CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208583Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208583
Drug Name:	Trade name (IDegLira)
Indication(s):	T2DM
Applicant:	Novo Nordisk
Date(s):	Stamp Date: 9/14/2015
	Review due date: 06/14/2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Anna Kettermann, Dipl. Math, MA
Concurring Reviewers:	Mark Rothmann, Ph.D., Statistical Team Leader
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Tania Condarco, M.D., Medical Officer
	Lisa Yanoff, M.D., Medical Team Leader
Project Manager:	Marisa Petruccelli

Keywords:
longitudinal data analysis, missing data, mixed models, imputation/data imputation

Table of Contents

LIST OF TABLES

LIST OF FIGURES

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 submission consisted of five phase 3 trials. 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) were examining HbA1c reduction properties of IDegLira in comparison to other drugs (placebo, IGlar, and 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 trial start, the applicant submitted primary analysis using the LOCF approach. Upon our request (prior to NDA submission), the applicant also submitted the HbA1c analyses utilizing the Mixed-Effect Model Repeated Measure (MMRM) approach. We no longer recommend LOCF as the approach for dealing with missing data. We recommend study conduct that collects all efficacy measurements regardless of treatment adherence and analyses that use all efficacy measurements regardless of treatment adherence.

In all of the five trials, subjects in the IDegLira arm demonstrated 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:

- **Limitations of study design:**
  The magnitude of the difference in HbA1c levels in subjects given IDegLira and those on insulin, and perhaps even the finding of superiority, were affected by the study design. Insulin was titrated too slowly, i.e. a large fraction of subjects did not reach a stable dose of insulin prior to study conclusion. Since a large number of subjects did not reach a stable dose of insulin, i.e. , did not have an FPG in the normal range, insulin did not reach

its efficacy for those subjects. Because of this issue, the difference in HbA1c levels between subjects given IDegLira and those on insulin at 26 weeks was larger than it would have been if subjects on insulin had reached an FPG-based stable insulin dose. Therefore, it is not clear whether a conclusion of superiority would have been reached if subjects on insulin had reached an FPG-based stable insulin dose.

Additionally, trial 3912 had a pre-specified limit (cap) on maximum insulin dose. Therefore, many of the subjects in the comparator treatment did not reach a stable state during the 26-week trial but might have if the trial had been longer or if dose had been changed more frequently. Clinical practice does not put a cap on insulin dose.

- **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 week 26 assessment.

- **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.

- **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 definition results in a sample size too small (n=9) to draw meaningful conclusions.

Conclusions:

The primary endpoint was met within the five trials as conducted. The missing data do not affect the conclusion of superiority of IDegLira on 26-week HbA1c. It is my recommendation to approve IDegLira for HbA1c reduction.

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 24, 2016 to discuss IDegLira program. The committee voted unanimously (16 to 0) for approval of IDegLira for HbA1c reduction.

2 INTRODUCTION

2.1 Overview

A brief description of the drug indication and history of the submission is presented below.

2.1.1 Indication

IDegLira is a combination of the basal insulin insulin degludec (IDeg, NDA 203314), and the GLP-1 analogue liraglutide (approved as NDA 022341). IDegLira is intended for improvement of glycemic control in adults with T2DM via once-daily subcutaneous injection.

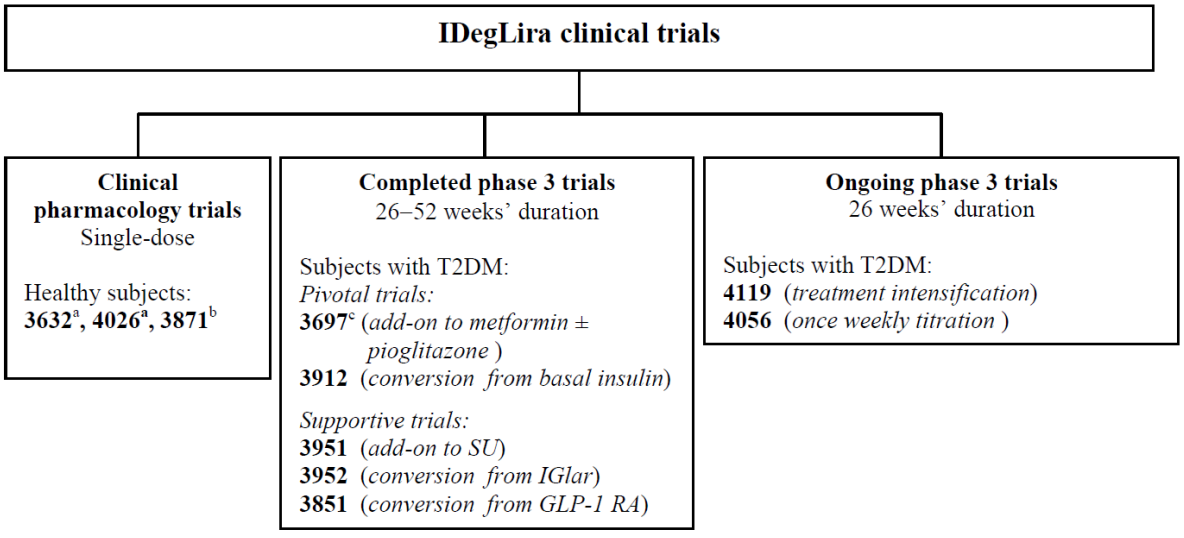
2.1.2 History of Drug Development

The development program for IDegLira was first discussed at the End of Phase 2 (EOP2) meeting on November 9, 2010, and IND 109121 was subsequently filed on January 7, 2011. In the Written Responses dated June 9, 2011, FDA agreed on the strategy for two proposed pivotal trials to adequately compare the combination product against each of the components and that the results could be used to support the filing of an NDA for IDegLira. A pre-NDA meeting was held with the FDA on June 16, 2015.

2.1.3 Specific Studies reviewed

A schematic description of IDegLira program is presented in Figure 1. This review focuses only on completed phase 3 trials.

Figure 1. A schematic description of IDegLira program



Source: Clinical overview p.12

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 glucagon-like peptide-1 receptor agonist (GLP-RA) users). In addition, study 3697 had a 26-week extension. The data from the extension part of this trial were not evaluated for efficacy.

Table 1. Summary of study designs

Trial	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

2.2 Data Sources

This submission is in electronic common technical document (eCTD) format. The submission is archived at the following link: \\CDSESUB1\evsprod\NDA208583\208583.enx

Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (SUBJID). The datasets were in poor organization. The applicant conducted their analysis using pooled datasets for all types of calculations. The datasets (variables in the database) provided for each separate study did not match the pooled dataset.

Define.pdf file did not provide clear explanations to the meaning of variables utilized in the analysis.

My analysis on the primary and secondary efficacy endpoints gives approximately the same results as those reported in the clinical study report (CSR).
I derived from the submitted datasets all of the results presented in this review. I created all tables and figures in this review unless otherwise noted.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

During my review I identified multiple issues with data quality. Specifically, the applicant excluded observations without providing any clarifications regarding the causes of those exclusions. The timeline (visit date) of observations was incongruent with visit numbers, i.e. some observations had visit number that were out of order compared to the study date. The applicant was contacted with requests to provide clarifications regarding those exclusions and discrepancies. The applicant provided information about causes for exclusions (Table 7). Upon our request, the applicant also updated efficacy datasets and define files.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

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 RA). 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

Trial	Primary hypothesis	Confirmatory hypotheses
OAD users 3697	Change in HbA1c baseline to week 26 *Superiority:* IDegLira to liraglutide *Noninferiority:* IDegLira to IDeg	Superiority of IDegLira to IDeg for: Change from baseline in body weight after 26 weeks of treatment Number of treatment emergent confirmed hypoglycemic episodes during 26 weeks of treatment
3951	Change in HbA1c baseline to week 26 *Superiority:* IDegLira to placebo	
Basal insulin users 3912	Change in HbA1c baseline to week 26 *Superiority* IDegLira to IDeg	
3952	Change in HbA1c baseline to week 26 *Non-inferiority* IDegLira to IGlar	Superiority of IDegLira to IGlar for: Change in HbA1c from baseline to week 26 Change from baseline in body weight after 26 weeks of treatment Number of treatment emergent confirmed hypoglycemic episodes during 26 weeks of treatment
GLP-1 RA users 3851	Change in HbA1c baseline to week 26 *Superiority:* IDegLira to GLP-1 RA therapy	

Source: Summary of clinical efficacy p. 43

3.2.2 Statistical Methodologies

Applicant's analysis: Continuous endpoints, for example HbA1c, were analyzed using an analysis of covariance (ANCOVA) model including treatment, pre-trial anti-diabetic treatment (for some trials), all stratification factors (if applicable), and country/region as fixed effects and the baseline value of the parameter as a covariate. For insulin dose analyses, baseline HbA1c was included as a covariate; in Trials 3697 and 3697-ext (52 weeks), baseline insulin dose was not

included as a covariate as the subjects were insulin-naïve prior to initiating treatment with IDegLira or IDeg.

In the pre-specified primary approach to handling missing data, missing values (including intermittently missing values) were imputed using the last observation carried forward (LOCF) method; therefore, this is the main approach used for data presentation in the applicant's document. However, we no longer recommend LOCF as the approach for dealing with missing data. We recommend study conduct that collects all efficacy measurements regardless of treatment adherence and analyses that use all efficacy measurements regardless of treatment adherence. Upon our request (prior to NDA submission), the applicant also submitted the HbA1c analyses utilizing the Mixed-Effect Model Repeated Measure (MMRM) approach. For this review, the MMRM analyses can be considered as the main analysis for evaluating effectiveness.

Repeated measures

This analysis included all subjects with at least one post-baseline observation. In this way, the repeated measures analysis was expected to estimate what would have been the result at the end of the trial had all subjects remained in the trial and on drug. The model relied on the assumption that data are missing at random (i.e., that the HbA1c response trajectories for subjects withdrawing from the trial prior to completing 26 weeks are comparable to those for subjects completing 26 weeks of treatment).

All non-imputed measurements at planned post-baseline visits were analyzed assuming an unstructured covariance matrix across visits, with testing performed at week 26. The model included treatment, pre-trial anti-diabetic treatment (for some trials), all stratification factors (if applicable), visit, country/region as fixed factors and baseline parameter value as a covariate. The model also included interaction terms between visit and all other factors and the covariate. Subject was included as a random factor when fitting the model.

