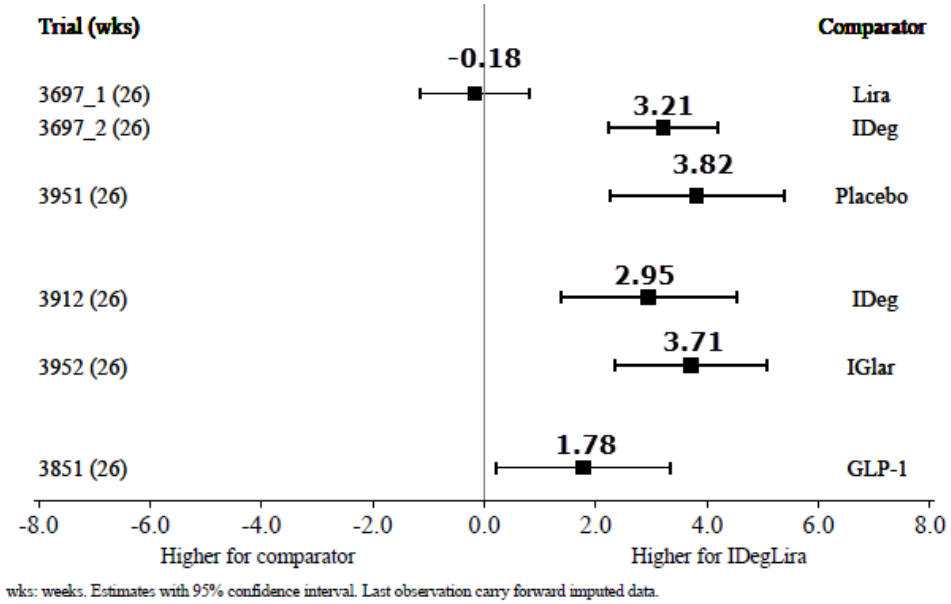
Source: ISS, page 197, table 2-39.

8.4 Heart rate increase

Liraglutide is associated with a 2-3 beat per minute heart rate increase. The clinical significance of this finding is unknown. 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 (Figure 6) 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 (see Figure 6).

Figure 6 – Mean change in heart rate from baseline to 26 weeks- completed phase 3 trials - plot of treatment contrasts - FAS



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.

9 Overdose

The Applicant carried out a pre-defined MedDRA[7] 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.

To more broadly evaluate the risk of overdose and the associated AEs, the FDA reviewer 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[8] 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.

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

[8] 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

IDegLira is currently approved in Switzerland and the EU. Review of a post-marketing safety update report submitted by the Applicant including data from 30 Sept 2014 to a cutoff of 31 Mar 2015 did not note any post-marketing reports related to medication errors.

10 Appendices

Tables of trial methodology

Table 19 – Overview of inclusion and exclusion criteria in Phase 3 trials

	PIVOTAL TRIALS (3697 AND 3912)	OTHER PHASE 3 TRIALS (3851, 3951,3952)
INCLUSION CRITERIA		
Common	-Adult >18 years old[9], male and non-pregnant female, subjects with T2DM -Able and willing to perform SMPG measurements, keep diabetes diary	
Previous antidiabetic OADs ^	**3697**: Met≥1500 mg/day¥ ± pio ≥ 30 mg/day **3912:** basal insulin (e.g. IGlar, insulin detemir, NPH insulin) with total daily dose of 20–40 units; individual fluctuations of ±10% within the 90 days prior to screening∞. Dose of basal insulin +met (≥ 1500 mg or MTD) with or without SU (≥ half of maximum approved dose according to local label) or glinides (≥ half of maximum approved dose according to local label)	**Trial 3851**: GLP-1 analog (1.8 mg lira once daily or 10 µg exenatide twice daily) or MTD (1.2 mg lira once daily or 5 µg exenatide twice daily) in combination with met (≥1500 mg or MTD) ± pio (≥30 mg) ± SU (≥half of the max approved dose according to local label) **Trial 3951**: stable daily dose of SU (≥half of the max approved dose according to local label) with or without metformin (≥1500mg or MTD) for at least 90 days prior to screening. **Trial 3952**: IGlar of 20−50 units (both inclusive) for at least 56 days prior to screening, and met (≥ 1500 mg or MTD)
HbA1c criteria	**3697:** 7-10% (inclusively) **3912:** 7.5-10% (inclusively)	**3851 & 3951:** 7.0 – 9.0% (inclusively) **3952:** 7.0- 10.0% (inclusively)
BMI	**3697:** ≤40 kg/m^2 **3912:** ≥ 27 kg/m^2	All: ≤40 kg/m^2
Exclusion criteria		
Safety specific to GLP-1	• screening calcitonin ≥ 50 ng/L • subjects with personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2) • history of chronic pancreatitis or idiopathic acute pancreatitis	
Other	• hypersensitivity to trial product(s) or related products • use of any drug which in the investigator's opinion could interfere with glucose levels • cancer (except basal cell skin cancer or squamous cell skin cancer), which in the investigator's opinion could interfere with the results of the trial, or cancer during the 5 past years	

[9] For Singapore age:21 years of above, Taiwan 20 years of above

∞Pre-trial treatment with basal insulin and SU or glinides (if applicable) was to be discontinued at Visit 2. Throughout the trial, OAD treatment should be maintained at the stable, pre-randomization dose and frequency, although dose adjustments for safety reasons were allowed.
^At stable dosage defined as no change in dose for 90 days prior to randomization
[£]For Argentinian sites in **3952** SBP≥150 mmHg or diastolic blood pressure ≥90 mmHg; in Argentina, subjects with active diabetic ulcer or a history of diabetic foot in a period of 1 year prior to screening were excluded
OADs=oral antidiabetic drugs, Met=metformin, SU=sulfonylurea, pio=pioglitazone, IGlar=insulin glargine, lira=liraglutide, IDeg=insulin degludec, DPP4=dipeptidyl peptidase 4 , TZD=thiazolidinedione, SMPG=self-monitored plasma glucose, MTD=maximum tolerated dose

Table 20- Adjudication criteria for evaluation of reported clinical events used by the EAC[10]

Event	Definition
Acute Coronary Syndrome	Acute Coronary Syndrome (ACS) conditions range from unstable angina pectoris (UAP) to non-ST elevation myocardial infarction (MI) (NSTEMI—subendocardial or nontransmural) and ST elevation MI (STEMI—transmural). **Criteria for STEMI**: New ST segment elevation of > 1millimeter (mm) or millivolt (mV) is present in 2 or more contiguous leads on the 12-lead ECG **Criteria for NSTEMI:** ST segment elevation of >1mm or mV is absent in 2or more contiguous leads on the 12-lead ECG In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.
Acute Myocardial Infarction	The term "MI" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available. MI is diagnosed based on any of the following criteria, based on the redefinitions suggested by the ESC (European Society of Cardiology)/ACCF (American College of Cardiology Foundation)/AHA (American Heart Association)/WHF (World Heart Federation) task force.[4] Under these conditions, any one of the following criteria meets the diagnosis for AMI: **Spontaneous MI:** Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least 1 of the following: Symptoms of ischemia ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) [5] Development of pathological Q waves in the ECG[6] Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

[4] Thygesen K, et al. "Universal Definition of Myocardial Infarction." J Am Coll Cardiol 2007 Nov 27; 50 (22): 2173-95.

[5] ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB): 1) ST elevation New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads. 2) ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1.

[6] Pathological Q waves: 1) Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF).

[10] An information request was sent to the Applicant to clarify differences between each trial's EAC charters. The Applicant replied on March 9, 2016 and clarified that for 3697 and 3912 the adjudication process and the definitions of events were identical. For trials subsequent to 3912, the charters included revised definitions of cardiovascular events. The chart presented in this section is for 3697and 3912.

Event	Definition
	CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin. **Sudden, Unexpected Cardiac Death.** Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. **Percutaneous Coronary Intervention-Related Myocardial Infarction.** For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized. If the cardiac biomarker is elevated prior to PCI, a ≥ 20% increase of the value in the second cardiac biomarker sample within 24 hours of the PCI and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction. Symptoms of cardiac ischemia are not required. **Coronary Artery Bypass Grafting-Related Myocardial Infarction.** For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI. If the cardiac biomarker is elevated prior to CABG, a ≥ 20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a periprocedural myocardial infarction after CABG. Symptoms of cardiac ischemia are not required **Silent Myocardial Infarction** Silent MI is defined by the following: 1. No evidence of acute myocardial infarction **AND** 2. Any one of the following criteria:

Event	Definition
	• New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause • Autopsy evidence of a healed or healing MI
Clinical Classification of Different Types of MI	For EAC adjudication the following classifications of MI will be identified. In addition to classification, the EAC Adjudicators will identify ranges of URL values. Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque fissuring or rupturing. Type 2: MI secondary to ischemia due to imbalance between oxygen demand and supplies, eg, coronary spasm. Type 3: Sudden cardiac death with symptoms of myocardial ischemia, accompanied by new ST elevation or LBBB, or verified coronary thrombus by angiography, but death occurring before blood samples could be obtained. Type 4a: MI associated with PCI; 4b: stent thrombosis documented by angiography or autopsy Type 5: MI associated with CABG.
Unstable Angina Pectoris requiring hospitalization	UAP is defined as cardiac ischemic events that do not fulfill the criteria of acute MI (NSTEMI or STEMI). If neither of these conditions is present by the criteria above in the MI sections of this document, then UAP may be present. The symptoms in UAP are often of shorter duration and/or are relapsing and represent a significant worsening of the patient's baseline symptoms to an extent as being the primary cause of unplanned hospitalization. For UAP to be present, NSTEMI and STEMI cannot be present. Severe recurrent ischemia (UAP) is defined as ischemic discomfort or equivalent meeting the following criteria in the absence of MI criteria: 1) No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis) AND 2) Clinical presentation lasting at least 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration, and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis. Rest angina *or* New-onset (< 2 months) severe angina (Canadian Cardiovascular Society Grading Scale* (or CCS classification system) classification severity ≥ III) *or* Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS class III AND 3) At least one of the following additional criteria for coronary artery disease and/or ischemia: New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of

Event	Definition
	LVH and LBBB: ST elevation New transient (known to be < 20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1. Evidence of ischemia on stress testing with cardiac imaging Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery *or* initiation/increased dosing of antianginal therapy. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery AND 4. Requiring an unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units During adjudication, it should then be noted if the event required: 1) Hospitalization (including an overnight stay on an inpatient unit) within 48 hours of the most recent symptoms. 2) Coronary revascularization during an unscheduled visit to a healthcare facility or during an unplanned (or prolonged) hospitalization for the symptoms.
Heart Failure Requiring Hospitalization	Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria: Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available). AND Clinical manifestations of heart failure including at least one of the following: New or worsening dyspnea orthopnea paroxysmal nocturnal dyspnea edema pulmonary basilar crackles jugular venous distension new or worsening third heart sound or gallop rhythm, or radiological evidence of worsening heart failure. AND Additional/Increased therapy Initiation of intravenous diuretic, inotrope, or vasodilator therapy Uptitration of intravenous therapy, if already on therapy Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the

Event	Definition
	use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure. Biomarker results (e.g., brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.
Coronary Revascularization	A coronary revascularization procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow. Insertion of a guidewire through a coronary guide catheter into a coronary vessel or bypass graft for the purpose of percutaneous coronary intervention (PCI) is considered intention for PCI. However, in the assessment of the severity of intermediate lesions with the use of intravascular ultrasound, Doppler flow velocity, or fractional flow reserve, insertion of a guidewire will NOT be considered PCI.
Cerebrovascular Event (Stroke)	Stroke is an acute episode of neurological dysfunction attributed to a vascular cause and determined to *not* be due to a readily identifiable cause, such as a tumor or seizure with residual symptoms at least 24 hours after onset, or leading to death. Stroke is documented by imaging (eg, CT or MRI scan). Evidence obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can also be supportive to the diagnosis. Ischemic cerebrovascular events lasting less than 24 hours will not be considered stroke and will be considered transient ischemic attacks, and will be identified as such in the eCRF. Micro-hemorrhages are defined as rounded <5-10 mm foci of of susceptibility artifact on gradient-echo (T2*) MRI sequences. These appear hypointense without signal characteristics of acute or subacute hemorrhage and are distinct from other causes of signal loss on gradient echo (T2*) MRI sequences (e.g. vascular flow voids, leptomeningeal hemasidarosis, or non-hemorrhagic subcortical mineralization). (NB: When found in the setting of acute or subacute stroke symptoms, hemosiderin alone [micro-hemorrhages] without MR signal changes consistent with acute or subacute stroke should be considered incidental and not the cause of the stroke symptoms.) While data pertaining to the occurrence of micro-hemorrhages will be collected as exploratory data, the occurrence of micro-hemorrhage will not be included in the primary endpoint.
Classification of Stroke	**A. Transient Ischemic Attack** Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. **B. Ischemic Stroke** Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue that results from a thrombus or embolus impairing central nervous system perfusion (not due to hemorrhage) and is documented by imaging. Evidence of ischemic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis. **C. Hemorrhagic stroke** Hemorrhagic stroke is defined as an acute episode of focal or global cerebral, spinal, or retinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage with documentation of cerebral

Event	Definition
	hemorrhage on imaging (eg, CT or MRI scan), ie, intraparenchymal, intraparenchymal with penetration into the ventricles, intraventricular, or subarachnoidal hemorrhage. Subdural and epidural bleedings are not included. Evidence of hemorrhagic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis. **D. Undetermined Stroke** Undetermined stroke is defined as a stroke with insufficient information to allow categorization as B or C. **Stroke Disability** Stroke disability should be classified using the modified Rankin Scale[7] (www.strokecenter.org/trials/scales/rankin.html)
Death	**Mortality from CV Causes** CV mortality includes includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as well as deaths for which there was no clearly documented non-vascular cause. **Sudden Cardiac Death**: refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths: a. Witnessed and instantaneous without new or worsening symptoms b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms c. Witnessed and attributed to an identified arrhythmia (eg, captured on an ECG recording or witnessed on a monitor by either a medic or paramedic) d. Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology e. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided) **Death due to Acute MI**: death occurring up to 30 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where

[7]

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Event	Definition
	there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence. Death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause. **Death due to Heart Failure or Cardiogenic Shock**: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following: a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration c. Confinement to bed predominantly due to heart failure symptoms d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypo-perfusion: Cool, clammy skin or Oliguria (urine output < 30 mL/hour) or Altered sensorium or Cardiac index < 2.2 L/min/m^2 Cardiogenic shock can also be defined as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study endpoint. This category will include sudden death occurring during an admission for worsening heart failure. **Death due to Cerebrovascular Event:** (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death. The FDA Stroke Team Definition of Death due to Stroke can also refer to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke. **Death due to Other Cardiovascular Causes** Death must be due to a fully documented cardiovascular cause not included in the above categories (eg, dysrhythmia, pulmonary embolism, or cardiovascular intervention). **Non-Cardiovascular Death**

Event	Definition
	Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death and will be categorized into following groups: pulmonary causes, renal causes, gastrointestinal causes, infection (includes sepsis), non-infectious (e.g., systemic inflammatory response syndrome (SIRS)), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage- not intracranial, accidental/trauma, suicide, non-cardiovascular system organ failure (e.g., hepatic failure), non-cardiovascular surgery, other non-cardiovascular. **Presumed Cardiovascular Death** All deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint. **Classification of Death Events** Causes of death events will be initially identified as either "Known" or "Unknown." If classified as Unknown, no further adjudication of the event will be performed. If Known is selected, the Adjudicator will then be prompted to rate the likelihood that the death can be classified as a CV death event, by making one of the following selections for CV-Related Death: 1) Documented, 2) Probable/Possible, or 3) Unlikely. If one of the first 3 choices is selected, the death event will be classified as CV-related. If "Unlikely" is selected or if cause of death is not suspected to be CV related, the Adjudicator will rate the likelihood that the death event was a non-CV death event by making one of the following selections for Non-CV-Related Death: 1) Documented, 2) Probable/Possible, or 3) Unlikely.. The definitions of classifications are as follows: • **Documented**—There is documented evidence for classification • **Probable/Possible**— There is good reason and sufficient documentation and/or it is conceivable and cannot be dismissed • **Unlikely—**The event is most likely related to an alternative cause other than a cardiovascular cause (eg, medical history relevant for cancer) For operational purposes, in case of doubt the CEC members are encouraged to consider the definitions at the end of this spectrum of definitions
Pancreatitis	Pancreatitis is an inflammatory process of the pancreas. Two of following diagnostic criteria meets the diagnosis of acute pancreatitis: severe acute upper abdominal pain elevated blood levels of pancreatic enzymes (lipase, amylase) 3xUNR characteristic imaging finding (ultrasound, CT, MRI) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.
Neoplasm	Neoplasm is defined as an abnormal growth of tissue. All neoplasms will be captured. In addition, events coded to MedDRA PT of Malignancies and PT Premalignant disorders will be compiled.