Multiple imputation
Jump to reference
A pattern mixture model was used mimicking an ITT scenario (i.e., estimating the effectiveness of IDegLira) where subjects who withdrew from the IDegLira group were assumed to be switched to the comparator treatment after withdrawal, while subjects treated with the comparator were assumed to remain on their assigned treatment throughout the trial. This approach does not rely on the assumption that data are missing at random, includes all randomized subjects and imputes missing data in a way that is less favorable for IDegLira. For the evaluation of non-inferiority, subjects who withdrew from the IDegLira group were assumed to be switched to a treatment inferior to the comparator used in the trial. This was implemented by adding a penalty corresponding to the non-inferiority limit to the subjects' parameter value at the last visit.

Copy reference
A pattern mixture model was used which mimicked an ITT scenario (i.e., estimated the effectiveness of IDegLira) where subjects who withdrew from the IDegLira group 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. For the evaluation of non-inferiority, subjects who withdrew from the IDegLira group were assumed to have received a treatment inferior to the comparator. This was implemented by adding a penalty corresponding to the non-inferiority limit to the subjects' parameter value at the last visit. This approach does not rely on the assumption that data are missing at random and imputes missing data in a way that is less favorable for IDegLira. The results obtained using this method are more conservative and less realistic since the treatment effect (particularly on HbA1c) is assumed to wear off in a slow, continuous manner.

Tipping point analysis
To further evaluate the robustness of the conclusions based on statistical significance in favor of IDegLira, a tipping point analysis of the approach assumed to be the most conservative, multiple imputation "copy reference", was performed. As described in the "copy reference" methodology above, in this analysis, subjects who withdrew from the IDegLira arm were assumed to have received a treatment inferior to the comparator. The extent of the inferiority (also termed a 'penalty') was gradually increased to evaluate at which point IDegLira was no longer statistically significantly better than a comparator. This penalty value, also known as the tipping point, corresponded to a hypothetical degree of efficacy deterioration in withdrawn subjects needed to shift the treatment effect of IDegLira from being statistically significantly better than the comparator to a non-statistically significant effect.

Numbers of 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 was considered treatment emergent as offset. The model included treatment, pre-trial anti-diabetic treatment (for some trials), all stratification factors (if applicable) and country/region as fixed factors.

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.

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

Body weight

To examine the hypothesis of reduction in body weight, an MMRM analysis was constructed in a similar way as for primary endpoint, i.e., the mixed effects model included treatment, pre-trial anti-diabetic treatment (for some trials), all stratification factors (such as pre-trial antidiabetic treatment and baseline HbA1c level, study 3697 was also stratified by sub-study participation), and country/region as fixed effects and the baseline value of the parameter as a covariate.

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

Hypoglycemia

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 considered to be the ADA definition 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.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Baseline characteristics are described in the table below.

Table 3. Baseline characteristics of subjects in completed phase 3 trials – FAS

	OAD users		Basal insulin users		GLP-1 RA users
	Trial 3697 N=1660	**Trial 3951** N=435	**Trial 3912** N=398	**Trial 3952** N=557	**Trial 3851** N=438
Age (years) at screening					
Mean (SD)	55.0 (9.9)	59.8 (10.0)	57.2 (9.7)	58.8 (9.5)	58.3 (9.5)
Min-max	24–84	27–87	30–86	28–82	22–78
Sex					
Female	817 (49.2)	208 (47.8)	180 (45.2)	277 (49.7)	214 (48.9)
Male	843 (50.8)	227 (52.2)	218 (54.8)	280 (50.3)	224 (51.1)
Race					
White	1028 (61.9)	328 (75.4)	308 (77.4)	527 (94.6)	400 (91.3)
Black or African American	123 (7.4)	29 (6.7)	19 (4.8)	11 (2.0)	27 (6.2)
Asian	464 (27.9)	72 (16.6)	69 (17.3)	18 (3.2)	8 (1.8)
American Indian or Alaska Native	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Native Hawaiian or other Pacific Islander	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Other	40 (2.4)	6 (1.4)	1 (0.3)	1 (0.2)	2 (0.5)
Ethnicity					
Hispanic or Latino	250 (15.1)	40 (9.2)	40 (10.1)	240 (43.1)	41 (9.4)
Not Hispanic or Latino	1408 (84.8)	395 (90.8)	358 (89.9)	317 (56.9)	397 (90.6)
Unknown	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)					
Mean (SD)	31.2 (5.1)	31.5 (4.7)	33.7 (5.7)	31.7 (4.5)	32.9 (4.3)
HbA_{1c} (%)					
Mean (SD)	8.3 (0.9)	7.9 (0.6)	8.8 (0.7)	8.3 (0.9)	7.8 (0.6)
FPG (mmol/L)					
Mean (SD)	9.2 (2.5)	9.1 (2.1)	9.6 (3.0)	8.9 (2.8)	9.1 (2.2)
FPG (mg/dL)					
Mean (SD)	165.8 (45.6)	164.5 (38.4)	173.4 (54.2)	160.1 (49.8)	164.2 (39.5)
Diabetes Duration (years)					
Mean (SD)	6.8 (5.4)	9.1 (5.9)	10.6 (6.5)	11.5 (7.0)	10.4 (5.8)

Source: Clinical Overview p.23

3.2.4 Results and Conclusions

3.2.4.1 Primary endpoints

The results of MMRM analyses for the primary endpoint are summarized in the Table 4. 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% respectfully. The outcomes of MMRM analyses show that the performance of IDegLira is dependent on 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, 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 4. Results of MMRM analyses

Study	Comparator	HbA1c at week 26 IDegLira	HbA1c at week 26 Comparator	IDegLira-Comparator Estimate (95%CI)
3697	IDeg	6.27	6.75	-0.47 (-0.58 , -0.37)
	Lira		6.9	-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 5. The outcomes of both sensitivity analyses were similar in directionality to the primary analyses. The results of both multiple imputation approaches demonstrated superiority of IDegLira win HbA1c reduction.

Table 5. Multiple Imputations

Study	Comparator	Jump to Reference (J2R) IDegLira-Comparator Estimate (95%CI)	Copy Reference (CR) IDegLira-Comparator Estimate (95%CI)
3697	IDeg	-0.42 (-0.52 , -0.31)	-0.41 (-0.52 , -0.31)
	Lira	-0.58 (-0.69, -0.47)	-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 sponsor conducted only tipping point analysis for Copy Reference approach. FDA also examined the outcomes of tipping point examination using Jump to Reference imputation. The results obtained by those two methods were very similar. The results of tipping point analysis (summary of clinical efficacy p.679-693) show that it would take impractical circumstances to tip the results from a conclusion of superiority to failing to conclude superiority.

Most of the study participants completed the 26-week study. The observed missing data rates (Table 6) were between 7.36% and 16.78% across the studies. A more detailed description of dropout rates is presented in Table 6.

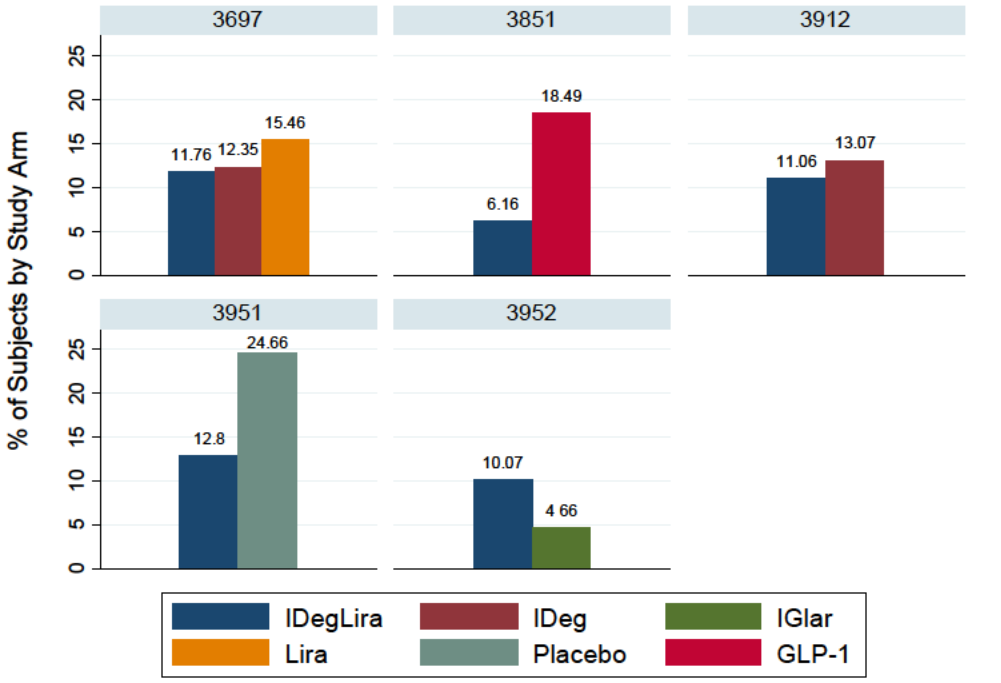
Table 6. Missing subjects at week 26

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. The overall largest missing data rate was observed in study 3951, where IDegLira was compared with Placebo. The missing data rate in IDegLira in that study (12.8%) was slightly higher, but still comparable to the dropout rate in the other studies. The missing data rate of placebo was 24.66% of all subjects in the trial arm. The second largest missing data rate was observed in GLP-1 arm. The lowest rates were observed in study 3952, where the dropout rate in the comparator arm was 4.66%. Figure 2 provides more detailed information on missing data rates in each arm.

Figure 2. Percent of subjects who did not complete 26-week study



Source created by reviewer

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

Table 7. 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.

3.2.4.2 Secondary endpoints

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

Results

Body weight

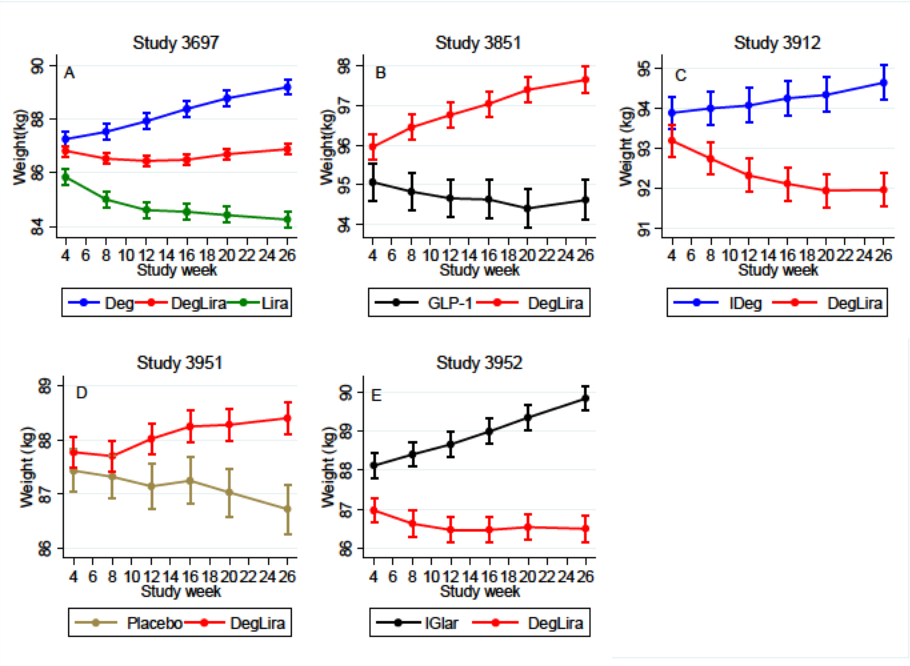
Although the outcomes based on results of MMRM analysis showed that body weight in IDegLira and IDeg arms were statistically different (study 3697), the difference between those two treatment groups at week 26 was only 2.3kg CI (2, 2.7). The adjusted estimates for each treatment arm obtained using the MMRM model are presented in Figure 3. The estimated differences between arms are presented in Table 8.

Table 8. Change in body weight

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 3. Longitudinal changes in body weight



Source created by reviewer

As seen in Figure 3, in study 3697, body weight changes favored IDegLira over IDegludec. At the same time, body weight changes were more favorable in Lira when compared to IDegLira. In study 3851, body weight changes favored GLP-1 over IDegLira and in study 3951, body weight changes favored placebo over IDegLira.

Among 1660 subjects who participated in the 3697 trial, only 255 (15.4%) achieved weight reduction of 5% or more of baseline body weight at week 26. Among those subjects, 23 (5.6% of the subjects in treatment arm) received IDeg, 98(11.8% of the subjects in treatment arm) received IDegLira and 134 (32.4% of subjects in treatment arm) received liraglutide.

In study 3851, only 28 subjects (6.4% of the entire study cohort) achieved 5% or more reduction in body weight. Most of the subjects were from GLP-1 arm (n=16) and 12 were from IDegLira arm. Table 9 shows the results for all five trials.

Table 9. Subjects who had weight reduction of 5% or more during 26-week period

Study	IDegLira n(%)	IDeg n(%)	Lira n(%)	GLP-1 n(%)	Placebo n(%)	IGlar n(%)	Total n(%)
3697	98 (11.76)	23 (5.57)	134 (32.37)				255(15.36)
3851	12 (4.11)			16 (10.96)			28 (6.39)
3912	53 (26.63)	14 (7.04)					67 (16.83)
3951	12 (4.15)				16 (10.96)		28 (6.44)
3952	48 17.27)					8(2.87)	56(10.05)

Source created by reviewer

Hypoglycemia

Overall, only 9 cases of severe hypoglycemia were recorded; 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 10. 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 reviewer

Below are the results provided by the applicant:

Table 11. Summary of overall confirmed hypoglycemia by trial

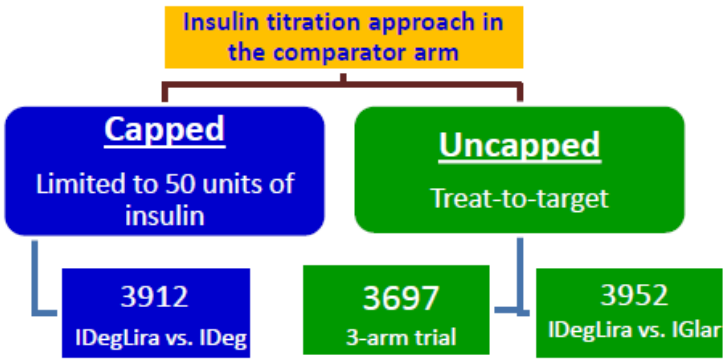
Trial	IDegLira			Basal insulin			GLP-1 RA			Placebo		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Pivotal trials												
3697 (26)	263 (31.9)	699	180.2	159 (38.6)	496	256.7	28 (6.8)	41	22.0			
3697 (52)	327 (39.6)	1247	176.7	203 (49.3)	977	279.1	44 (10.7)	64	19.1			
3912	48 (24.1)	141	153.4	49 (24.6)	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

3.2.5 Insulin dose

The applicant used titration in administration of 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 Trials 3697 and 3952, there was no restriction on the maximum IDeg dose in the comparator arm. In my review, I refer to this approach as an uncapped approach. In Trial 3912, the maximum dose in the IDeg treatment arm was capped at 50 units, equivalent to the maximum IDeg dose with IDegLira (Figure 4).

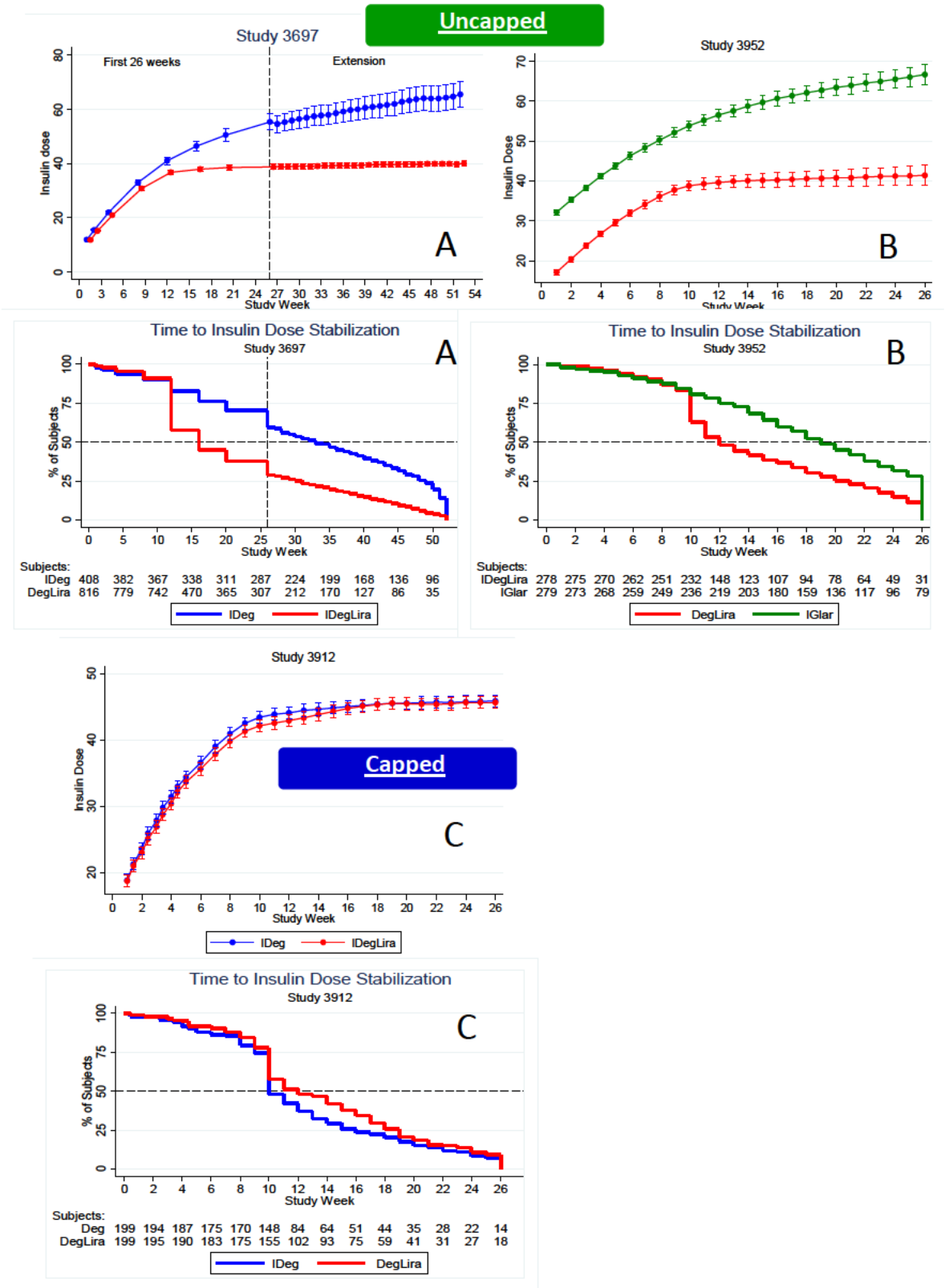
Figure 4. Titration approaches utilized in IDegLira program



Source created by reviewer

Only a half of the subjects who participated in IDeg arm of study 3697 reached their insulin target dose, i.e. finished their titration period. As their FPG levels continued to rise, the insulin dose was increased in attempt to stabilize the FPG levels. 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. The dose was not allowed to increase even if FPG did not stabilize. 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. I defer further discussions of this topic and its implications to the clinical reviewer.
The changes in insulin dose are shown in Figure 3 A, B, and C. The added Kaplan-Mayer plots illustrate the length of dose escalation periods by arm. The distributions of time to insulin dose stabilization by study are presented in Table 12.