Event	Definition
	Medullary carcinoma of the thyroid (MTC) is defined as a distinct thyroid carcinoma that originates in the calcitonin producing parafollicular C cells of the thyroid gland. According to the pathology report, thyroid neoplasms deriving from the C cells will be classified as C-cell hyperplasia, medullary microcarcinoma (carcinoma *in situ)* and medullary carcinoma. Neoplasms will be classified according to the tissue of origin, the organ system and to the malignancy status: • Benign • Malignant • Pre malignant/Carcinoma in situ/borderline • Unclassified

Source: EAC charter, Table 33. \\cdsesub1\evsprod\NDA208583\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t2dm\5351-stud-rep-contr\study-report-nn9068-3697\16-1-01-protocol.pdf

Clinical narratives in phase 3 trials

Table 21 – Fatal events in completed phase 3 trials

SUBJECT/TRIAL/ AGE/SEX/BMI/ COUNTRY/ *TREATMENT ARM*	STUDY DAY	PREFERRED TERM/ **EAC CAUSE OF DEATH**	RELEVANT MEDICAL HISTORY	NARRATIVE
454031/ 3697/ 49/F/32.0 South Africa/ *IDegLira*	68	Death/ **CV death**	Hypertension, hypercholesterolemia	On Day 68, the subject died due to an unknown cause. The subject had been well the days prior to the event. The subject collapsed at home in the evening and resuscitation by family and neighbor was unsuccessful. An autopsy was not performed. According to the death certificate, the subject died from natural causes.
954006/ 3697/ 66/F/32.7/ US/ *IDegLira*	182	Urinary tract infection+ septic shock/ **CV death**	Hypertension, hyperlipidemia, aortic stenosis, prosthetic valve replacement, congestive heart failure, hypercholesterolemia	On Day 182, the subject was hospitalized and diagnosed with urinary tract infection, sepsis and mild congestive heart failure. Upon arrival, gram-negative rods were identified in urine cultures. The subject died the following day from cardiopulmonary arrest.
107001/ 3951/ 77/M/26.4/ Germany/ *IDegLira*	21	Pleural mesothelioma malignant/ **Non-CV death**	Asthma bronchial	On Day 21, the subject presented with symptoms of pleural effusion. CT of thorax had shown advanced pleural mesothelioma with lymph node metastases and infiltration of the pericardium. The diagnosis was confirmed by histology. The subject died from malignant pleural mesothelioma on Day 116. The subject had been working with asbestos during most of his working life.
457014/ 3697/ 46/F/34.5/ South Africa /*IDegLira*	295	Gunshot wound/ **non-CV death**	none	On Day 295, the subject was fatally wounded in a gunshot attack and died on the same day. The last confirmed date of trial product intake was 8 days earlier (day before Visit 44). The date of the last actual dose of trial product is unknown, and the autopsy report was not

				available.
600013/ 3952/ 50/M/24.2/ Mexico/ *IGlar*	78	Hemorrhagic stroke/**CV death**	None	On Day 78, the subject was found dead in the middle of a field, where he was sowing. The death certificate reported edema and cerebral hemorrhage due to hypertensive stroke. No autopsy was performed.

Grayed boxes are for the fatal events after the treatment- emergent period
BMI: body mass index, CT: computerized axial tomography; CV: cardiovascular: EAC: event adjudication committee; age and BMI are baseline values; Source: ISS, table 2-6, page 117-118.

Table 22 – IDegLira Narratives of serious gastrointestinal disorders SOC

SUBJECT ID / TRIAL/ AGE/SEX/ COUNTRY	TRIAL DAY ONSET	PREFERRED TERM	NARRATIVE
872010/ 3697/ 53/M/ USA	107	Pancreatitis acute	53 year old man randomized to IDegLira (50 dose steps) with history of cholelithiasis and smoking was hospitalized. Patient had right upper quadrant abdominal pain, and nausea. Right upper quadrant ultrasound revealed acute and chronic cholelithiasis and acute pancreatitis was confirmed. Lipase on admission was 701 U/L (reference 23- 300 U/L). The patient had a laparascopic cholecystectomy.
903002/ 3697/ 59/F USA	9	Colitis ischemic	59 year old woman with history of hyperlipidemia, hypertension, diabetic neuropathy was randomized to 14 dose steps of IDegLira . Patient developed abdominal cramps and 3-4 episodes of bright red blood from rectum. CT of the abdomen/pelvis without contrast revealed findings that could represent infectious colitis or isolated crohn's disease. Patient was admitted and a CT (no further details provided) revealed diffuse bowel wall thickening in the descending and sigmoid colon. Patient underwent an esophagoduodenoscopy, wire-guided esophageal dilation with antral biopsies and colonoscopy to the cecum with biopsies. Biopsies were negative for H. Pylori. Colonoscopy showed resolving ischemic colitis in the descending colon. Patient was treated with antibiotics
907008 3697/ 53/M USA	4	Small intestinal obstruction	53 year old man with history of hypertension, bilial small bowel obstruction was randomized to 10 dose steps of IDegLira. Patient developed abdominal pain and was diagnosed with bilial small bowel obstruction. No imaging studies were reported. Laboratory data was not collected
921008 3697/ 70/M USA	184	Gastrointestinal hemorrhage	70 year old man with history of dyslipidemia, hypertension, diverticulitis, gastroesophageal reflux, nausea, who was on Coumadin (with indication not reported). Patient developed 'black stools'. Patient underwent colonoscopy and 'endoscopy,' and per patient were normal, report is not available. CT showed arteriosclerotic vascular disease.
302013 3951/ 63/F Bulgaria	28	Gastritis	63 year old woman with history of hypertension, and cholelithiasis. On a routine visit, patient was found to have general deterioration of the medical condition and was hospitalized due to decompensated diabetes mellitus. The patient was discharged with the final diagnosis of 'decompensated diabetes mellitus', gastritis, iron deficiency anemia and cyst in left kidney. Patient was treated with ceftriaxone, iron , omeprazole and metronidazole.

Source: Information obtained from narratives in Appendix 8 of ISS and SAE dataset for trial day onset , labeled 'TRLDSTAE'

Table 23 – Narrative of IDegLira patient with elevated calcitonin level

ID/CASE# STUDY LOCATION	AGE SEX	DRUG	NARRATIVE
750003/ 3912/ USA	61 M	IDegLira	61 year old male, with +smoking history, who at screening was found to have an elevated calcitonin of 45 pg/mL (reference range: 0 to 8.4 ng/L). At visit 2, 2 weeks later his calcitonin decreased to 28.7 pg/mL. At week 12, the subject's calcitonin was 96.2 pg/mL; 6 months after study start, the subject's calcitonin was 29.5 pg/mL, while still continuing treatment with IDegLira.

Table 24 – Events of severe hypoglycemia- treatment- emergent – completed phase 3 trials

ID/ STUDY/ LOCATION	AGE SEX	DRUG DOSE	NARRATIVE	BLINDED REVIEW MET SEVERE (Y/N)
ID 177007/, 3697/ UK	43 F	**IDegLira*** 46 units	The subject had symptoms of "weakness" and inability to walk. Subject called her daughter who checked her glucose (46.8 mg/dL) and got her a sugary drink. The hypoglycemia abated over the next hour.	Y
205007/ 3697/ Germany	56 F	**IDegLira *** 18 units	Had hypoglycemic unconsciousness 2 months after start of treatment the subject collapsed at work and was unconscious for a maximum of one minute. The subject regained consciousness. Blood sugar was 58 mg/dL. Subject was treated with IV glucose. The dose of IDegLira was decreased form 18 dose steps to 14 dose steps.	Y
921008/ 3697/ USA	70 M	**IDegLira** 34 units	Experienced feeling shaky/weak and collapsed. The subject was given a glucose tablet and blood sugar was 51 mg/dL. The dose of trial product was decreased.	Y
454023/ 3697/ South Africa	51 F	Degludec 26 units	The subject was reported as conscious and had an IV line placed by paramedics, blood sugar reported was 2.0 mmol/L (36 mg/dL). There were no details regarding neither symptoms nor glucose administration for this narrative. There were no changes to trial drug due to event.	Y
508002/ 3697/ Australia	38 M	Degludec 64 Units	Subject developed light headedness, took 7 "lollies", then walked to a petrol station but fell unconscious for 5-10 minutes. An off duty nurse gave him lollies. An ambulance measured blood sugar as 4.7 mmol/L (84.6 mg/dL). The dose of Degludec was decreased to 60 units due to this event.	Y
711002/ 3697/ Canada	68 M	Liraglutide 1.8 mg	Subject felt light headed, and lost consciousness for 5 minutes. Subject required assistance from his wife to drink the orange juice; after a few sips he recovered. Blood sugar was not checked. The investigator decreased the dose of metformin from 2 TID to 2 BID.	y
828003/ 3697/ USA	61 M	Liraglutide 1.8 mg	The subject had a syncopal episode and reported that he had been unconscious. The subject was give candy by a bystander and recovered. Blood glucose measures were not done at the time of the event.	y
601014/ 3912/ Slovenia	62 W	**IDegLira** 42 units	Subject felt "very bad" while she was mountain climbing. Subject was not able to help herself, so her sister gave her something to drink at 11 am and at 13:00 while being physically active. The subject felt better after interventions. Subject did not measure blood sugars. The subject continued climbing.	N
172003/	58	**IDegLira**	Developed an episode of "dizziness, lightheadedness and	N

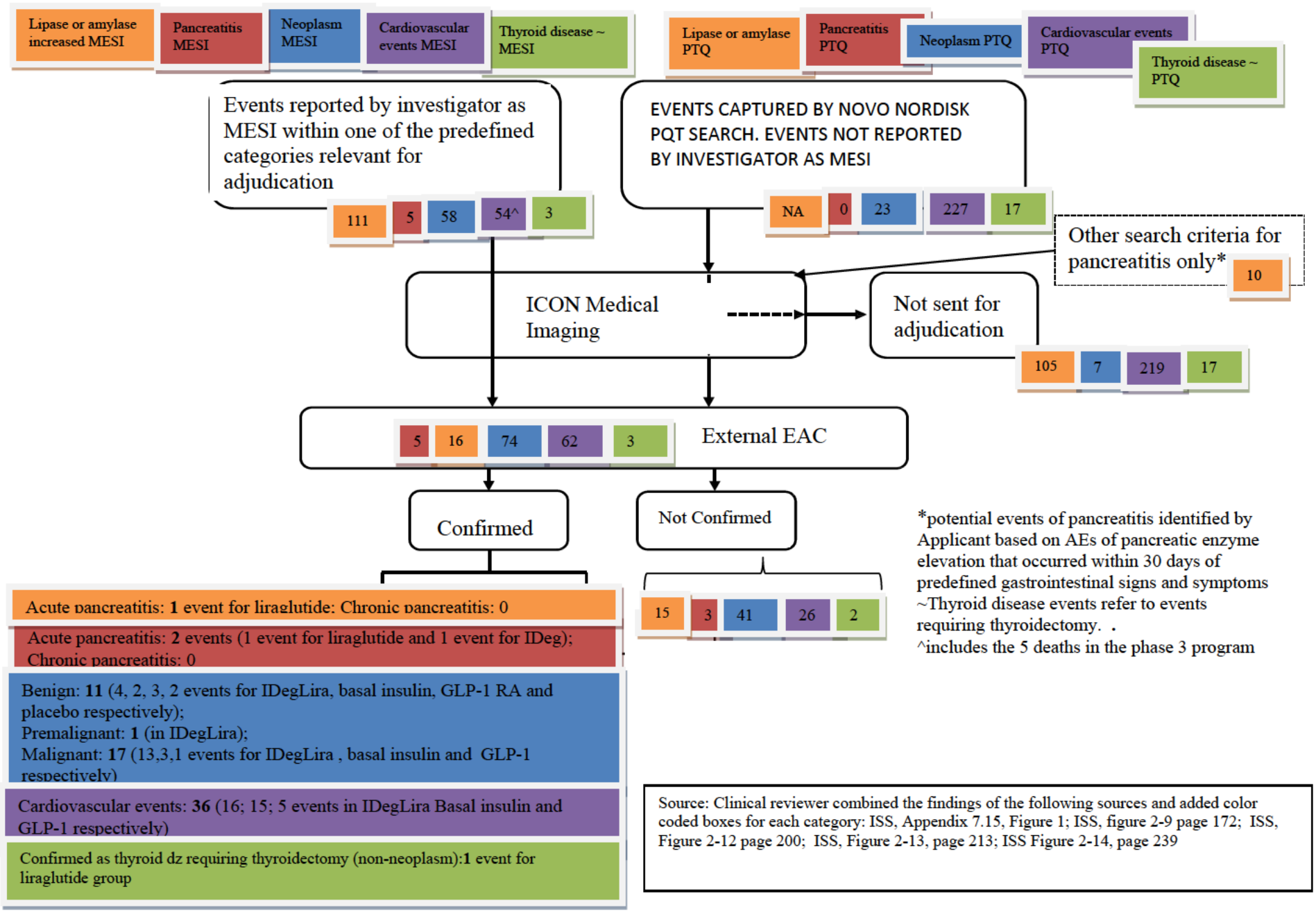
3851/ USA	F	50 units	nausea". Subject was not unconscious. Blood glucose at the time of the event was 45 mg/dL. The subject was treated with oral carbohydrates with assistance from family member. Of note, subject was also taking a sulfonylurea.	
817008/ 3951/ USA	60 M	**IDegLira*** 22 units	Experienced "hypoglycemic unconsciousness" with blood sugar of 22 mg/dL. The subject required assistance and had to be treated by others. Of note subject was also taking a sulfonylurea OAD.	Y
708002/ 3951/ Canada	58 M	**IDegLira** Unknown	Subject woke up around 06:00 blood glucose was at 5.3 mmol/L (95.4 mg/dL). The subject took his glibenclamide and Metformin. Around 08:00, the subject felt weak and fell. Two paramedics administered subcutaneous glucagon. The subject does not remember anything. No glucose value was available before the event. About 30 minutes after the event, the blood glucose was 9.0 mmol/L (162 mg/dL).	Y
710010/ 3952/ Slovenia	63 F	Lantus* 40 units	Subject had changes in mood and behavior. The subject's husband called an ambulance. 15 minutes later blood sugar was 2.0 mmol/L (36 mg/dL) and she received 40% IV glucose and she improved blood sugar was 7.1 mmol/l (127.8 mg/dL).	Y

Shaded boxes refer to events that were not considered to be meeting severe criteria by blinded review
* Marks hypoglycemic events that were also SAEs.