Figure 5. Insulin dose



Source created by reviewer

Table 12. Time to end of titration phase (weeks)

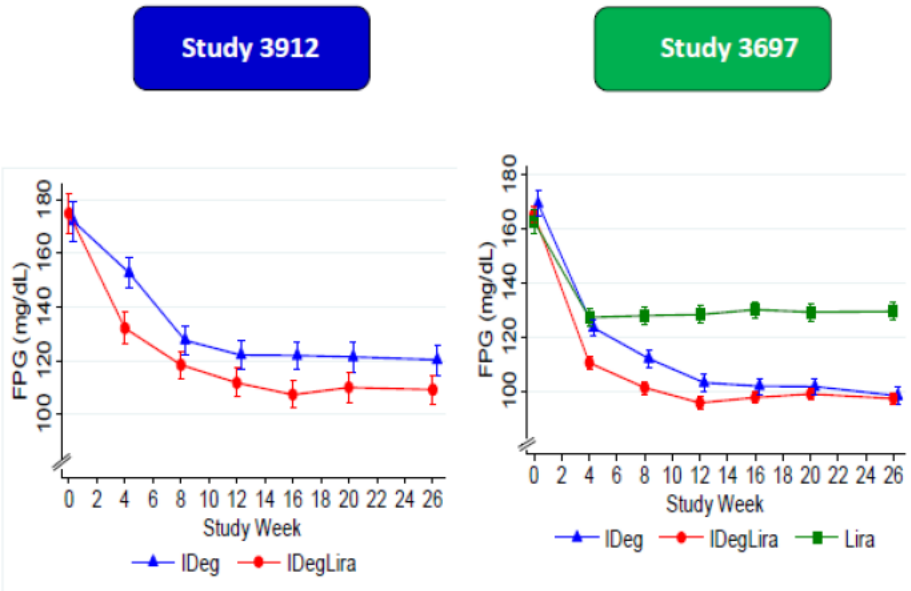
Study	Arm	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev	Coeff of Variation
3697	IDeg	26.0	1.0	26.0	19.5	18.7	20.2	7.8	39.8
	IDegLira	16.0	1.0	26.0	15.8	15.3	16.2	6.5	41.1
3952	IGlar	19.0	1.0	26.0	18.1	17.2	19.0	7.4	40.9
	IDegLira	12.0	1.0	26.0	14.7	13.9	15.5	6.8	46.2
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 reviewer

The centrally measured fasting plasma glucose (FPG) by study week for trials 3912 and 3697 is presented in Figure 6. In the graph on the left, showing the capped dose trial 3912, FPG levels stabilize in both arms around week 12 and remain parallel for the duration of the trial. This pattern is consistent with the dose stabilization curves.

In the graph on the right (Figure 6) in study 3697, it is clear that FPG for subjects on IDegludec was continuously dropping during the entire trial and approximated FPG for subjects on IDegLira only towards the end of the trial.
Therefore, the framework and objectives of the IDegLira program should be viewed within the context of the capped and uncapped dose stabilization approaches.

Figure 6. Fasting Plasma Glucose (FPG) by study week



*Results from MMRM analysis

Source created by reviewer

3.3 Evaluation of Safety

Safety events were reviewed by Dr. Tania Condarco from Medical Division of Metabolism and Endocrinology Products. Please refer to Dr. Condarco's review for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, And Geographic Region

4.1.1 Gender

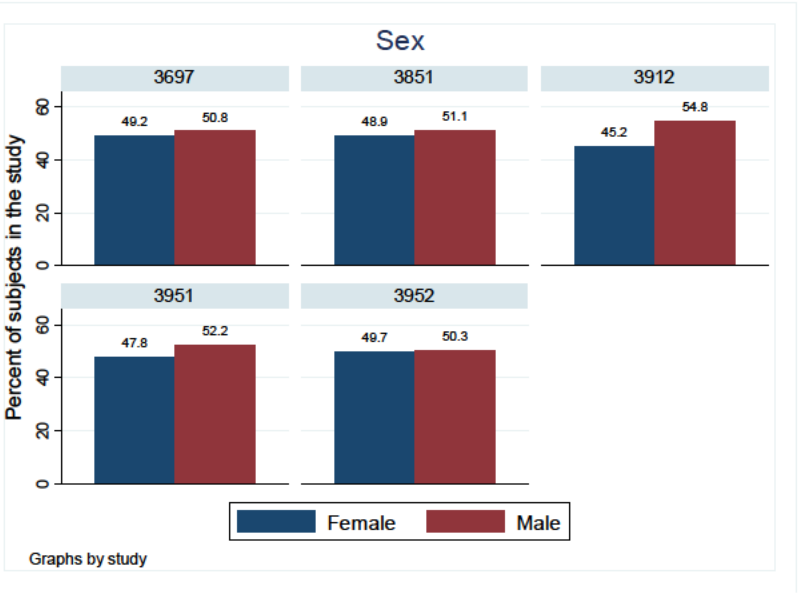
Overall, both males and females were represented equally with 48.6% females and 51.4% males in the entire program. The largest difference between percentage of males and females was observed in study 3912 (45.2% females and 54.8% males).

Table 13. Number of subjects by sex

SEX	Study					
	3697	3851	3912	3951	3952	Total
Female	817	214	180	208	277	1696
Male	843	224	218	227	280	1792
Total	1660	438	398	435	557	3488

Source created by reviewer

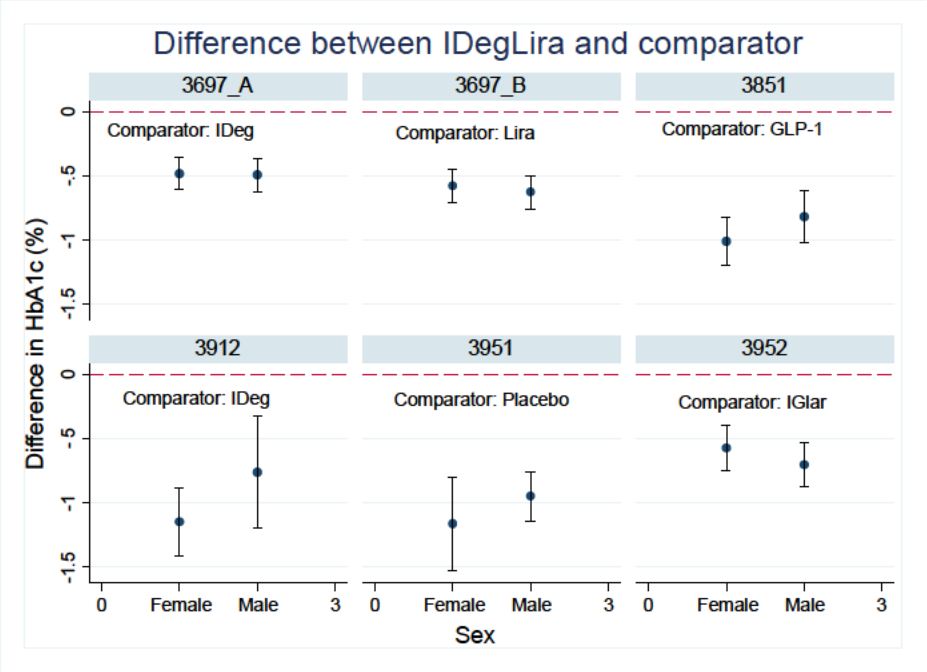
Figure 7. Sex subgroups



Source created by reviewer

The subgroup analysis by sex is presented in the Figure below. In all studies, the outcomes in both subgroups favored IDegLira vs comparator. A more detailed description of primary outcomes by sex is located in Appendix (Table 23).

Figure 8. Difference between IDegLira and comparator by sex



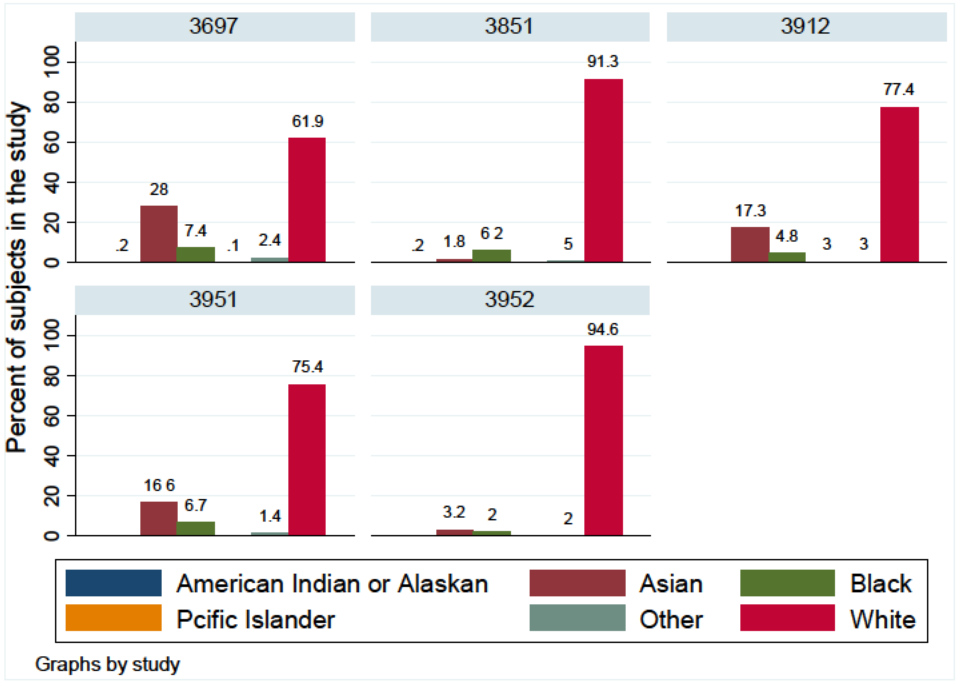
Source created by reviewer

4.1.2 Race

Of 3488 subjects who participated in IDegLira program, the majority were white (74.3%), 18.1% of all subjects were Asian, and 6% were black or African American. All other race groups were small, 0.06% for Native Hawaiian, 0.14% of American Indian for Alaska natives, and 1.43% for all others. A detailed description of racial composition by study is presented in Figure 7 . White subjects represented 61.9% (study 3697) to 94.6% (study 3952) of each individual study. The largest amount of Asian participants was observed in study 3697 (28%). The smallest fraction of Asian subjects was observed in study 3952 (3.2%). The fraction of Black or African American subjects was similar in studies 3851 and 3951 (6.2% and 6.7% respectfully). The largest fraction of Black participants was in study 3697 (7.4%) and the lowest (2%) in study 3952.