Table 25 – Serious but non-severe case of hypoglycemia

ID/CASE# STUDY LOCATION	AGE SEX	DRUG DOSE ONSET DAY	NARRATIVE
765013/ 3912/ USA	56 M	**IDegLira*** 45 dose steps	56 year old man randomized to IDegLira who on day 146 reported feeling "not good." Subject had an episode of chest tightness lasting seconds, weakness, headache, and diaphoresis (the constellation of symptoms spanned 2 days). Subject went to the emergency department where he was hospitalized. Imaging including cardiac enzymes, CT brain, MRI and 2D echocardiogram were negative. Subject's blood sugar was 157 mg/dL in the morning of admission. During the hospitalization his blood sugars ranged from 79 to 131 mg/dL. The subject was discharged 2 days after admission with "suspected hypoglycemic episode secondary to diabetic study medication" as a diagnosis.

Figure 7- Overview of Adjudication Procedures for Phase 3 trials



Source: Clinical reviewer combined the findings of the following sources and added color coded boxes for each category: ISS, Appendix 7.15, Figure 1; ISS, figure 2-9 page 172; ISS, Figure 2-12 page 200; ISS, Figure 2-13, page 213; ISS Figure 2-14, page 239

Table 26-Serious adverse events by SOC, HLGT and PT- treatment emergent-completed phase 3 trials- adjusted frequencies and rates

System organ class (SOC) High level group term (HLGT) Preferred term (PT)	IDegLira				Basal insulin				GLP-1 RA				Placebo			
	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	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
Coronary artery disorders	8	(0.4)	9	0.7	6	(0.5)	6	0.8	2	(0.2)	3	0.5				
Acute myocardial infarction	4	(0.2)	4	0.3	2	(0.2)	2	0.3	1	(0.2)	1	0.3				
Acute coronary syndrome					2	(0.2)	2	0.3								
Angina unstable					2	(0.3)	2	0.4								
Angina pectoris	2	(0.1)	2	0.2					2	(0.2)	2	0.3				
Myocardial ischaemia	1	(<0.1)	1	<0.1												
Coronary artery disease	1	(<0.1)	1	<0.1												
Coronary artery dilatation	1	(<0.1)	1	<0.1												
Cardiac arrhythmias	6	(0.3)	7	0.6	1	(<0.1)	1	0.2	1	(0.5)	1	0.9	1	(0.3)	1	0.6
Atrial fibrillation	3	(0.2)	3	0.2					1	(0.2)	1	0.4				
Supraventricular tachycardia	1	(<0.1)	1	<0.1												
Arrhythmia	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.2								
Ventricular fibrillation	1	(<0.1)	1	<0.1												
Atrioventricular block second degree													1	(0.7)	1	1.6
Ventricular tachycardia	1	(<0.1)	1	<0.1												
Heart failures	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.2								
Cardiac failure					1	(<0.1)	1	0.2								
Cardiac failure congestive	1	(<0.1)	1	<0.1												
Infections and infestations	9	(0.5)	12	1.0	5	(0.5)	5	0.9	2	(0.3)	4	1.0	2	(0.9)	2	1.1
Infections - pathogen unspecified	7	(0.4)	10	0.8	4	(0.3)	4	0.6	2	(0.2)	3	0.6	1	(0.7)	1	0.6
Pyelonephritis chronic	1	(<0.1)	2	0.2												
Urinary tract infection	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.1	1	(<0.1)	1	0.1				
Appendicitis					1	(<0.1)	1	0.2								
Pneumonia	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1								
Appendicitis perforated	1	(<0.1)	1	<0.1												
Bronchitis					1	(0.2)	1	0.2					1	(0.7)	1	1.6
Diverticulitis	1	(<0.1)	1	<0.1												
Gastroenteritis									1	(0.2)	1	0.2				
Septic shock	1	(<0.1)	1	<0.1												
Anal abscess	1	(<0.1)	1	<0.1												
Subcutaneous abscess	1	(<0.1)	1	<0.1												
Localised infection	1	(<0.1)	1	<0.1												
Abscess									1	(0.2)	1	0.2				
Viral infectious disorders	1	(<0.1)	1	<0.1	1	(0.2)	1	0.2	1	(0.2)	1	0.2	1	(0.7)	1	1.6
Gastroenteritis viral					1	(0.2)	1	0.2	1	(0.2)	1	0.2				
Dengue fever													1	(0.7)	1	1.6
Vestibular neuronitis	1	(<0.1)	1	<0.1												
Bacterial infectious disorders	1	(<0.1)	1	<0.1												
Meningitis haemophilus	1	(<0.1)	1	<0.1												
Nervous system disorders	10	(0.5)	10	0.8	6	(0.6)	6	1.0	1	(0.1)	1	0.2				
Central nervous system vascular disorders	4	(0.2)	4	0.3	2	(0.1)	2	0.2								
Transient ischaemic attack	1	(<0.1)	1	<0.1												
Haemorrhagic stroke					1	(<0.1)	1	0.2								
Thalamic infarction	1	(<0.1)	1	<0.1												
Lacunar infarction	1	(<0.1)	1	<0.1												
Ischaemic stroke					1	(<0.1)	1	0.2								
Vertebrobasilar insufficiency	1	(<0.1)	1	<0.1												

System organ class (SOC) High level group term (HLGT) Preferred term (PT)	IDegLira			Basal insulin			GLP-1 RA			Placebo		
	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate
Neurological disorders NEC	3	(0.2)	3	0.2	1	(<0.1)	1	0.2								
Hypoglycaemic unconsciousness	2	(0.1)	2	0.2												
Syncope	1	(<0.1)	1	<0.1												
Vertigo CNS origin					1	(<0.1)	1	0.2								
Peripheral neuropathies					2	(0.2)	2	0.4								
Guillain-Barre syndrome					1	(0.2)	1	0.2								
Mononeuropathy					1	(<0.1)	1	0.2								
Encephalopathies	1	(<0.1)	1	<0.1												
Hypertensive encephalopathy	1	(<0.1)	1	<0.1												
Headaches	1	(<0.1)	1	<0.1												
Complicated migraine	1	(<0.1)	1	<0.1												
Cranial nerve disorders (excl neoplasms)	1	(<0.1)	1	<0.1												
VIIth nerve paralysis	1	(<0.1)	1	<0.1												
Spinal cord and nerve root disorders									1	(0.2)	1	0.4				
Sciatica									1	(0.2)	1	0.4				
Seizures (incl subtypes)					1	(<0.1)	1	0.2								
Convulsion					1	(<0.1)	1	0.2								
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	(0.5)	9	0.7	3	(0.3)	3	0.6	2	(0.3)	2	0.5				
Reproductive neoplasms male malignant and unspecified	2	(0.1)	2	0.2	1	(0.1)	1	0.2								
Prostate cancer	1	(<0.1)	1	<0.1	1	(0.2)	1	0.2								
Prostate cancer stage II	1	(<0.1)	1	<0.1												
Reproductive neoplasms female malignant and unspecified					1	(0.2)	1	0.2								
Endometrial adenocarcinoma					1	(0.2)	1	0.2								
Plasma cell neoplasms	1	(<0.1)	1	<0.1												
Plasmacytoma	1	(<0.1)	1	<0.1												
Mesotheliomas	1	(<0.1)	1	<0.1												
Pleural mesothelioma malignant	1	(<0.1)	1	<0.1												
Breast neoplasms malignant and unspecified (incl nipple)	1	(<0.1)	1	<0.1												
Inflammatory carcinoma of breast stage III	1	(<0.1)	1	<0.1												
Endocrine neoplasms malignant and unspecified	1	(<0.1)	1	<0.1					1	(0.2)	1	0.2				
Thyroid neoplasm									1	(0.2)	1	0.2				
Pituitary tumour	1	(<0.1)	1	<0.1												
Renal and urinary tract neoplasms malignant and unspecified	1	(<0.1)	1	<0.1												
Bladder cancer stage 0, with cancer in situ	1	(<0.1)	1	<0.1												
Gastrointestinal neoplasms malignant and unspecified	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.2	1	(0.2)	1	0.2				
Rectal adenocarcinoma	1	(<0.1)	1	<0.1												
Pancreatic carcinoma metastatic					1	(<0.1)	1	0.2								
Pancreatic carcinoma stage IV									1	(0.2)	1	0.2				
Skin neoplasms malignant and unspecified	1	(<0.1)	1	<0.1												
Malignant melanoma	1	(<0.1)	1	<0.1												
Respiratory, thoracic and mediastinal disorders	1	(<0.1)	1	<0.1	5	(0.7)	8	1.4								

System organ class (SOC) High level group term (HLGT) Preferred term (PT)	IDegLira				Basal insulin				GLP-1 RA				Placebo			
	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate
Bronchial disorders (excl neoplasms)	1	(<0.1)	1	<0.1	4	(0.5)	6	1.1								
Chronic obstructive pulmonary disease	1	(<0.1)	1	<0.1	2	(0.3)	3	0.5								
Asthma					2	(0.2)	2	0.4								
Bronchitis chronic					1	(0.2)	1	0.2								
Pleural disorders					1	(0.2)	1	0.2								
Pleural effusion					1	(0.2)	1	0.2								
Lower respiratory tract disorders (excl obstruction and infection)					1	(0.2)	1	0.2								
Lung consolidation					1	(0.2)	1	0.2								
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
Injuries NEC	5	(0.3)	5	0.4	1	(0.2)	1	0.3	1	(0.2)	1	0.3	1	(0.3)	1	0.4
Fall	3	(0.2)	3	0.2	1	(0.2)	1	0.3								
Road traffic accident	2	(0.1)	2	0.2					1	(0.2)	1	0.3				
Stab wound													1	(0.7)	1	1.6
Bone and joint injuries	3	(0.2)	3	0.2	3	(0.4)	4	0.8	1	(0.2)	1	0.4				
Foot fracture					2	(0.2)	2	0.4	1	(0.2)	1	0.4				
Humerus fracture	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.2								
Fibula fracture	1	(<0.1)	1	<0.1												
Spinal fracture	1	(<0.1)	1	<0.1												
Acetabulum fracture					1	(<0.1)	1	0.2								
Medication errors					1	(0.2)	1	0.2								
Wrong drug administered					1	(0.2)	1	0.2								
Gastrointestinal disorders	5	(0.3)	5	0.4					5	(0.5)	6	1.0	1	(0.5)	1	0.9
Gastrointestinal inflammatory conditions	2	(0.1)	2	0.2					1	(0.2)	1	0.3				
Gastritis	1	(<0.1)	1	<0.1					1	(0.2)	1	0.2				
Colitis ischaemic	1	(<0.1)	1	<0.1												
Abdominal hernias and other abdominal wall conditions									2	(0.4)	2	0.4				
Umbilical hernia									2	(0.4)	2	0.4				
Gastrointestinal motility and defaecation conditions									1	(0.2)	2	0.4	1	(0.7)	1	1.6
Gastrooesophageal reflux disease									1	(0.2)	2	0.4				
Impaired gastric emptying													1	(0.7)	1	1.6
Exocrine pancreas conditions	1	(<0.1)	1	<0.1												
Pancreatitis acute	1	(<0.1)	1	<0.1												
Gastrointestinal haemorrhages NEC	1	(<0.1)	1	<0.1												
Gastrointestinal haemorrhage	1	(<0.1)	1	<0.1												
Gastrointestinal signs and symptoms									1	(0.2)	1	0.2				
Vomiting									1	(0.2)	1	0.2				
Gastrointestinal stenosis and obstruction	1	(<0.1)	1	<0.1												
Small intestinal obstruction	1	(<0.1)	1	<0.1												
Hepatobiliary disorders	5	(0.3)	5	0.4	5	(0.6)	6	1.2	2	(0.3)	2	0.6				
Gallbladder disorders	3	(0.2)	3	0.2	4	(0.5)	4	0.6	2	(0.3)	2	0.4				
Cholecystitis acute	2	(0.1)	2	0.2	1	(<0.1)	1	0.2								
Cholelithiasis	1	(<0.1)	1	<0.1	2	(0.3)	2	0.4	2	(0.4)	2	0.6				
Cholecystitis					1	(0.2)	1	0.2								
Bile duct disorders	2	(0.1)	2	0.2	1	(<0.1)	1	0.2								
Biliary colic	2	(0.1)	2	0.2	1	(<0.1)	1	0.2								

System organ class (SOC) High level group term (HLGT) Preferred term (PT)	IDegLira			Basal insulin			GLP-1 RA			Placebo		
	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate
Hepatic and hepatobiliary disorders					1	(0.2)	1	0.2								
Jaundice cholestatic					1	(0.2)	1	0.2								
Musculoskeletal and connective tissue disorders	5	(0.3)	5	0.4	2	(0.2)	2	0.3	4	(0.4)	4	0.6				
Joint disorders	1	(<0.1)	1	<0.1					3	(0.2)	3	0.4				
Osteoarthritis	1	(<0.1)	1	<0.1					3	(0.2)	3	0.4				
Musculoskeletal and connective tissue disorders NEC	2	(0.1)	2	0.2												
Spinal pain	1	(<0.1)	1	<0.1												
Musculoskeletal pain	1	(<0.1)	1	<0.1												
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	2	(0.1)	2	0.2	1	(<0.1)	1	0.2								
Lumbar spinal stenosis	1	(<0.1)	1	<0.1												
Intervertebral disc protrusion	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.2								
Fractures									1	(0.2)	1	0.2				
Pseudarthrosis									1	(0.2)	1	0.2				
Tendon, ligament and cartilage disorders					1	(0.2)	1	0.2								
Tendonitis					1	(0.2)	1	0.2								
Surgical and medical procedures	5	(0.3)	5	0.4	3	(0.3)	3	0.5	1	(0.1)	2	0.4				
Vascular therapeutic procedures	5	(0.3)	5	0.4	3	(0.3)	3	0.5	1	(0.1)	2	0.4				
Coronary artery bypass	2	(0.1)	2	0.2	1	(<0.1)	1	0.1								
Coronary revascularisation	2	(0.1)	2	0.2	2	(0.2)	2	0.4								
Thrombectomy	1	(<0.1)	1	<0.1												
Percutaneous coronary intervention									1	(0.2)	1	0.2				
Coronary arterial stent insertion									1	(0.2)	1	0.2				
General disorders and administration site conditions	4	(0.2)	4	0.3												
Body temperature conditions	2	(0.1)	2	0.2												
Pyrexia	2	(0.1)	2	0.2												
Fatal outcomes	1	(<0.1)	1	<0.1												
Death	1	(<0.1)	1	<0.1												
General system disorders NEC	1	(<0.1)	1	<0.1												
Non-cardiac chest pain	1	(<0.1)	1	<0.1												
Metabolism and nutrition disorders	4	(0.2)	4	0.3	1	(<0.1)	1	0.2								
Glucose metabolism disorders (incl diabetes mellitus)	3	(0.2)	3	0.2	1	(<0.1)	1	0.2								
Hypoglycaemia	2	(0.1)	2	0.2	1	(<0.1)	1	0.2								
Diabetes mellitus inadequate control	1	(<0.1)	1	<0.1												
Appetite and general nutritional disorders	1	(<0.1)	1	<0.1												
Obesity	1	(<0.1)	1	<0.1												
Reproductive system and breast disorders	3	(0.2)	3	0.2												
Prostatic disorders (excl infections and inflammations)	1	(<0.1)	1	<0.1												
Benign prostatic hyperplasia	1	(<0.1)	1	<0.1												
Menopause related conditions	1	(<0.1)	1	<0.1												

System organ class (SOC) High level group term (HLGT) Preferred term (PT)	IDegLira			Basal insulin			GLP-1 RA			Placebo		
	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate	N	(adj. pct)	E	adj. rate
Postmenopausal haemorrhage	1	(<0.1)	1	<0.1												
Menstrual cycle and uterine bleeding disorders	1	(<0.1)	1	<0.1												
Dysfunctional uterine bleeding	1	(<0.1)	1	<0.1												
Vascular disorders	3	(0.2)	3	0.2												
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	1	(<0.1)	1	<0.1												
Peripheral artery stenosis	1	(<0.1)	1	<0.1												
Embolism and thrombosis	1	(<0.1)	1	<0.1												
Peripheral artery thrombosis	1	(<0.1)	1	<0.1												
Decreased and nonspecific blood pressure disorders and shock	1	(<0.1)	1	<0.1												
Hypotension	1	(<0.1)	1	<0.1												
Renal and urinary disorders	3	(0.2)	3	0.2	3	(0.5)	3	0.5	2	(0.4)	2	0.4				
Renal disorders (excl nephropathies)	3	(0.2)	3	0.2	1	(0.2)	1	0.2	2	(0.4)	2	0.4				
Renal failure acute	2	(0.1)	2	0.2	1	(0.2)	1	0.2								
Renal failure									1	(0.2)	1	0.2				
Renal impairment									1	(0.2)	1	0.2				
Renal cyst	1	(<0.1)	1	<0.1												
Urolithiases					1	(0.2)	1	0.2								
Nephrolithiasis					1	(0.2)	1	0.2								
Urinary tract signs and symptoms					1	(0.2)	1	0.2								
Renal colic					1	(0.2)	1	0.2								
Investigations	1	(<0.1)	2	0.2												
Gastrointestinal investigations	1	(<0.1)	2	0.2												
Amylase increased	1	(<0.1)	1	<0.1												
Lipase increased	1	(<0.1)	1	<0.1												
Eye disorders	2	(0.1)	2	0.2	1	(0.1)	1	0.2	1	(0.2)	2	0.5				
Retina, choroid and vitreous haemorrhages and vascular disorders									1	(0.2)	1	0.2				
Vitreous haemorrhage									1	(0.2)	1	0.2				
Ocular infections, irritations and inflammations	1	(<0.1)	1	<0.1												
Necrotising retinitis	1	(<0.1)	1	<0.1												
Glaucoma and ocular hypertension	1	(<0.1)	1	<0.1					1	(0.2)	1	0.2				
Angle closure glaucoma									1	(0.2)	1	0.2				
Normal tension glaucoma	1	(<0.1)	1	<0.1												
Anterior eye structural change, deposit and degeneration					1	(0.2)	1	0.2								
Cataract					1	(0.2)	1	0.2								
Ear and labyrinth disorders	1	(<0.1)	1	<0.1	1	(<0.1)	1	0.2								
Inner ear and VIIIth cranial nerve disorders	1	(<0.1)	1	<0.1												
Vertigo positional	1	(<0.1)	1	<0.1												
External ear disorders (excl congenital)					1	(<0.1)	1	0.2								
Auricular perichondritis					1	(<0.1)	1	0.2								
Skin and subcutaneous tissue disorders									1	(0.2)	1	0.2				

System organ class (SOC) High level group term (HLGT) Preferred term (PT)	IDegLira N	(adj. pct)	E	adj. rate	Basal insulin N	(adj. pct)	E	adj. rate	GLP-1 RA N	(adj. pct)	E	adj. rate	Placebo N	(adj. pct)	E	adj. rate
Epidermal and dermal conditions									1	(0.2)	1	0.2				
Stevens-Johnson syndrome									1	(0.2)	1	0.2				
Blood and lymphatic system disorders	1	(<0.1)	1	<0.1												
Anaemias nonhaemolytic and marrow depression	1	(<0.1)	1	<0.1												
Iron deficiency anaemia	1	(<0.1)	1	<0.1												
Endocrine disorders	1	(<0.1)	1	<0.1					1	(0.2)	1	0.2				
Thyroid gland disorders									1	(0.2)	1	0.2				
Goitre									1	(0.2)	1	0.2				
Adrenal gland disorders	1	(<0.1)	1	<0.1												
Adrenal insufficiency	1	(<0.1)	1	<0.1												
Psychiatric disorders	1	(<0.1)	1	<0.1					1	(0.2)	1	0.2				
Anxiety disorders and symptoms									1	(0.2)	1	0.2				
Anxiety									1	(0.2)	1	0.2				
Depressed mood disorders and disturbances	1	(<0.1)	1	<0.1												
Major depression	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 summarised by SOC and PT and sorted by descending frequency.

Source: Information request on October 22, 2015, table 4 \\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

STATISTICAL SUMMARY

1 Executive Summary

Novo Nordisk (the applicant) submitted a new drug application (NDA) for IDegLira, a fixed ratio combination of basal insulin degludec and the glucagon-like peptide 1 receptor agonist liraglutide available in a pre-filled pen containing an IDeg/liraglutide ratio of 100 units/3.6 mg per ml. The applicant proposes IDegLira be indicated as an adjunct to diet and exercise, for improvement in glycemic control in the treatment of adults with type 2 diabetes mellitus (T2DM). The submission contains five phase 3 efficacy trials evaluating change in HbA1c over 26 weeks. This document summarizes the results of these trials.

The primary endpoint of all five trials was change in HbA1c from baseline to the end of week 26. The goal of trials 3697 and 3912 was to evaluate clinical benefit of IDegLira versus IDeg and liraglutide and to assess the contribution of the individual components of the combination product in reduction of HbA1c. Three other studies (Trials 3951, 3952 and 3851) examined HbA1c reduction properties of IDegLira in comparison to other drugs (placebo, insulin glargine [IGlar], and GLP-1 receptor agonist [referred to as GLP-1]).

The overall results were found to be consistent across the applicant's analysis of the primary endpoint. IDegLira achieved superiority on 26-week HbA1c reduction to liraglutide (study 3697), IDeg (study 3912), placebo (study 3951), and GLP-1.

Because Last Observation Carried Forward (LOCF) analysis was pre-specified prior to the start of the trials, the applicant submitted primary analyses using the LOCF approach. Upon our request (at the pre-NDA submission meeting), the applicant also submitted the HbA1c analyses utilizing the Mixed-Effect Model Repeated Measure (MMRM) approach. While the MMRM analyses are preferred over the LOCF analyses, the MMRM analyses makes the unlikely assumption that data are missing at random and ignores treatment adherence. Sensitivity analyses involving multiple imputations (MI) and tipping point analyses were thus provided by the applicant.

In all of the five trials subjects in the IDegLira arm had a larger reduction in HbA1c than subjects in the corresponding comparator arm (active and placebo). Based on 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, the average difference in reduction of HbA1c was 1% in study 3951.

Statistical issues and limitations of study design:

- **Missing data**:
  The percentage of subjects who dropped out of the trial prior to 26-week efficacy period was from 7% to 17% across the five trials.

- **No retrieved dropouts**:
  Subjects who discontinued protocol treatment were not asked to come back for the week 26 assessment.

- **Concerns about generalizing results to clinical practice**:
  Definition of hypoglycemia: The applicant's claim that the trial results show reduction in hypoglycemia stems from their definition, which substantially differs from that recommended by the American Diabetes Association (ADA). The ADA severe hypoglycemia definition results in a sample size too small to draw meaningful conclusions.

  Titration schedule: Insulin was titrated too slowly and a large fraction of subjects did not reach a stable dose of insulin prior to study conclusion. Trial 3912 had a pre-specified limit on maximum insulin dose. Therefore, many of the subjects in the comparator treatment did not reach a stable insulin dose during the trial but might have if the trial had been longer or if insulin dose had been titrated more frequently. Clinical practice does not put a limit on insulin dose.

- **Non-inferiority comparison of IDegLira to insulin degludec is inappropriate**:
  IDegLira contains insulin degludec. Reduced dosing of insulin degludec would likely be non-inferior to standard dosing of insulin degludec in HbA1c reduction. A non-inferiority conclusion of IDegLira to insulin degludec does not inform whether liraglutide (or even insulin degludec) contributes to the effectiveness of IDegLira.

2 Overview of Individual Trials

An overview of the 5 trials reviewed is provided in Table 1. All trials were randomized. Three of the trials were open-label and two were double-blinded. Overall, 3488 subjects were randomized, 1891 (54.2%) of them received IDegLira. The background medications and prior history of anti-diabetic medications was different among trials (two of the trials involved oral antidiabetic (OAD) drug users, the other two trials involved basal insulin users, and one trial involved GLP-1 users. In addition, study 3697 had a 26-week extension. The data from the extension part of this trial was not evaluated for efficacy.

Table 1. Summary of study designs

Trial/previous therapy	Population	Background therapy	Design	Treatment arms (n randomized)
3697 OAD users	HbA1c 7.0-10.0% BMI ≤ 40 kg/m^2	metformin ± pioglitazone	Randomization 2:1:1 26 weeks + 26 Weeks extension Open-label	IDegLira: 833 IDeg: 413 Liraglutide: 414
3951 OAD users	HbA1c 7.0-9.0%, BMI ≤ 40 kg/m^2	SU ± metformin	Randomization 2:1 26 weeks Double-blinded	IDegLira: 289 Placebo: 146
3912 basal insulin users	HbA1c 7.5-10.0% BMI ≥ 27 kg/m^2	basal insulin + metformin ± SU or glinides	Randomization 1:1 26 weeks Double-blinded	IDegLira: 199 IDeg: 199
3952 basal insulin users	HbA1c 7-10.0%, BMI ≤ 40 kg/m^2	IGlar + metformin	Randomization 1:1 26 weeks Open-label	IDegLira: 278 IGlar: 279
3851 GLP-1 RA users	HbA1c 7.0-9.0% BMI ≤ 40 kg/m^2	GLP-1 RA+ metformin ± SU ± pioglitazone	Randomization 2:1 26 weeks open-label	IDegLira: 292 GLP-1 RA: 146

Abbreviations: GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycosylated hemoglobin; IDeg = insulin degludec; IDegLira = insulin degludec/liraglutide; IGlar = insulin glargine; OAD = oral antidiabetic drug
Source: Summary of clinical efficacy p. 16

All five trials had the same primary objective: change in HbA1c from baseline to week 26. Superiority of IDegLira to the comparator was tested in trials 3697 (liraglutide), 3951 (placebo), 3912 (IDeg), 3851 (GLP-1). Non-inferiority of IDegLira was examined in trials 3697 (IDeg) and 3952 (IGlar). Studies 3697 and 3952 had reduction in body weight and amount of hypoglycemia episodes during the first 26 weeks of treatment as their secondary objectives. A detailed description of study goals is presented in Table 2.

Table 2. Summary of study objectives (baseline to week 26)

Trial	Primary hypothesis	Confirmatory hypotheses
OAD users **3697**	Superiority of IDegLira to Lira for: Change in HbA1c Noninferiority of IDegLira to IDeg for: Change in HbA1c	Superiority of IDegLira to IDeg for: Change from baseline in body weight Number of treatment emergent "Novo Confirmed" hypoglycemic episodes
3951	Superiority of IDegLira to placebo for: Change in HbA1c	None specified
Basal insulin users **3912**	Superiority of IDegLira to IDeg for: Change in HbA1c	None specified
3952	Non-inferiority of IDegLira to IGlar for: Change in HbA1c	Superiority of IDegLira to IGlar for: Change in HbA1c Change in body weight Number of treatment emergent "Novo Confirmed' hypoglycemic episodes
GLP-1 users **3851**	Superiority of IDegLira to GLP-1 for: Change in HbA1c	None specified
Note: all hypothesis tests compare change from baseline to week 26		

Source: Summary of clinical efficacy p. 43

3 Analysis of HbA1c Change at Week 26

3.1 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.

3.2 Missing HbA1c values

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 in Table 3.

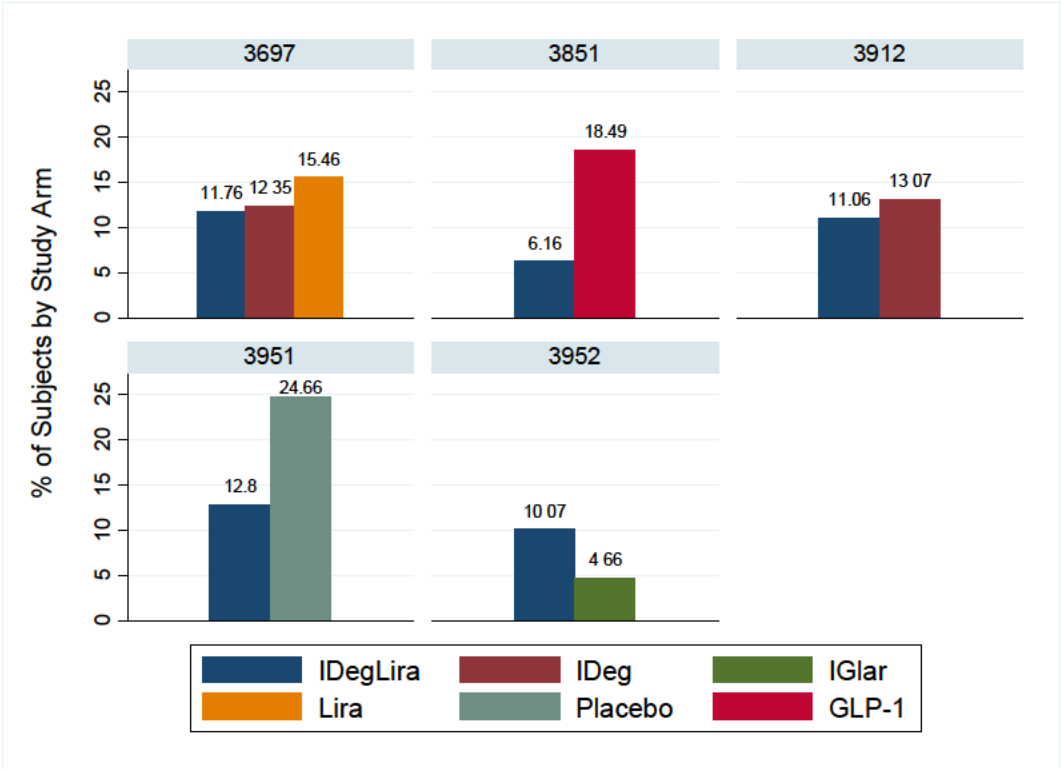
Table 3. Missing subjects at week 26

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. Figure 1 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%.