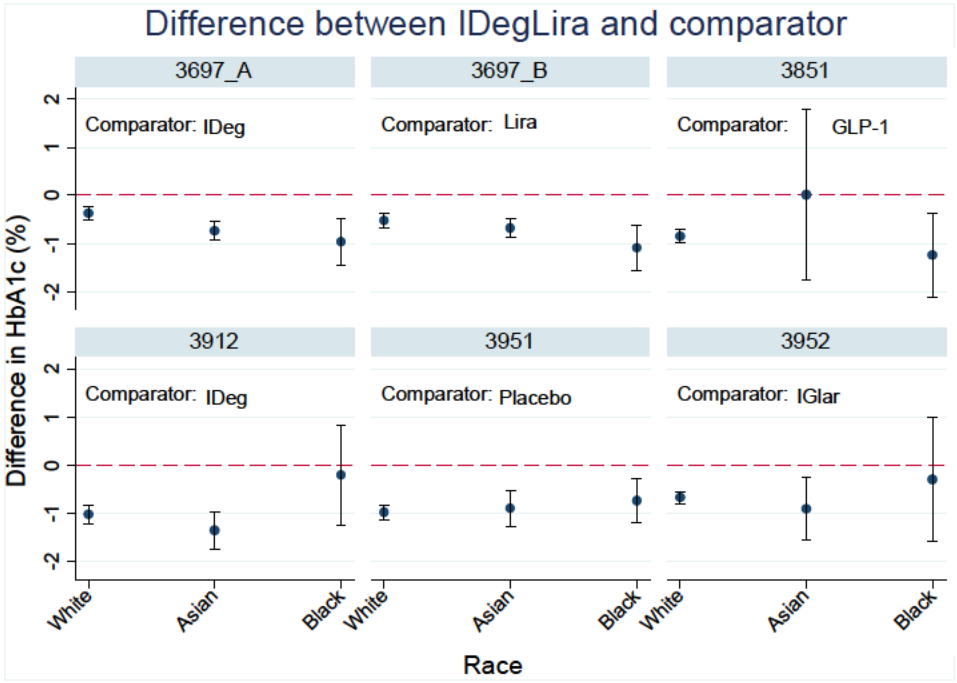
Because all other race groups represented such a small fraction of the entire IDegLira program, the primary analyses were repeated only using data from three major race groups (white, Asian, black or African American). The graphical results of those calculations are presented in Figure 8. A more detailed table of results is presented in the Appendix.

Figure 9. Race groups by study



Source created by reviewer

Figure 10. Difference between IDegLira and comparator by race



Source created by reviewer

All but one of the estimates of the difference between treatments were below the zero line, i.e. favoring IDegLira results. Only in study 3851, the results for Asian subgroup were on the zero line. That could be explained by a relatively small number of Asian participants n=8 (1.8%). Similarly, confidence intervals for Black subgroups (studies 3912 and 3952) went above the zero line. In those studies Black subjects represented 4.8% and 2% of study population, respectively.

4.1.3 Age

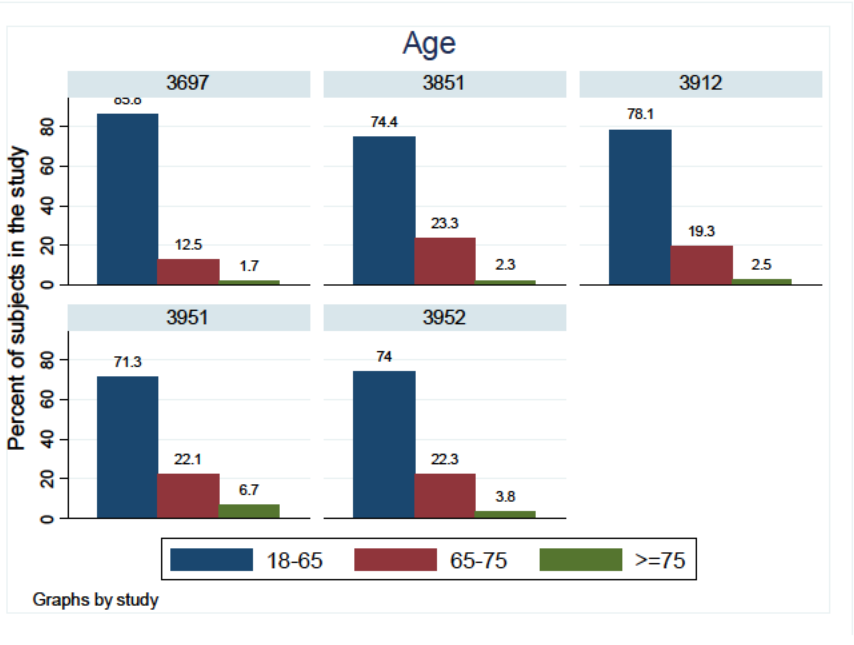
The majority of the program participants were between ages 18 and 65 (79.8%). The smallest group was of subjects aged 75 and older (2.8%). A more detailed description of each trial is presented in Table 13 and Figure 9 below.

Table 14. Subjects by age

Age Group	Study					
	3697	3851	3912	3951	3952	Total
>=18 - <65 years	1424	326	311	310	412	2783
>=65 - <75 years	207	102	77	96	124	606
>=75 years	29	10	10	29	21	99
Total	1660	438	398	435	557	3488

Source created by reviewer

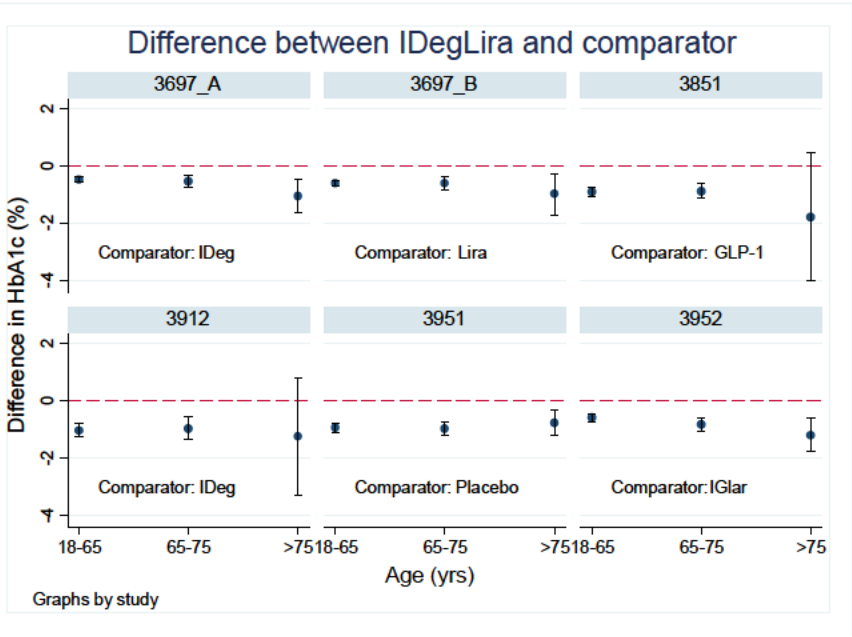
Figure 11. Age subgroup



Source created by reviewer

The results of analyses based on age of study participants are presented below. All estimated differences between IDegLira and comparator arms were below zero, i.e. favoring outcomes on IDegLira. The confidence intervals obtained in age 75 and older groups were larger because the number of subjects in those groups was small. A more detailed description of primary outcomes by age group is located in Appendix (Table 21).

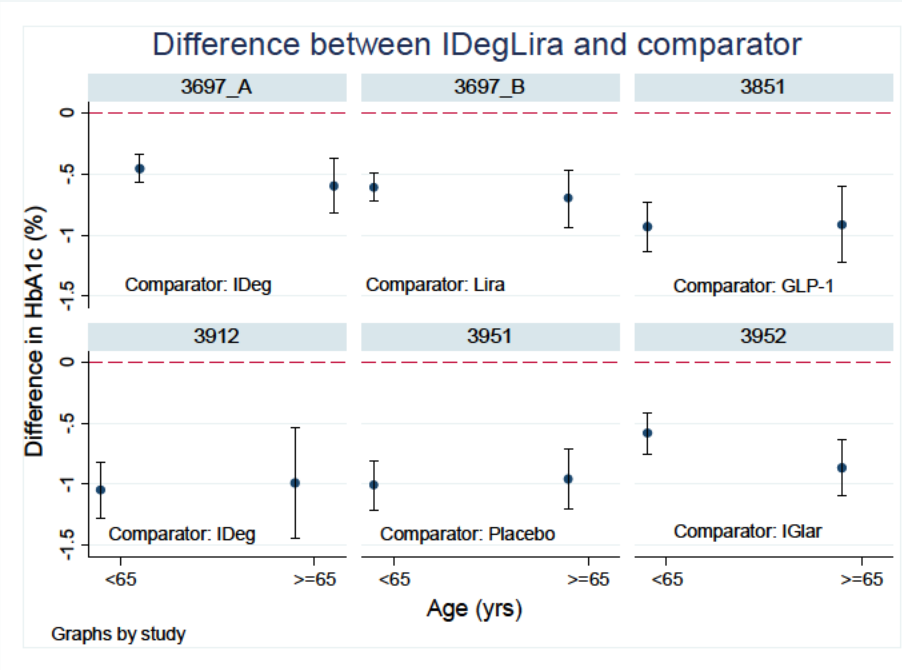
Figure 12. Difference between IDegLira and comparator by age (3-group classification)



Source created by reviewer

The results were similar when age was stratified at 65 years (Figure 11). A more detailed description of primary outcomes by age group is located in Appendix (Table 21).

Figure 13. Difference between IDegLira and comparator by age (stratified by age 65)



Source created by reviewer

4.1.4 Region

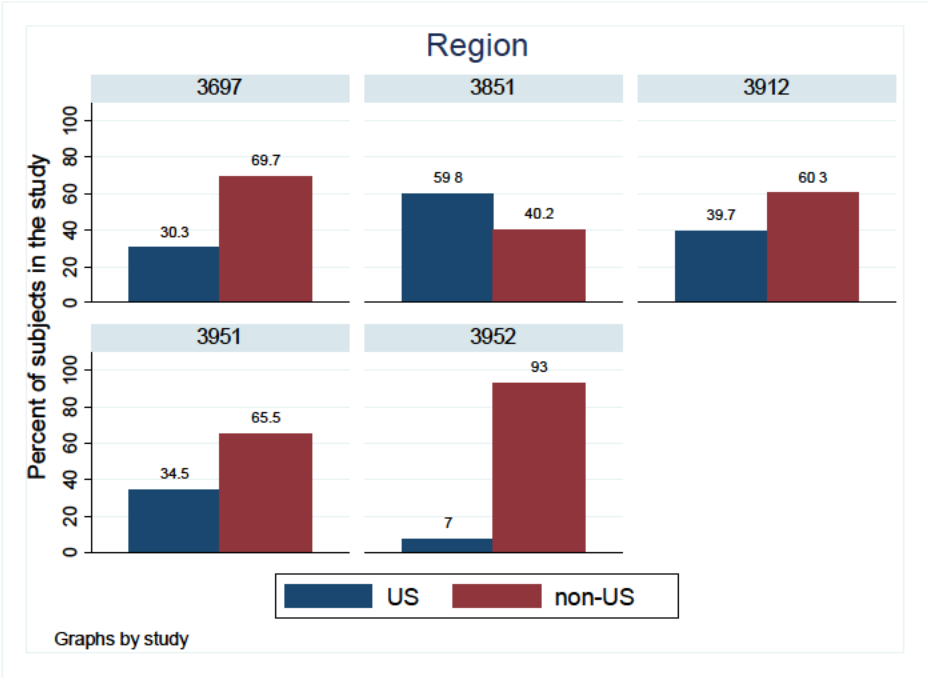
The majority of subjects (68.1%) were not from the US. Only in trial 3851 were the majority of subjects were from the US (59.8%). The largest difference in percentage between US and non-US was observed in study 3952 (7% US vs. 93% non-US).

Table 15. Number of subjects by geographical region (US vs other)

	Study					
Region (US/non-US)	**3697**	**3851**	**3912**	**3951**	**3952**	**Total**
US	503	262	158	150	39	1112
non-US	1157	176	240	285	518	2376
Total	1660	438	398	435	557	3488

Source created by reviewer

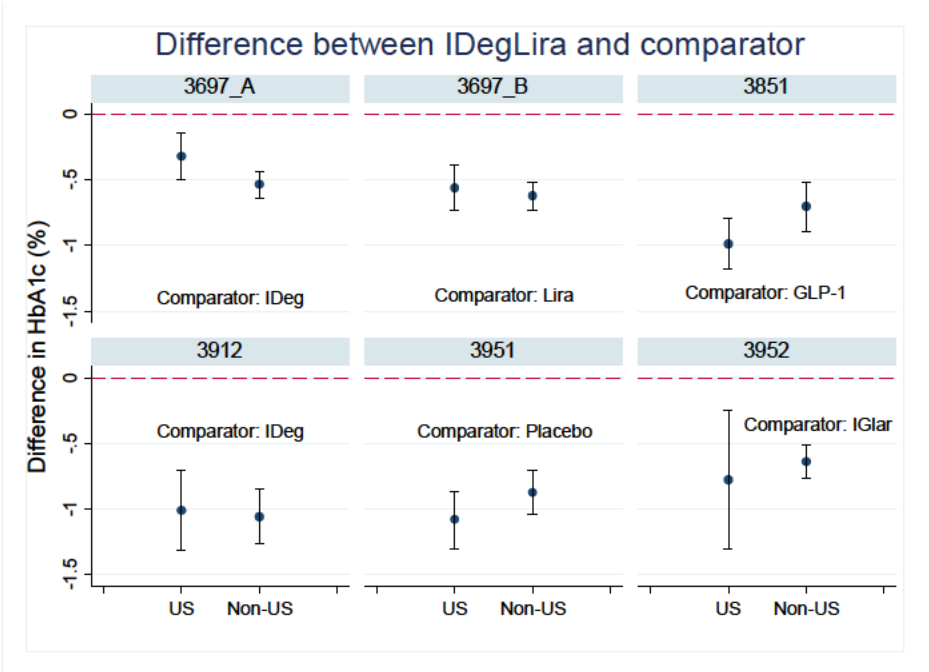
Table 16. Distribution by geographical region (US vs other)



Source created by reviewer

The subgroup analysis by geographical region is presented in the Figure below. In all studies, the outcomes in both subgroups favored IDegLira vs comparator. A more detailed description of primary outcomes by region is located in Appendix (Table 20).

Figure 14. Difference between IDegLira and comparator by geographical region



Source created by reviewer

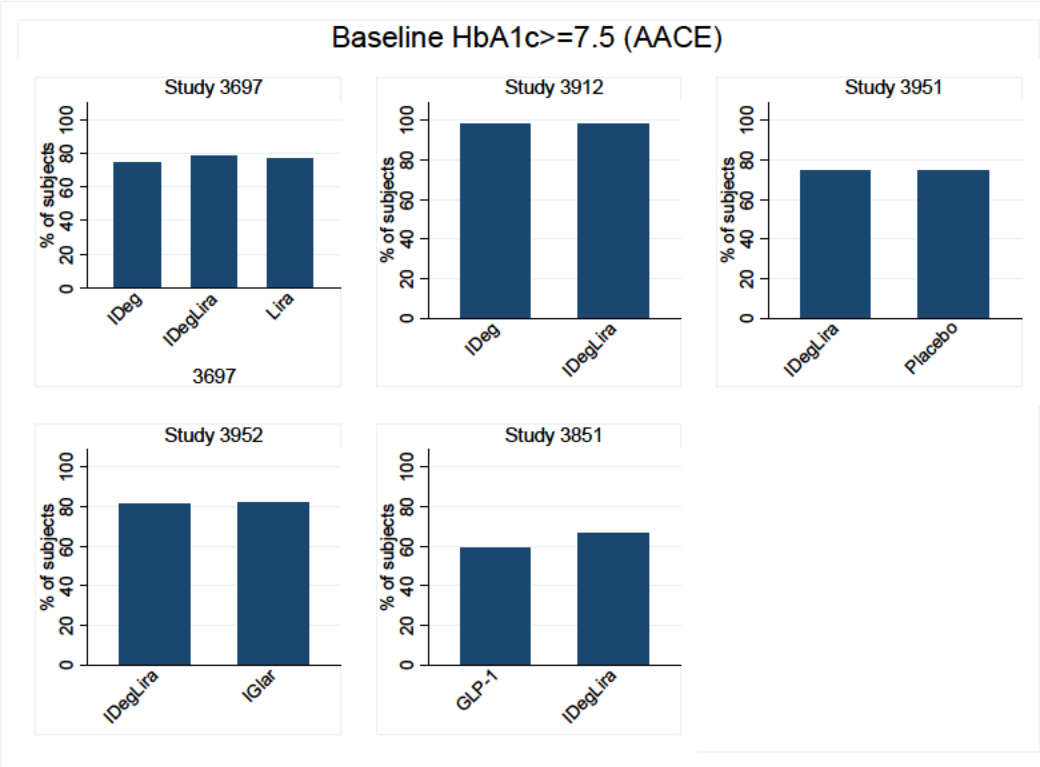
4.2 Other special Subgroup/subgroup populations

4.2.1 Baseline HbA1c

According to the American Association of Clinical Endocrinologists (AACE), dual therapy is recommended for subjects who failed first line therapy and have HbA1c≥7.5%. Similar recommendations were made by American Diabetes Association (ADA) using the cut off of 9%. In my review, the above listed cut points are used to create patient subgroups.

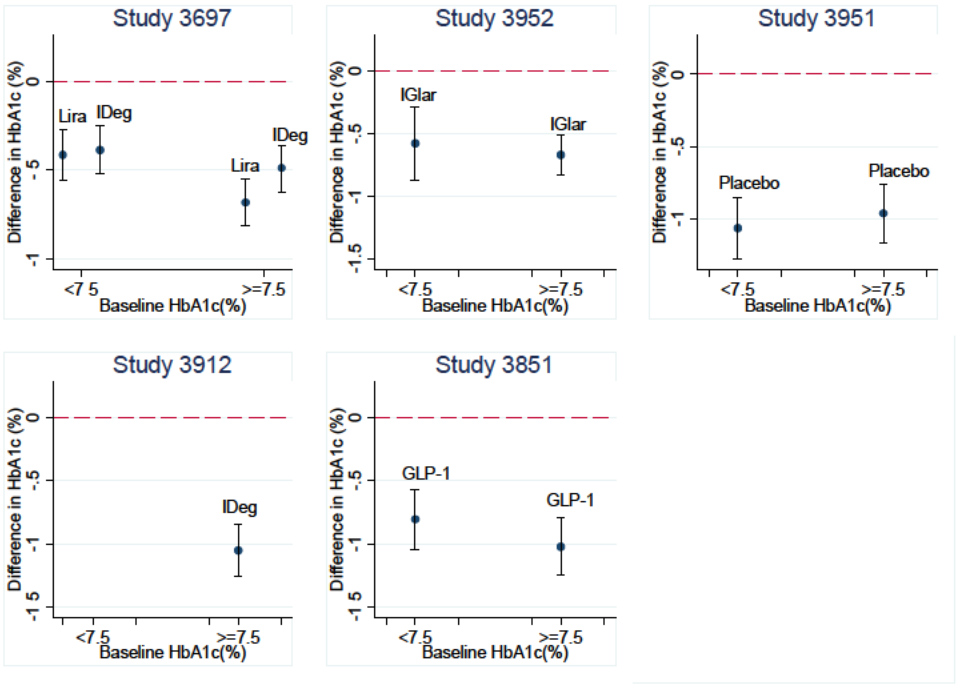
Because of the difference in study designs and trial populations, the fraction of subjects with baseline HbA1c at or above 7.5% was different among trials. Most subjects in study 3912 had baseline HbA1c above that threshold. That could be explained by the fact that those subjects were previous insulin users and those subjects had a more progressed disease. The smallest fraction of subjects with HbA1c of 7.5% or higher was observed in trial 3851 (Figure 15).