Figure 1. Percent of subjects who did not complete 26-week study



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. See Table 4. These types of exclusions, such as multiple retests and visit reallocations altered the shape of the Hba1c history curve for individual subjects.

Table 4. Number of observations excluded from analysis

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

***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

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.

3.3 Primary Efficacy Results

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.

The results of MMRM analyses for the primary endpoint are summarized in Table 5. 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.

Table 5. Results of MMRM analyses

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 Table 6. The outcomes of both sensitivity analyses were similar to the primary analyses.

Table 6. Multiple Imputations

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.

4 Secondary Efficacy Endpoints

4.1 Overview of Secondary Endpoints

Secondary hypotheses were pre-specified only for trials 3697 and 3952.

Type I error adjustments

In order to ensure that the overall type I error rate was not inflated, the confirmatory secondary endpoints of Trial 3697 (examining superiority of IDegLira versus IDeg on body weight and confirmed hypoglycemia) as well as the confirmatory secondary endpoints/hypotheses of Trial 3952 (examining superiority of IDegLira versus IGlar with respect to HbA1c, body weight and confirmed hypoglycemia) were only to be tested for superiority if the primary hypothesis was confirmed. In addition, the family-wise type I error rate for testing the confirmatory secondary endpoints/hypotheses was controlled at a 2.5% level (1-sided) in the strong sense using the Holm-Bonferroni method.

Overall, this 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.

Body weight

To examine the hypothesis of change in body weight, an MMRM analysis constructed in the similar way as for primary endpoint was provided, 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.

FDA also conducted an additional analysis to identify a percentage of subjects who achieved a 5% or larger reduction in body weight from baseline to week 26.

Hypoglycemia
As discussed in the Clinical Summary, Novo Nordisk 'confirmed hypoglycemia' was defined as severe hypoglycemia (subject not able to treat him-/herself) or episodes of hypoglycemia confirmed by a plasma glucose <3.1 mmol/L (56 mg/dL) irrespective of symptoms. Episodes of hypoglycemia were self-reported based on the subjects' SMPG recordings. This definition was uniquely created by the applicant and is not consistent with the ADA definitions of hypoglycemia.

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.

Insulin dose
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.

FDA also conducted time to dose stabilization; time to the stable dose was estimated for each study participant. The distribution of those values was compared between study arms for each trial.

4.2 Secondary Endpoints - Results

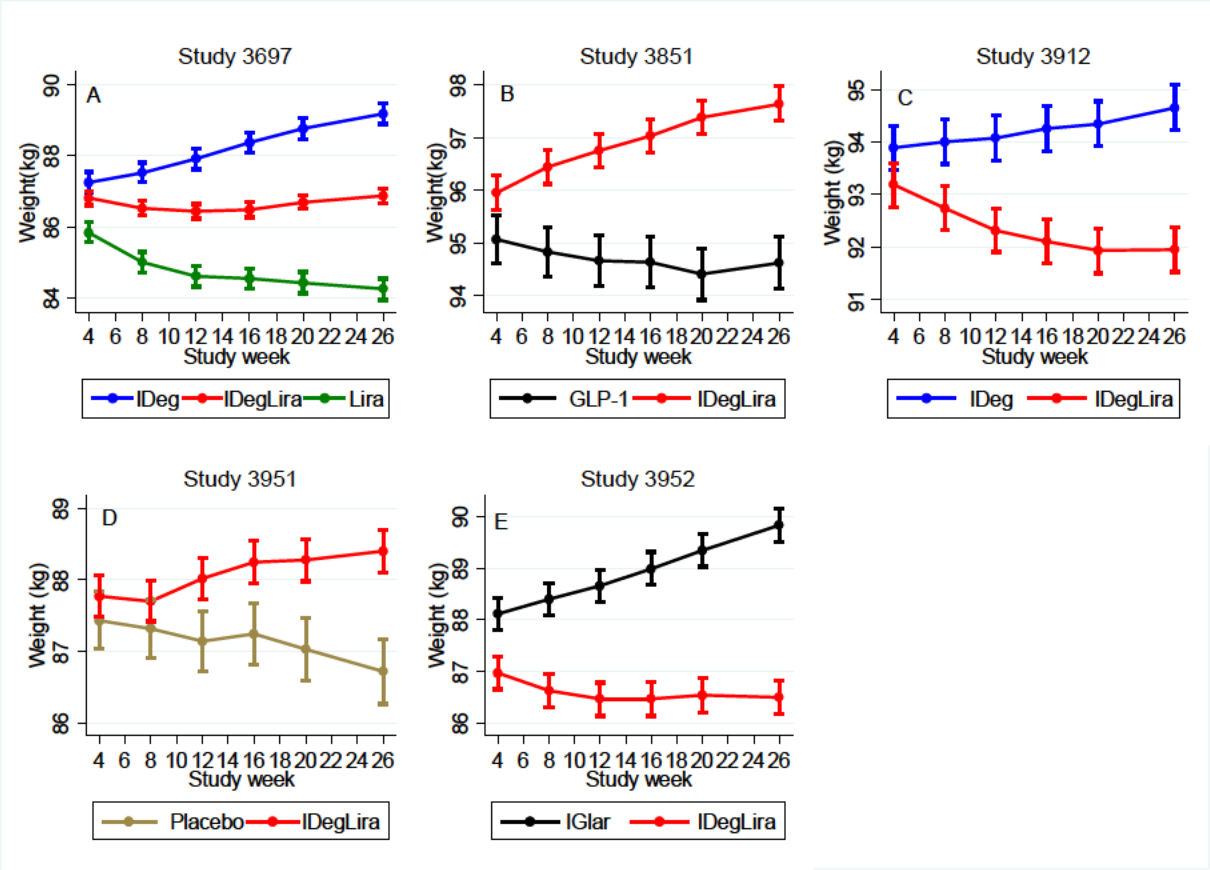
Body weight
The outcomes based on results of the MMRM analysis showed that body weight change in all studies after 26 weeks in the IDegLira arm vs. comparator arm was statistically different. However, the difference between treatment groups at week 26 was small, for example only 2.3 kg [95% CI (2, 2.7)] in trial 3697. The clinical relevance of this change in body weight after 26 weeks is unclear. The estimated differences between arms for all five phase 3 trials are presented in Table 7. Longitudinal changes in body weight for each treatment arm obtained using the MMRM model are presented in Figure 2. Note that the scale on the y-axis of each figure is rather narrow (3 to 6 kg).

Table 7. Change in body weight (kg) at week 26

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 reviewer

Figure 2. Longitudinal changes in body weight – phase 3 trials



Source created by statistical reviewer

Hypoglycemia

Overall, only 9 cases of severe hypoglycemia were recorded during the 26 week trial periods; six of those 9 cases were in IDegLira arm. Three more cases of severe hypoglycemia were observed during the extension period of study 3697 (2 in liraglutide arm and one in IDegLira arm). Because the number of severe hypoglycemia events was so small, it is difficult to make any conclusions about effect of IDegLira with respect to severe hypoglycemia.

Table 8. Hypoglycemia counts

STUDY	Arm	Number of *subjects* who experienced hypoglycemia* n(% of subject within arm)	Average number of hypoglycemia* events per person**	95%CI		Number of *episodes* of severe hypoglycemia
3697	IDeg	159(38.5%)	3.1	2.6	3.7	2
	IDegLira	263(31.6%)	2.7	2.4	3.0	2
	Lira	28(6.8%)	1.5	1.2	1.8	
3851	GLP-1	4(2.7%)	2.0	0.7	3.3	
	IDegLira	93(31.8%)	4.3	3.1	5.5	1
3912	IDeg	49(24.6%)	4.8	2.9	6.8	
	IDegLira	48(24.1%)	2.9	1.9	4.0	1
3951	Placebo	25(17.1%)	3.4	1.7	5.0	
	IDegLira	120(41.5%)	3.9	3.1	4.7	2
3952	IGlar	137(49.1%)	5.0	3.7	6.2	1
	IDegLira	79(28.4%)	3.7	2.5	4.8	

*Based on applicant's definition
**Among subjects who experienced hypoglycemia
Source created by statistical reviewer

Below are the results provided by the applicant.

Table 9. Summary of overall confirmed hypoglycemia by trial

Trial	IDegLira			Basal insulin			GLP-1 RA			Placebo		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Pivotal trials												
3697 (26)	263 (31.9)	699	180.2	159 (38.6)	496	256.7	28 (6.8)	41	22.0			
3697 (52)	327 (39.6)	1247	176.7	203 (49.3)	977	279.1	44 (10.7)	64	19.1			
3912	48 (24.1)	141	153.4	49 (24.6)	237	263.3						
Other phase 3 trials												
3851	93 (32.0)	397	281.7				4 (2.8)	8	12.1			
3951	120 (41.7)	467	351.7							25 (17.1)	84	135.2
3952	79 (28.4)	289	223.0	137 (49.1)	683	505.4						

E stands for number of events
R stands for the rate
Source: ISS p.319

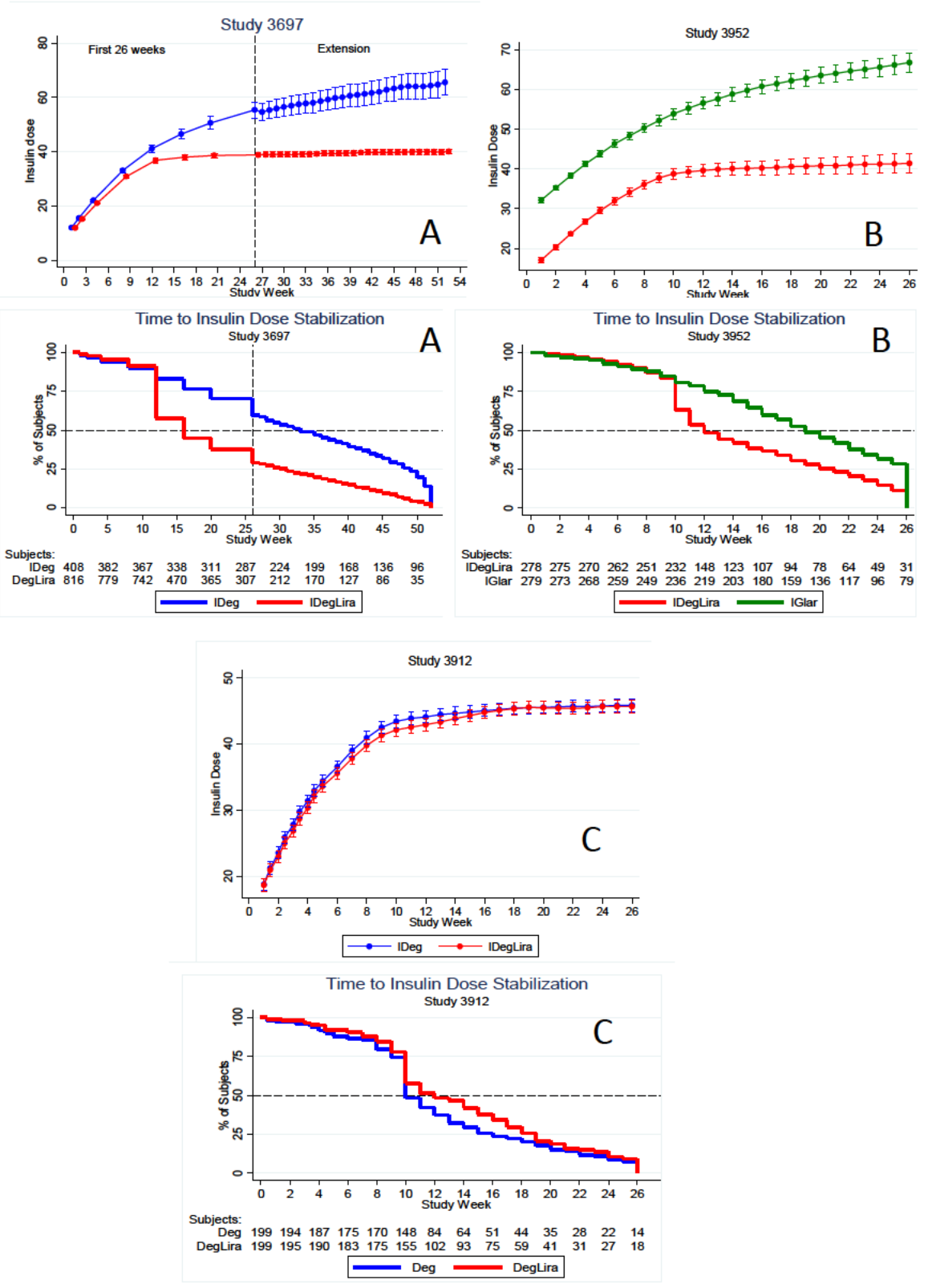
Insulin dose

The applicant used titration in IDegLira. Because this drug is a fixed dose combination, both drugs were titrated in the same ratio. In all phase 3 trials, the maximum dose of IDegLira was 50 dose steps (50 units of IDeg and 1.8 mg of liraglutide). In Trial 3697, there was no restriction on the maximum IDeg dose in the comparator arm. In Trial 3912, the maximum dose in the IDeg treatment arm was 50 units, equivalent to the maximum IDeg dose with IDegLira.

Only a half of subjects who participated in the IDeg arm of study 3697 reached their insulin target dose, i.e. finished their titration period. A similar pattern was observed in study 3952. In study 3952, only a half of subjects achieved a stable insulin dose prior to week 19, i.e. seven weeks before the conclusion of the study. Dose stabilization in study 3912 IDeg was achieved early (median 10 weeks and mean 12 weeks) because maximum dose was artificially limited by the study design. In all of these cases, the dosing schedule may have artificially limited the stabilization or reduction in HbA1c in the comparator arms during the trial period.

The changes in insulin dose are shown in Figure 3. A, B, and C. The added Kaplan-Mayer plots provide illustration to the length of dose escalation periods by arm.