Figure 15. Distribution of baseline HbA1c (threshold 7.5%) by study



Source created by reviewer

Figure 16. Differences between IDegLira and comparators by baseline HbA1c (7.5% threshold)

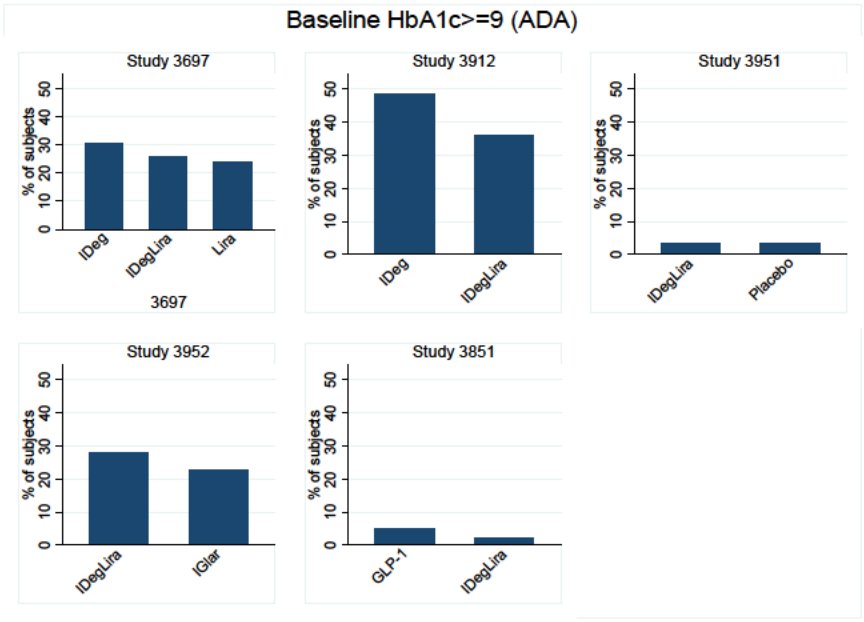


Source created by reviewer

Stratification at 9%

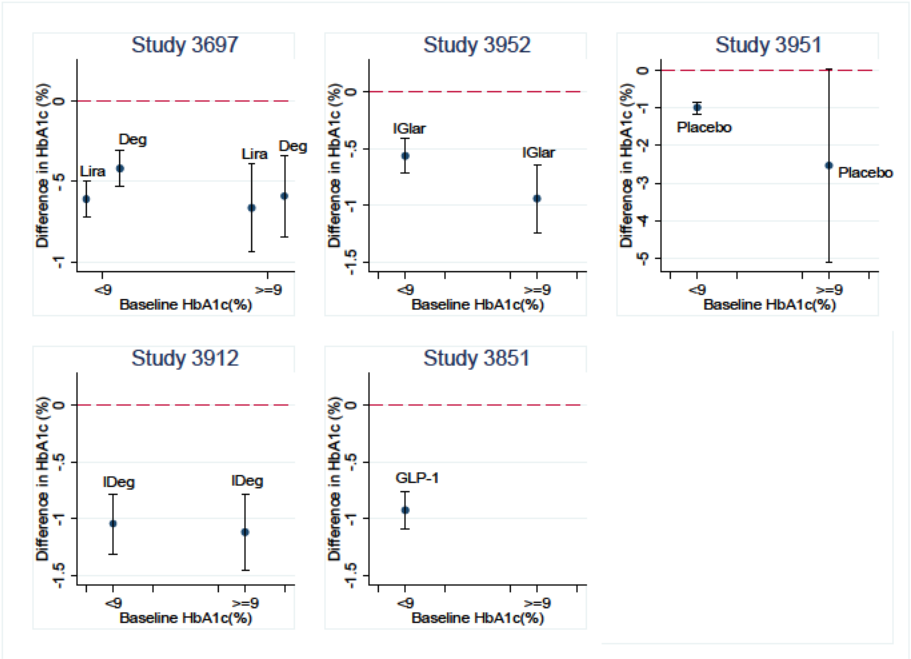
Similarly to the results with 7.5% threshold, the fraction of subjects who had baseline HbA1c at or above 9% varied among trials (Figure 17). The numbers of those subjects were particularly low in studies 3851 and 3951. The largest proportion of subjects meeting the 9% threshold was observed in trial 3912.

Figure 17. Distribution of baseline HbA1c (threshold 9%) by study



Source created by reviewer

Figure 18. Differences between IDegLira and comparators by baseline HbA1c (9% threshold)



Source created by reviewer

Similar to the previous subgroup analyses, I utilized the MMRM model to examine differences among baseline HbA1c subgroups. The estimates of treatment differences between subjects in IDegLira and comparator arms are presented in Figures Figure 16 and Figure 18. The results of my analysis suggest that for the subjects in the higher group, i.e. the subjects who had HbA1c ≥7.5% or ≥9% at baseline, had a larger reduction in HbA1c than subjects who were in the group with low HbA1c, i.e. <7.5% or <9%.

The plots presented in Figures Figure 16 and Figure 18 show that the confidence intervals between the subgroups in each trial overlap. Additionally, some of the trials did not have a sufficient amount of data to run the MMRM model in some of the categories (the trials were not powered for these types of analyses). Therefore, it is difficult to draw robust conclusions from these analyses.

A more detailed description of primary outcomes by baseline HbA1c is located in Appendix (Table 22).

4.2.2 BMI

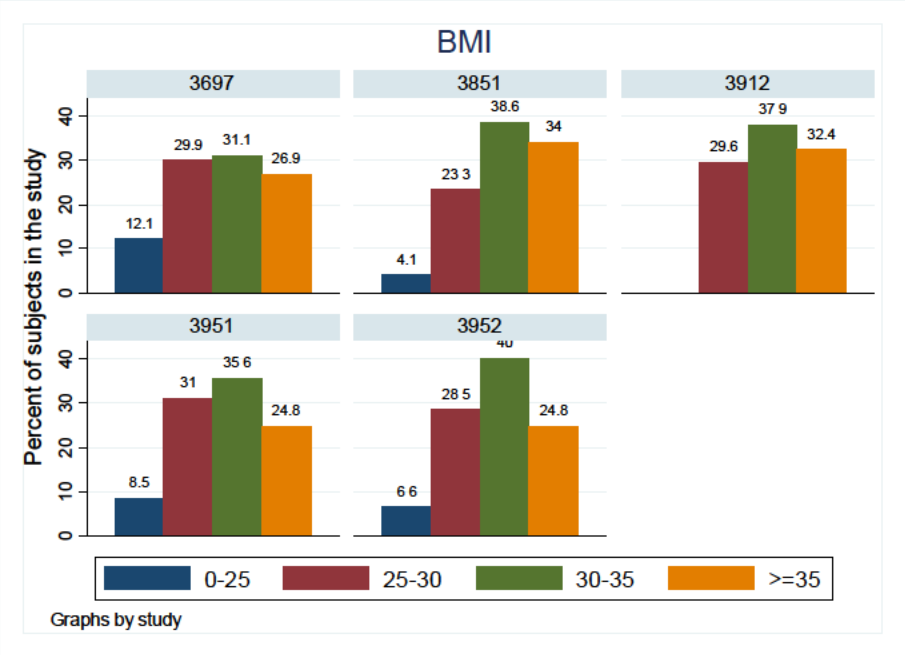
Because increased weight is known to be associated with development and progression of diabetes, I examined the impact of baseline BMI on the outcome. The BMI was distributed relatively evenly among the highest three categories (25-30, 30-35, and 35 and higher). Each of those categories contained between 27.8 and 34.8% of subjects. The smallest category was in the subgroup with the lowest BMI (<25), which contained only 8.4% of all subjects. Study 3697 had a slightly larger fraction of subjects in the low- BMI group at baseline (12.1%). Study 3912 did not have any subjects with BMI below 25.

Table 17. Number of subjects by baseline BMI

BMI group	Study					
	3697	**3851**	**3912**	**3951**	**3952**	**Total**
[0;25[	201	18	0	37	37	293
[25;30[	496	102	118	135	159	1010
[30;35[	517	169	151	155	223	1215
[35;[	446	149	129	108	138	970
Total	1660	438	398	435	557	3488

Source created by reviewer

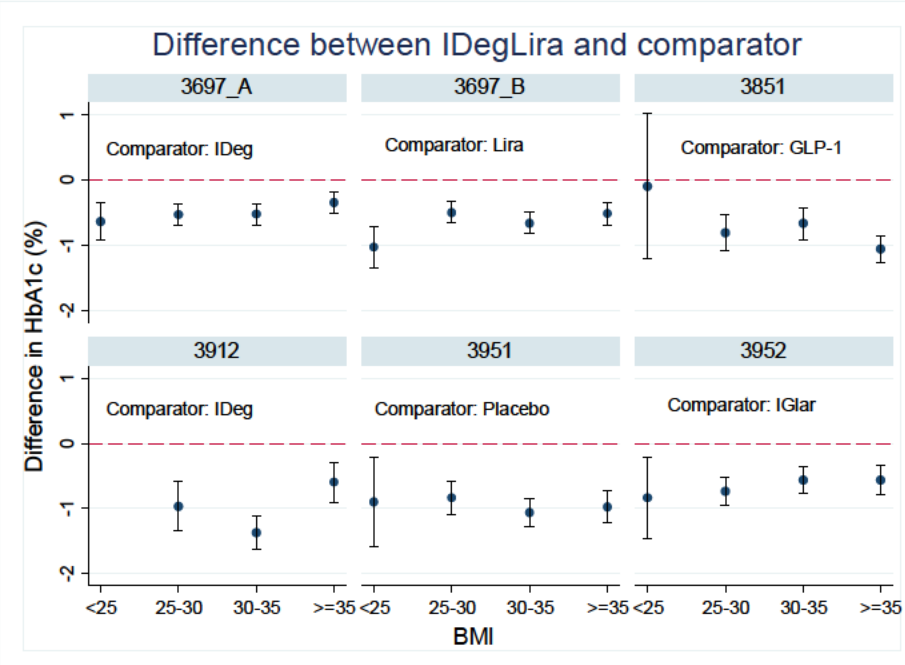
Figure 19. Distribution of subjects by baseline BMI



Source created by reviewer

The results of MMRM analysis based on BMI subgroup favored IDegLira. Only in study 3851, the difference between IDegLira and GLP-1 among subjects with BMI<25 was very small. A more detailed description of primary outcomes by baseline BMI is located in Appendix (Table 24).

Figure 20. Difference between IDegLira and comparator by baseline BMI



Source created by reviewer

5 SUMMARY AND CONCLUSIONS

5. 1 Statistical Issues

There were several issues that were of concern:

Limitations of study design:

Insulin was titrated too slowly, i.e. a large fraction of subjects did not reach a stable dose of insulin prior to study conclusion. Since a large number of subjects did not reach a stable dose of insulin, i.e. , did not have an FPG in the normal range, insulin did not reach its efficacy for those subjects. Because of this issue, the difference in HbA1c levels between subjects given IDegLira and those on insulin at 26 weeks was larger than it would have been if subjects on insulin had reached an FPG-based stable insulin dose. Therefore, it is not clear whether a conclusion of superiority would have been reached if subjects on insulin had reached an FPG-based stable insulin dose.