Figure 3. Changes in insulin dose



Source created by reviewer

Table 10. Time to end of titration phase (weeks)

Study	Arm	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev	Coeff of Variation
3697	IDeg	26.0	1.0	26.0	19.5	18.7	20.2	7.8	39.8
	IDegLira	16.0	1.0	26.0	15.8	15.3	16.2	6.5	41.1
3952	IGlar	19.0	1.0	26.0	18.1	17.2	19.0	7.4	40.9
	IDegLira	12.0	1.0	26.0	14.7	13.9	15.5	6.8	46.2
3912	IDeg	10	0.4	26	12.6	11.7	13.5	6.4	51.2
	IDegLira	12	0.4	26	13.9	13	14.9	6.6	47.1

Source created by statistical reviewer

Statistical Appendix

Exploratory analysis of study 3697 that included extension period

Trial 3697 was the only study that had data beyond week 26. Of note, out of 1660 subjects who joined the study, 359 (21.6%) participated only in the first 26-week core part of the trial, i.e. discontinued before week 27.

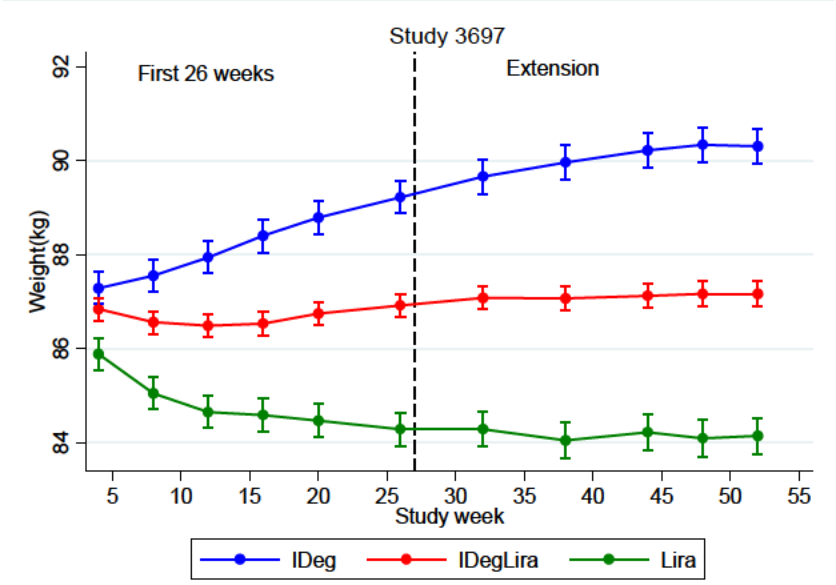
Body weight
Additionally, FDA examined body weight change from baseline to week 52. The results at week 52 are presented in Table . Figure 3. shows that after the period of initial 26 weeks, the estimates of body weight stabilize for IDegLira and liraglutide arms. The results achieved by subjects in IDeg arm show that the body weight was increasing over time.

Table 11. Study 3697 body weight after 52 weeks

Treatment arm	Comparator arm	Estimate	95%CI
IDegLira	IDeg	-3.1	(-3.6, -2.7)
IDegLira	Lira	3.0	(2.5, 3.5)
IDeg		90.3	(89.9, 90.7)
IDegLira		87.2	(86.9, 87.4)
Lira		84.1	(83.7, 84.5)

Source created by reviewer

Figure 3. Longitudinal changes in body weight Study 3697



Source created by reviewer

Insulin titration

The median titration time in IDegLira arm did not change, i.e. stayed identical to the first 26-week period of the study. The median titration time for IDeg arm increased to 33 weeks.

According to the documentation submitted by applicant, the data for insulin dose was collected weekly during the entire 52-week trial. The data that was provided to FDA contained bi-weekly data points that were not imputed by LOCF. The data points between those bi-weekly values were marked as values obtained by LOCF. Because FDA does not accept LOCF, all LOCF measurements of insulin dose were excluded from analysis.

The changes in insulin dose are presented in Figure 3. shown previously.

Table 12. Time to end of titration phase study 3697 with extension (weeks)

Study	Arm	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev	Coeff of Variation
3697 with extension	IDeg	33.0	1.0	52.0	32.4	30.8	34.0	16.0	49.5
	IDegLira	16.0	1.0	52.0	21.9	21.0	22.8	13.5	61.4

Source created by reviewer

CLINICAL PHARMACOLOGY SUMMARY

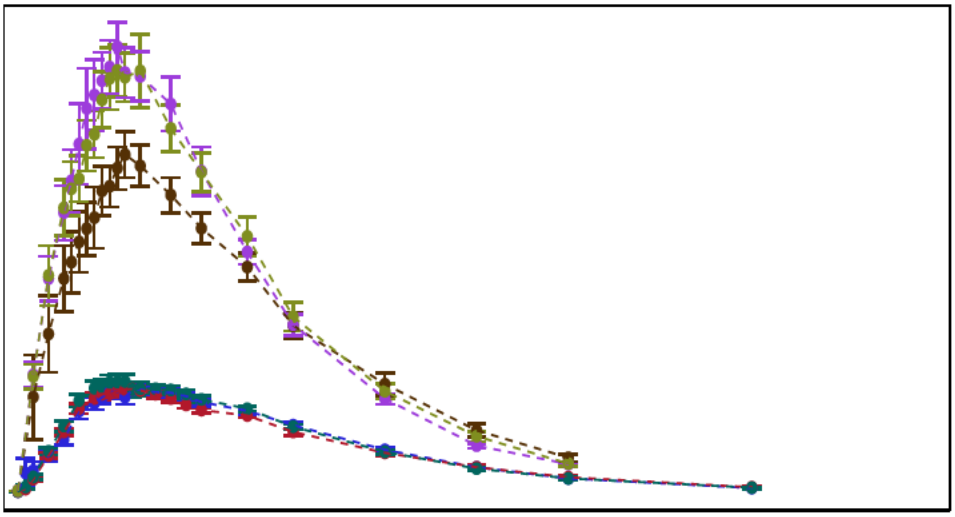
1 Insulin Degludec and Liraglutide Pharmacokinetics and Pharmacodynamics Following the Administration of the Fixed-Ratio Combination

1.1 Insulin Degludec and Liraglutide Pharmacokinetics

Data from the 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) showed the following with regard to PK (Figure 1).

- Insulin degludec exposure following administration of the FRC was not significantly different from that of insulin degludec alone (geometric mean ratios (GMR) for AUC and Cmax were 1.03 and 1.12, respectively).
- Liraglutide maximum concentration following administration of the FRC was 23% lower (90% CI; 0.68, 0.87) without any significant change in overall exposure (GMR for AUC=0.89 with 90% CI; 0.82, 0.96) when compared to those of liraglutide alone.

Figure 1. 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

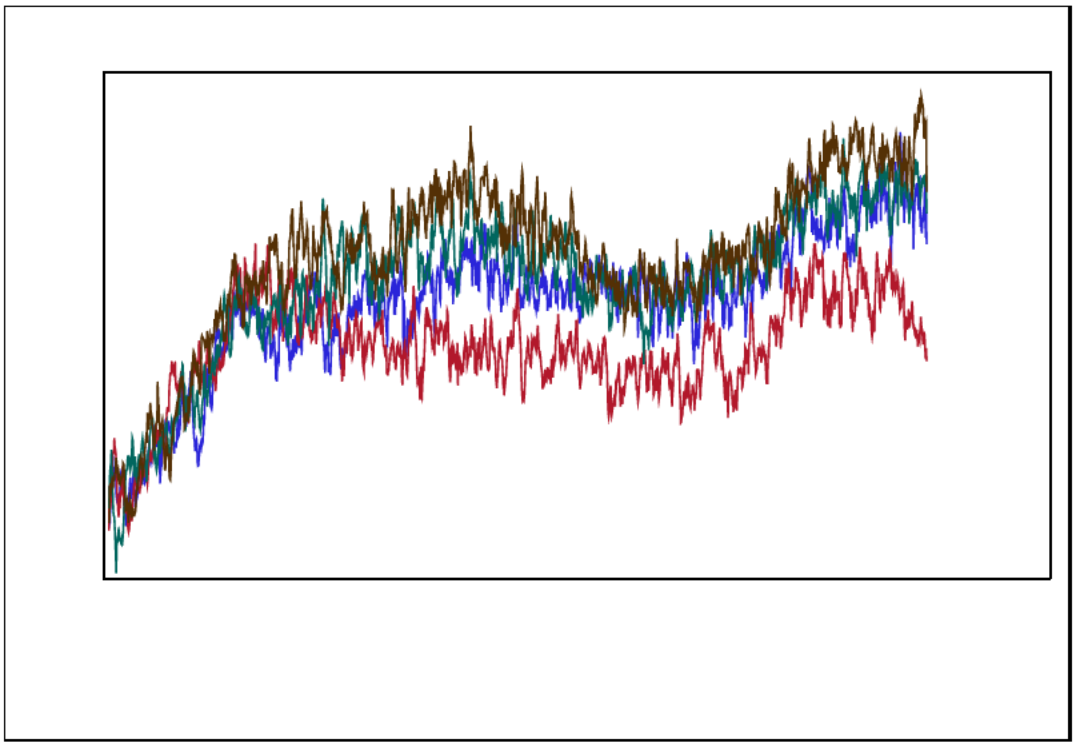
Further, population PK analyses using plasma concentration data from the Phase 3 study showed that exposure of both insulin degludec and liraglutide was proportional to clinically relevant FRC doses, and there was no significant covariate for insulin degludec or liraglutide exposure other than already known covariates (e.g., body weight) affecting individual drugs.

1.2 Insulin Degludec and Liraglutide Pharmacodynamics

While the interpretation of the glucose infusion rate (GIR) from the euglycemic clamp study for exogenous insulin is straightforward, the interpretation of GIR data is challenging for the liraglutide administered alone or insulin degludec plus liraglutide as part of the FRC, specifically in the subjects capable of secreting endogenous insulin

(healthy volunteers/type 2 diabetes patients) (see Figure 2). The primary challenge is posed by the capability of liraglutide to facilitate endogenous insulin secretion in a glucose dependent manner, which could be triggered by the infused glucose to maintain the target blood glucose within acceptable range under a clamp experimental setting.

Figure 2 - Mean Glucose Infusion Rate by Treatment-Trial 3632

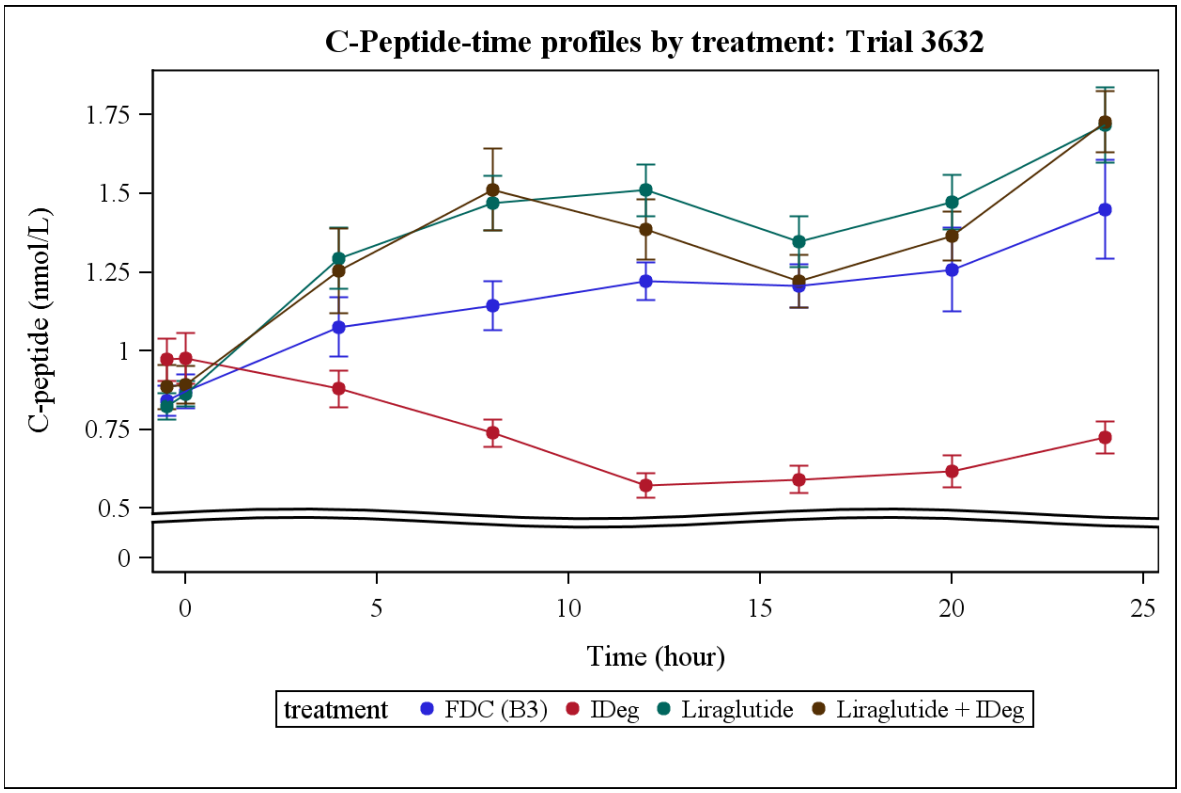


Nevertheless, C-peptide/endogenous insulin concentration data provide useful insight into any interference from exogenous insulin with the liraglutide pharmacodynamic effect, or, in other words, whether insulin degludec and liraglutide exert their pharmacodynamic effects, in a somewhat independent manner. Insulin secretion was measured using C-peptide concentrations following a single dose of FRC or each drug given alone in healthy subjects under euglycemic clamp procedure. Pharmacodynamic data indicate that there is mutual interplay between insulin degludec and liraglutide pharmacodynamic effects following administration of FRC as follows:

- C-peptide levels decreased from baseline following insulin degludec administration. This decline in C-peptide following insulin administration is a usual observation in the euglycemic clamp studies. Generally the objective of clamp experiments is to measure the exogenous insulin effect by keeping the euglycemic target lower than normoglycemia to avoid triggering endogenous insulin secretion.
- In contrast, for liraglutide alone and FRC treatments, C-peptide increased from baseline (Figure 3). Data indicate that there is net positive stimulation of endogenous insulin release by liraglutide in the presence of inhibition action by insulin degludec after FRC administration. The magnitude of C-peptide increase with the FRC was lower than that for liraglutide alone or insulin plus liraglutide administration. The

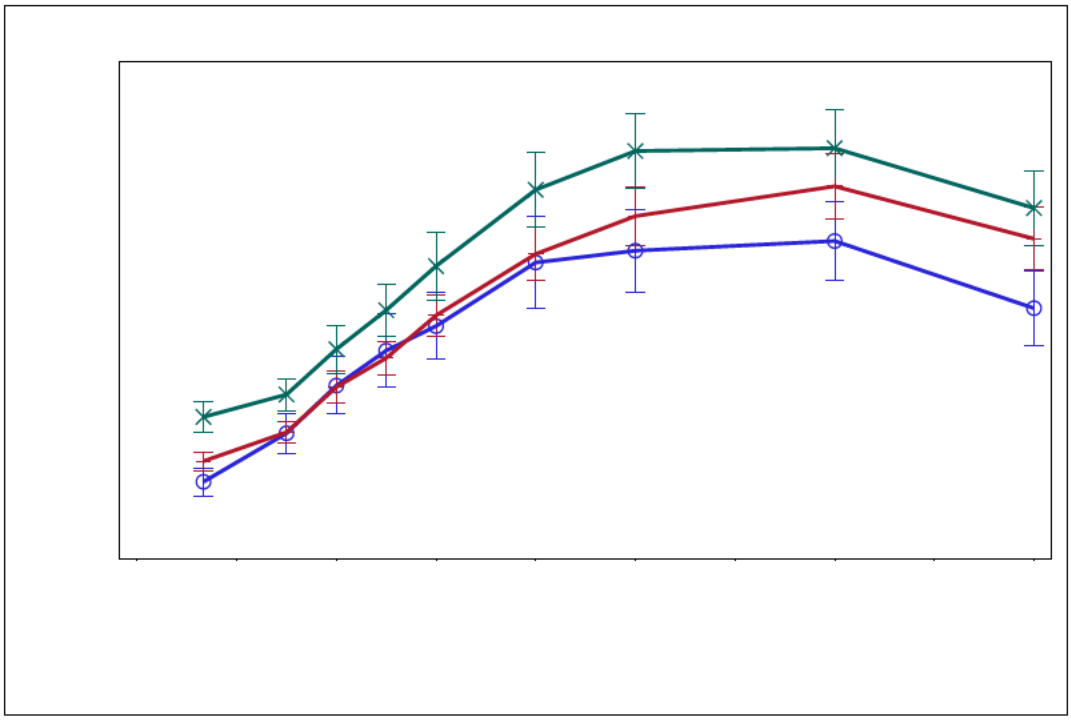
GIR profiles are consistent with the observed the insulin secretion differences noted among treatments (Figure 2). The higher GIR profile after FRC administration compared to that of insulin degludec alone may result from the endogenous insulin secretion by liraglutide.

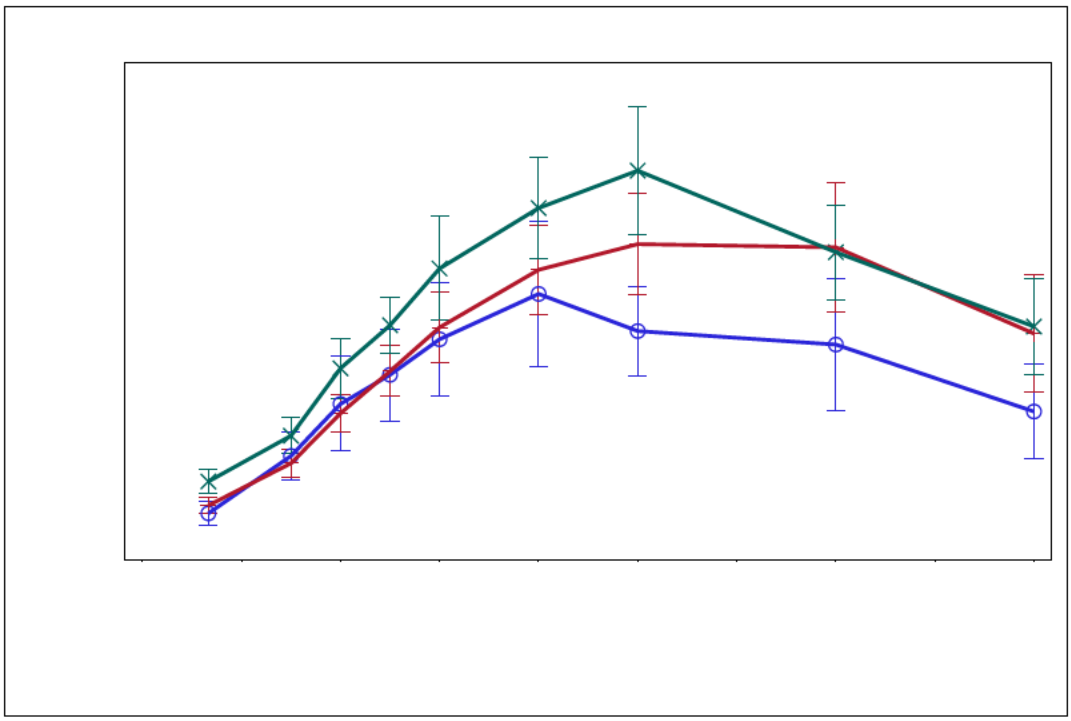
Figure 3. C-peptide versus time profiles following a single dose of FRC (FDC(B3)), liraglutide alone, insulin degludec alone, and insulin degludec plus liraglutide (separate injections) in healthy subjects



A modest increase in C-peptide and insulin levels was reported in response to insulin degludec and liraglutide administration as FRC as compared to the administration of insulin degludec alone during the meal challenge (Figure 4), and data are consistent with PK/PD study results. However, clinical relevance of C-peptide and insulin data, and magnitude of post-prandial glucose (PPG) change towards HbA1c reduction observed with different treatments are not fully understood from a quantitative perspective.

Figure 4. C-peptide (upper) and insulin (lower) – time profiles during meal challenge in a sub-set subject (Trial 3697)

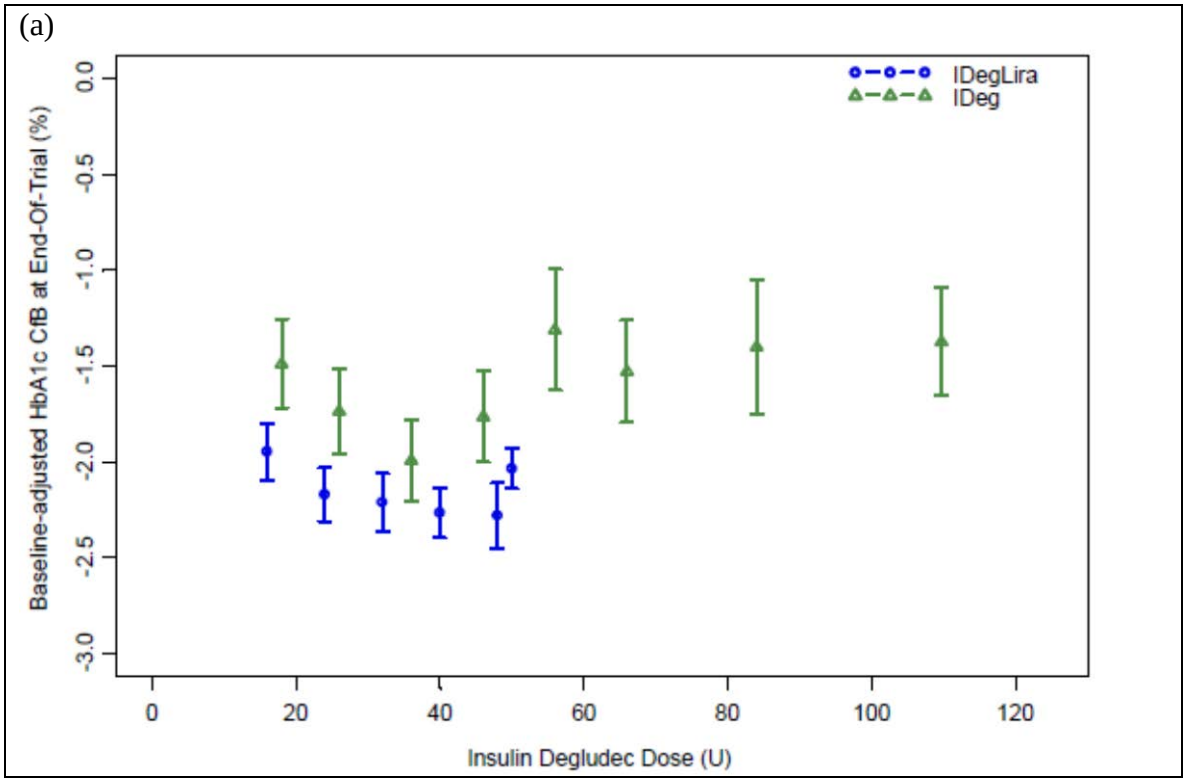




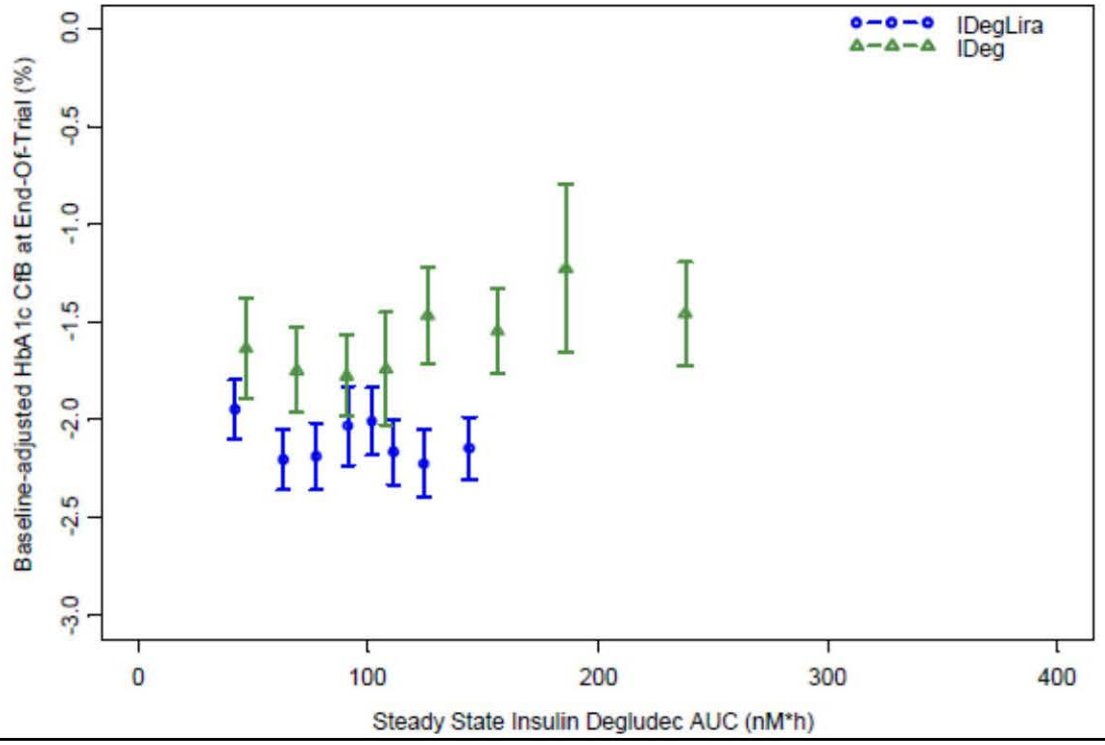
2 Dose/Exposure-Response information

For the same dose or exposure of insulin degludec or liraglutide for the FRC treatment, there was additional HbA1c reduction following FRC compared to that of insulin degludec or liraglutide administered alone (Figure 5). These dose-response data do not permit the assessment of dose-response relationship for the entire range of insulin degludec or liraglutide doses a patient may have been administered during the titration of the FRC. The interpretation of data is limited to the observation that greater HbA1c reduction was achieved at lower doses with the combination treatment in comparison to that of insulin degludec or liraglutide administered alone.

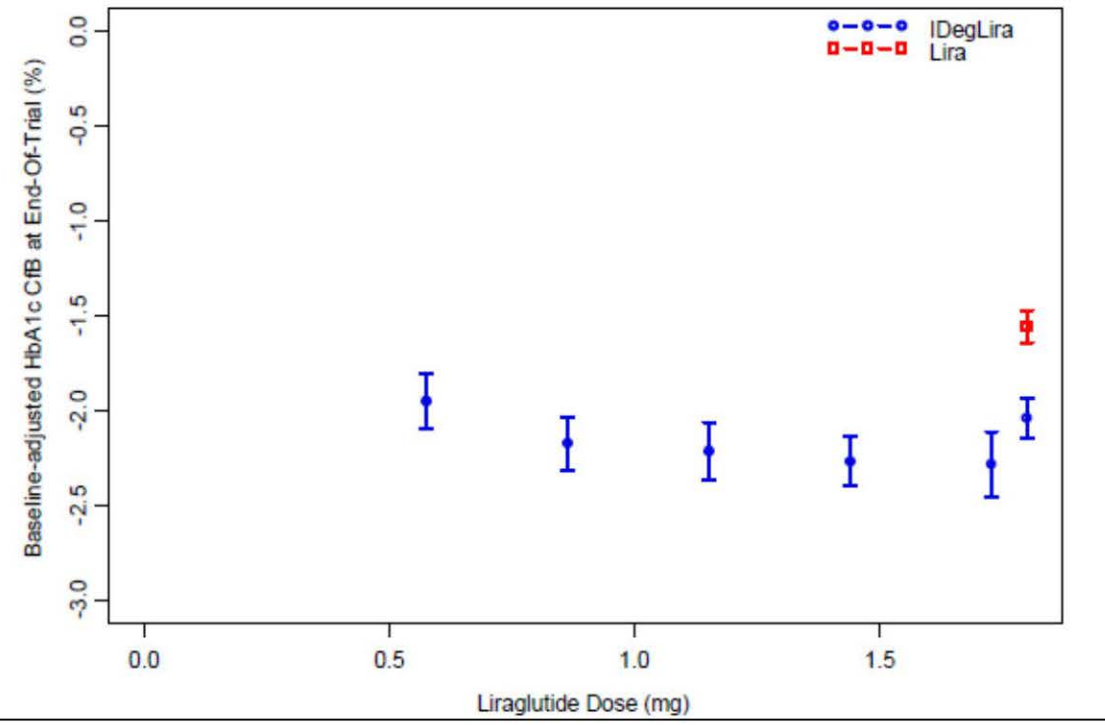
Figure 5. Effects of FDC (blue), IDeg (green) or liraglutide (red) on HbA1c change from baseline to end-of-trial versus percentiles of (a) insulin degludec or (b) liraglutide doses, and (c) insulin degludec or (d) liraglutide exposure at steady-state

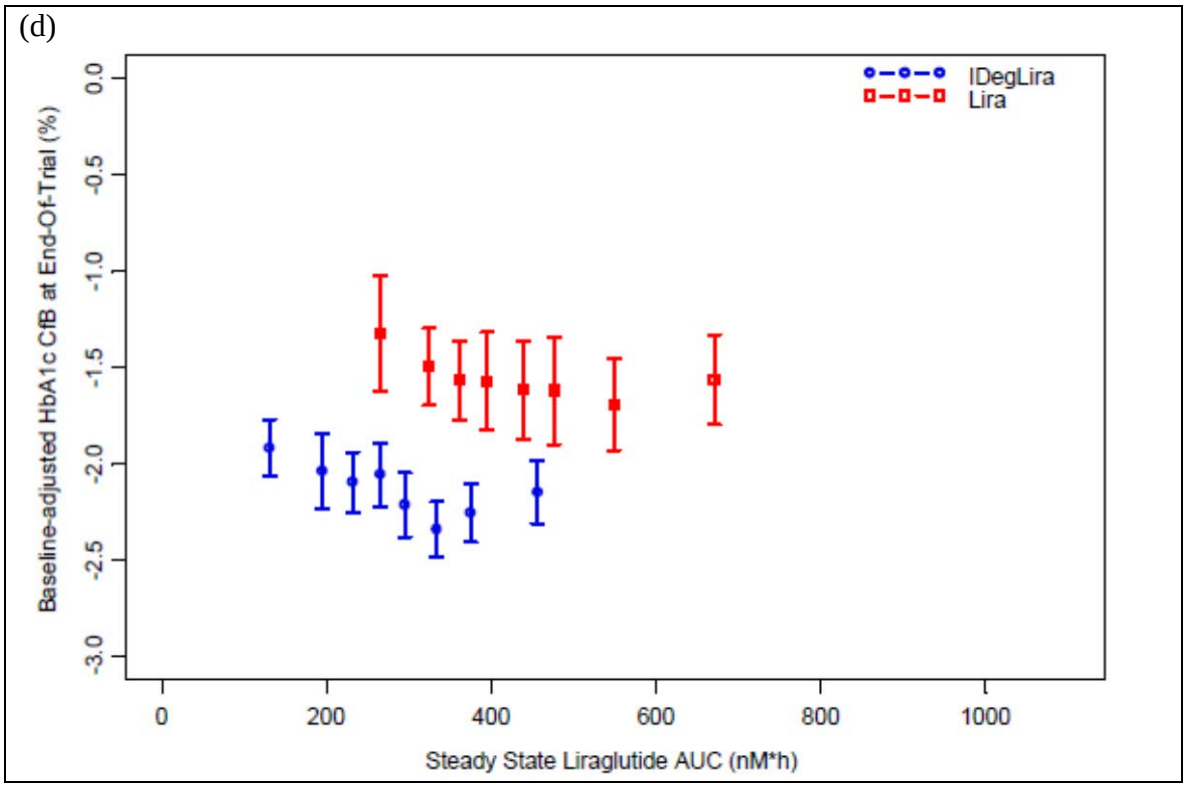


(b)


IDegLira
IDeg
Baseline-adjusted HbA1c CfB at End-Of-Trial (%)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
0
100
200
300
400
Steady State Insulin Degludec AUC (nM*h)

(c)


IDegLira
Lira
Baseline-adjusted HbA1c CfB at End-Of-Trial (%)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
0.0
0.5
1.0
1.5
Liraglutide Dose (mg)



(SOURCE: Figure 1 and 2, Modeling Report; study-report-nn9068-3679-er)

The dose response of liraglutide alone was evaluated from the dedicated trials from the original NDA (NDA 022341) for liraglutide (i.e., NN2211-1310 and NN2211-1571). The dose-response analysis using a conventional non-linear Emax model indicated ED50 (liraglutide dose for half-maximal effect) and Emax (maximum liraglutide treatment effect as HbA1c change from baseline of 8%) as 0.60 mg (95% CI; 0.21, 1.71) and -2.11% (95% CI; -2.92, -1.30), respectively (Figure 6), see the predicted HbA1c reduction based on the model parameters in Table 1.

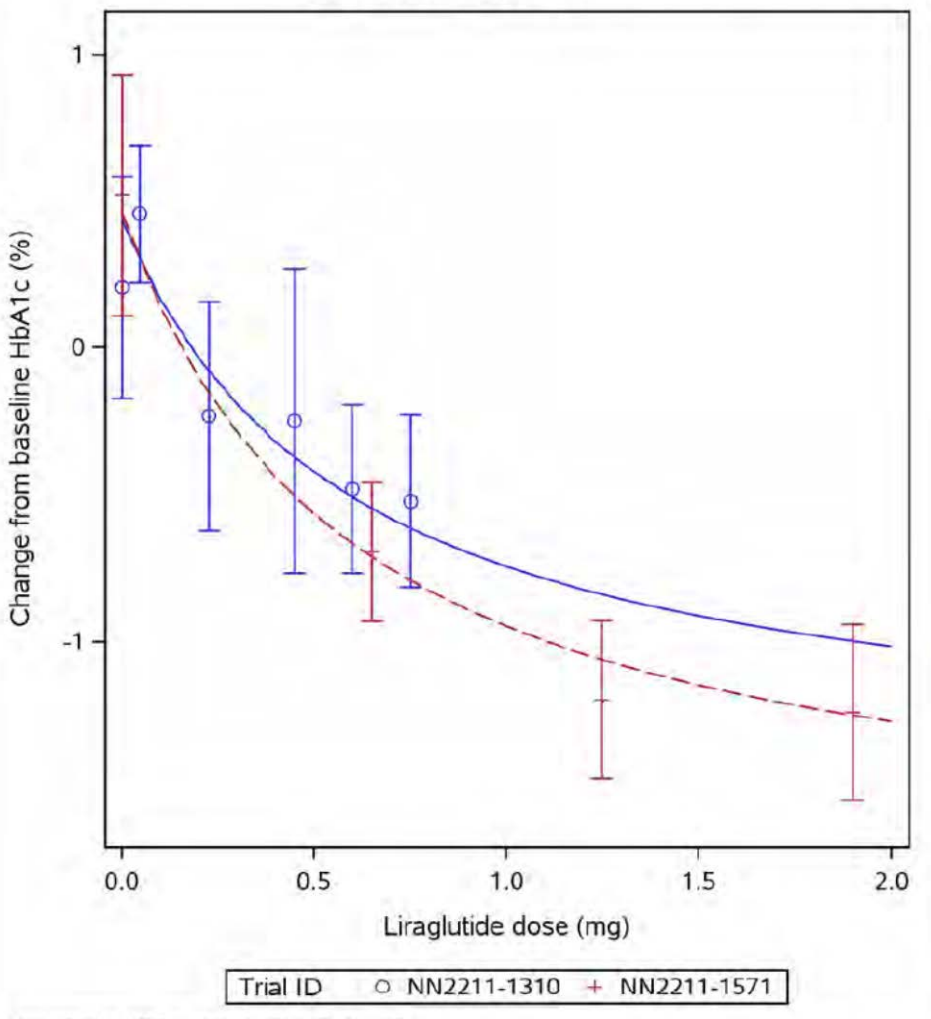
Table 1. Predicted HbA1c reduction for Phase 2 trials of Trials 1310 and 1571

Trial	Liraglutide (mg)	Predicted change HbA1c (%)
NN2211-1310*	0.36	-0.28
	0.72	-0.60
	1.08	-0.78
	1.44	-0.90
	1.80	-0.98
NN2211-1571*	0.36	-0.39
	0.72	-0.77
	1.08	-0.99
	1.44	-1.13
	1.80	-1.23

* Baselines of HbA1c were 7.52 and 8.29% for Trial 1310 and 1571, respectively.

However, 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. Dose-HbA1c plots in Figure 5a and Figure 5c indicate a shift in the dose-response relationship for HbA1c reduction for the two components when administered as FRC in comparison to the insulin degludec and liraglutide administered alone.

Figure 6. Observed (symbols) and estimated (line) change from baseline HbA_{1c} (%) for Trials 1310 and 1571, ITT analysis sets from the original liraglutide NDA: Dose-response model with additive and multiplicative baseline HbA_{1c} covariate effects



(Source: Response to FDA Information Request dated 3/18/2016)

Overall, based on the design of trial conducted to support insulin degludec and liraglutide FRC product, pharmacodynamic and dose/exposure-efficacy data indicate there is contribution of each component to the pharmacodynamic effect following FRC administration compared to that of single agent alone. The PK/PD data showed that liraglutide exerted pharmacodynamic effect with regards to enhancement of glucose based insulin secretion in the presence or absence of insulin degludec. However, the Clinical Pharmacology data and modeling approaches have limitations in extrapolation of the efficacy of IDegLira to clinical use.

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA) SUMMARY

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.

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. 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.

The applicant proposes to simplify the expression of dose for this product in labeling by focusing dosing on the insulin component alone. 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. The Applicant also proposes to label the product's dose without any measurement designation to accompany the numeric portion that would describe the amount delivered (i.e., the label would '10' and not 10 units or 10 units/0.36 mg). However, this raises some concerns because doses are typically communicated with some measurement designation in the labeling and in practice.

It is unclear what terminology would be best facilitate the appropriate dosing this product. Since the product dosing is centered upon the insulin component, practitioners may be inclined to express the dose using the unit terminology. However, applying a designation of the term "units" in labeling could potentially mislead practitioners since it only references the insulin component (insulin degludec) and does not impart the presence of the GLP-1 component. On the other hand, expressing both measurement designations (units for insulin and mg for liraglutide) may also create confusion for practitioners and patients since this product is proposed to be dosed relying on the insulin component alone.

We considered whether our experience with other multi-ingredient products could inform this issue. However, in the examples we identified where the products contained two or more active ingredients with different unit of measure, we note that the dosing of the product could be conveyed using the presentation [11] or the dosage form [12] to be administered. In these instances, the dose of each single ingredient would generally not be specified on the prescription order since there are other more simple terms available to accurately and efficiently describe the dose.

To address these concerns related to the expression of dose for this product, the Applicant has been asked to conduct a labeling comprehension study with potential prescribing physicians. This study has recently been initiated. The labeling comprehension study will also assess whether prescribers will be aware that there are two components to be considered when initiating therapy, making dose conversions, and changing therapy. Lack of awareness of these issues may lead to drug duplications and/or inappropriate dosing if the conversion from insulin and GLP-1 to IDegLira is assumed to be 1:1, even when the active ingredients are clearly labeled. These additional data are not yet available for review.

In the course of reviewing this proposed product, we 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. The Agency has requested that the Applicant assess in the labeling comprehension study the prescribers' comprehension regarding the dose limitation for this product (i.e., when the product is not appropriate for patients that need higher doses of insulin degludec).

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 elderly diabetes patients). The study was designed to simulate use tasks and provide data to support that intended users can dispense,

[11] 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.

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

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.

We plan to review the ongoing prescriber labeling comprehension study results when they are available.

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY DRUG UTILIZATION SUMMARY

To satisfy the combination drug rule, a product should be safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug[5]. In order to determine the proportion of patients with type 2 diabetes who concurrently use a GLP-1 agonist with a basal insulin, using proprietary drug utilization databases available to the Agency, (see DEPI Appendix for full database descriptions) FDA investigated the utilization patterns for GLP-1 agonists in combination with basal insulin from April 2010 through March 2015, annually. This review examined proprietary drug utilization databases available to the Agency, specifically, national cross-sectional outpatient retail data to assess the extent of use of GLP-1 agonists and longitudinal healthcare plans claims data to assess the proportion of concurrent use of a GLP-1 agonist and basal insulin.

The nationally estimated total number of unique patients who received dispensed prescriptions through the U.S. outpatient retail pharmacies for all GLP-1 agonists increased from approximately 535,000 patients in the 12-month period ending in March 2011 to 882,000 patients in the 12-month period ending in March 2015. The patients who were dispensed GLP-1 agonists accounted for 5% of the total number of patients who received dispensed prescriptions for any OAD (oral anti-diabetic) and/or GLP-1 agonists in the 12-month period ending in March 2015 (data not shown).[13]

For the concurrency analysis, Table 2 below provides the proportion of patients on concurrent therapy with GLP-1 agonist and basal insulin from a sample of the commercially insured population. The percentage of patients who had prescription claims for a GLP-1 agonist out of total patients captured with 2+ claims for OAD and/or basal insulin was small and increased from approximately 7% in year one (April 2010 through March 2011) to 9.5% in year five (April 2014 through March 2015). Of these patients on GLP-1 agonists, the proportion of patients who had concurrent therapy with a GLP-1 agonist and a basal insulin increased from 17% of GLP-agonist patients in the 12-month period ending in March 2011 to 27% of GLP-agonist patients in the 12-month period ending in March 2015.[14]

The concurrency analysis was conducted using a sample of U.S. commercially insured population captured in the IMS Health Real-World Data (RWD) Adjudicated Claims – US database. When interpreting the IMS RWD Adjudicated Claims – US data, the numbers should not be trended because each reporting time period is distinct. Between each distinct 12 month time periods within the study, the pool of patients and healthcare

[13] Source: IMS, Total Patient Tracker. April 2010 through March 2015. Data extracted March 2016.
[14] IMS LifeLink PharMetrics Plus. Reporting Time: April 2010 Through March 2015 Extracted March 2015. File: DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

plans contributing to the data sample may change over time. Since the data was not projected, it is imperative to focus on the proportion of patients throughout the study period.

Table 1– Patients on Concurrent Therapy with GLP-1 Agonist and Basal Insulin

Patients with concurrent prescriptions for a GLP-1 agonist and basal insulin from a sample of the commercially insured * U.S. population, stratified by patient age, by reporting years, April 2010 through March 2015

	Year 1		Year 2		Year 3		Year 4		Year 5	
	April 2010 - March 2011		April 2011 - March 2012		April 2012 - March 2013		April 2013 - March 2014		April 2014 - March 2015	
	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share
Total Number of Patients on OAD/GLP-1 Agonist	**644,695**	**100.0%**	**664,629**	**100.0%**	**610,265**	**100.0%**	**578,363**	**100.0%**	**486,477**	**100.0%**
Patients On A GLP-1 Agonist	**45,647**	**7.1%**	**51,570**	**7.8%**	**55,343**	**9.1%**	**53,696**	**9.3%**	**46,216**	**9.5%**
1-17 years	78	0 2%	68	0 1%	47	0 1%	25	0 0%	25	0 1%
18-44 years	7,286	16 0%	7,986	15 5%	8,266	14 9%	7,796	14 5%	6,945	15 0%
45-64 years	33,857	74 2%	38,333	74 3%	41,821	75 6%	41,045	76 4%	35,152	76 1%
65+ years	4,426	9 7%	5,183	10 1%	5,209	9 4%	4,830	9 0%	4,094	8 9%
Patients On Both GLP-1 Agonist & Basal Insulin	**7,837**	**17.2%**	**9,799**	**19.0%**	**13,162**	**23.8%**	**13,807**	**25.7%**	**12,360**	**26.7%**
1-17 years	4	0 1%	9	0 1%	6	0 0%	2	0 0%	6	0 0%
18-44 years	826	10 5%	1,050	10 7%	1,440	10 9%	1,515	11 0%	1,432	11 6%
45-64 years	6,054	77 2%	7,502	76 6%	10,264	78 0%	10,828	78 4%	9,606	77 7%
65+ years	953	12 2%	1,238	12 6%	1,452	11 0%	1,462	10 6%	1,316	10 6%

** Commercially insured excludes Medicare and Medicaid*

Reporting Year: rolling 12 month period (i.e. April 2010 through March 2011 = reporting year 1)

Due to the study being unprojected, the data should not be trended between years. Inference may be made on precentage changes between years. Age groups may not be representative of the population.

Source: IMS LifeLink PharMetrics Plus. Reporting Time: April 2010 Through March 2015 Extracted March 2015. File: DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

DEPI Appendix: Drug Utilization Database Descriptions

IMS, Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS Health Real-World Data (RWD) Adjudicated Claims – US

The IMS Health Real-World Data Adjudicated Claims - US Database is a health plan claims database representing approximately 101 managed care plans and covering approximately **65.8** million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected; however, it represents approximately 9% of the United States commercially insured population based on year 2007 Unites States Census.