Additionally, trial 3912 had a pre-specified cap on maximum insulin dose. Therefore, many of the subjects in the comparator treatment did not reach a stable state during the 26-week trial but might have if the trial had been longer or if dose had been changed more frequently. Clinical practice does not put a cap on insulin dose.

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 week 26 assessment.

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.

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 definition results in a sample size too small to draw meaningful conclusions.

5. 2 Collective Evidence

The primary endpoint was met within the five trials as conducted. The missing data do not affect the conclusion of superiority of IDegLira on 26-week HbA1c. The titration approach utilized in the IDegLira program might have an impact on external validity of the findings.

The body weight analysis had the following limitations:

1. Only one study had 52-week data. The last 26 weeks were an extension and not part of primary efficacy analysis. For drug intended for weight management, efficacy and safety are evaluated in 52-week trials.
2. The study did not continue follow-up for subjects who prematurely discontinued treatment.

The number of ADA defined hypoglycemia cases was insufficiently small to draw robust conclusions. For more information on hypoglycemia, please see Dr. Condarco's review.

5. 3 Conclusions and Recommendations

The superiority of IDegLira over its components in the studies documented here might have been an artifact of the study design which did not give subjects in the comparator insulin arms a chance to reach a stable insulin dose. Without conducting a study which allows stabilization early enough in the study period to have meaningful comparisons of HbA1c, which is slower to respond than FPG, it is impossible to say with certainty how the outcome would be seen in clinical practice.

Statistically, weight changes were different between IDegLira and comparators, but those changes were small. Overall, subjects on IDegLira gained less weight than subject on insulin, in contrast, weight reduction among subjects on IDegLira was significantly smaller than weight reduction among subjects on GLP-1 and subjects on placebo.

Additionally, the interpretation of the comparisons on body weight change are also limited by the study duration and the lack of retrieved dropouts.

It is my recommendation to approve IDegLira for HbA1c reduction. In addition to the issues with weight loss results listed above, the IDegLira studies were not set up to meet the regulatory standard for weight management program that required an appropriate duration and accounting for dropouts. (b) (4)

5. 4 Labeling Recommendations

For the Tables 5-9 of section 14 of IDegLira lable, I would recommend replacing LOCF estimates with estimates that more approperiately reflect the treatment effect in the ITT population. The sponsor could be asked to propose the appropriate analyses.

Regarding labeling of the trial 3912, i.e. the trial where the maximum amount of insulin in the comparator arm was capped at 50 units, the label should clarify that despite the internal validity of this trial, the resluts of that specific trial are not valid externally because of the study dsign.

Aditionally the label indicates that insulin in all five trials was titrated to target and it does not point out the issue of artifical limit that was set in the capped trial 3912 (lines 1253-1258).

APPENDICES

Table 18. Subgroup analyses Age

study	AGE Group	Comparator	Estimate	Lower	Upper
3697	>=18 - <65 years	IDeg	-0.4719	-0.57163	-0.37216
3697	>=18 - <65 years	Lira	-0.6026	-0.7029	-0.5023
3697	>=65 - <75 years	IDeg	-0.5403	-0.76131	-0.31929
3697	>=65 - <75 years	Lira	-0.6010	-0.8287	-0.3733
3697	>=75 years	IDeg	-1.0608	-1.63581	-0.48577
3697	>=75 years	Lira	-0.9809	-1.7094	-0.2524
3851	>=18 - <65 years	GLP-1	-0.9104	-1.0709	-0.7499
3851	>=65 - <75 years	GLP-1	-0.8774	-1.1510	-0.6038
3851	>=75 years	GLP-1	-1.7883	-4.0311	0.4546
3912	>=18 - <65 years	IDeg	-1.0321	-1.2658	-0.80
3912	>=65 - <75 years	IDeg	-0.9664	-1.3612	-0.5716
3912	>=75 years	IDeg	-1.2400	-3.3014	0.8214
3951	>=18 - <65 years	Placebo	-0.9366	-1.1062	-0.7671
3951	>=65 - <75 years	Placebo	-0.9651	-1.2015	-0.7287
3951	>=75 years	Placebo	-0.7568	-1.2059	-0.3078
3952	>=18 - <65 years	IGlar	-0.5866	-0.7368	-0.4364
3952	>=65 - <75 years	IGlar	-0.8242	-1.0437	-0.6048
3952	>=75 years	IGlar	-1.2013	-1.7863	-0.6163

Table 19. Subgroup analyses race

Obs	RACE	Comparator	Estimate	Lower	Upper
3697	WHITE	IDeg	-0.37	-0.51	-0.23
3697	WHITE	Lira	-0.52	-0.66	-0.38
3697	AMERICAN INDIAN OR ALASKA NATIVE	IDeg	0.7824	-1.4039	2.9686
3697	ASIAN	IDeg	-0.7358	-0.9244	-0.5472
3697	ASIAN	Lira	-0.6759	-0.8717	-0.4802
3697	BLACK OR AFRICAN AMERICAN	IDeg	-0.9679	-1.4571	-0.4788
3697	BLACK OR AFRICAN AMERICAN	Lira	-1.0965	-1.5738	-0.6191
3697	OTHER	IDeg	0.3001	-0.2915	0.8916
3697	OTHER	Lira	-0.6289	-1.2063	-0.05143
3851	Asian	GLP-1	0.01450	-1.7631	1.7921
3851	Black	GLP-1	-1.2470	-2.1138	-0.3801
3851	White	GLP-1	-0.8493	-0.9889	-0.7098
3912	Asian Indian	IDeg	-1.3455	-1.7387	-0.9523
3912	Black	IDeg	-0.2006	-1.2465	0.8454
3912	White	IDeg	-1.0083	-1.2100	-0.8067
3951	Asian	Placebo	-0.8895	-1.2723	-0.5066
3951	Black	Placebo	-0.7305	-1.1938	-0.2671
3951	Other	Placebo	-0.6677	-4.2982	2.9627
3951	White	Placebo	-0.9655	-1.1211	-0.8098
3952	Asian	IGlar	-0.8987	-1.5493	-0.2482
3952	Black	IGlar	-0.2833	-1.5770	1.0105
3952	White	IGlar	-0.6643	-0.7958	-0.5327

Table 20. Subgroup analyses region

study	Region	Comparator	Estimate	Lower	Upper
3697	US	IDeg	-0.3222	-0.4967	-0.1476
3697	US	Lira	-0.5605	-0.7315	-0.3894
3697	non-US	IDeg	-0.5388	-0.6428	-0.4348
3697	non-US	Lira	-0.6209	-0.7274	-0.5144
3851	US	GLP-1	-0.9884	-1.1813	-0.7955
3851	Non-US	GLP-1	-0.7050	-0.8960	-0.5139
3912	US	IDeg	-1.0151	-1.3191	-0.7111
3912	non-US	IDeg	-1.0584	-1.2687	-0.8480
3951	US	Placebo	-1.0834	-1.3031	-0.8638
3951	non-US	Placebo	-0.8746	-1.0433	-0.7059
3952	US	IGlar	-0.7788	-1.3068	-0.2508
3952	non-US	IGlar	-0.6406	-0.7720	-0.5093

Table 21. Subgroup analysis by age

Study	AGE	Comparator	Estimate	Lower	Upper
3912	<65	IDeg	-1.0507	-1.28121	-0.82016
3912	>=65	IDeg	-0.9908	-1.44322	-0.53848
3697	<65	IDeg	-0.4555	-0.57226	-0.33867
3697	<65	Lira	-0.6106	-0.72813	-0.49307
3697	>=65	IDeg	-0.5974	-0.82157	-0.37327
3697	>=65	Lira	-0.7017	-0.93782	-0.46553
3851	<65	GLP-1	-0.9328	-1.13320	-0.73244
3851	>=65	GLP-1	-0.9187	-1.23229	-0.60520
3951	<65	Placebo	-1.0102	-1.21276	-0.80772
3951	>=65	Placebo	-0.9562	-1.20359	-0.70885
3952	<65	IGlar	-0.5834	-0.75445	-0.41230
3952	>=65	IGlar	-0.8668	-1.09610	-0.63756

Table 22. Subgroup analysis by baseline HbA1c

Study	Baseline HbA1c	Comparator	Estimate	Lower	Upper
3912	<9	IDeg	-1.0438	-1.31015	-0.77749
3912	>=9	IDeg	-1.1175	-1.44871	-0.78636
3697	<9	IDeg	-0.4165	-0.52892	-0.30404
3697	<9	Lira	-0.6068	-0.71776	-0.49582
3697	>=9	IDeg	-0.5899	-0.84100	-0.33883
3697	>=9	Lira	-0.6603	-0.92962	-0.39092
3851	<9	GLP-1	-0.9220	-1.08915	-0.75483
3951	<9	Placebo	-0.9970	-1.15557	-0.83841
3951	>=9	Placebo	-2.5342	-5.09844	0.03010
3952	<9	IGlar	-0.5622	-0.71925	-0.40509
3952	>=9	IGlar	-0.9403	-1.24153	-0.63912
3912	>=7.5	IDeg	-1.0535	-1.25926	-0.84782
3697	<7.5	IDeg	-0.3871	-0.52338	-0.25084
3697	<7.5	Lira	-0.4125	-0.55222	-0.27286
3697	>=7.5	IDeg	-0.4898	-0.62177	-0.35788
3697	>=7.5	Lira	-0.6808	-0.81263	-0.54902
3851	<7.5	GLP-1	-0.8088	-1.05010	-0.56746
3851	>=7.5	GLP-1	-1.0238	-1.25001	-0.79766
3951	<7.5	Placebo	-1.0664	-1.28133	-0.85146
3951	>=7.5	Placebo	-0.9628	-1.16431	-0.76123
3952	<7.5	IGlar	-0.5781	-0.87338	-0.28290
3952	>=7.5	IGlar	-0.6708	-0.83139	-0.51029

Table 23. subgroup analyses by sex

Study	Sex	Comparator	Estimate	Lower	Upper	study
3697	Female	IDeg	-0.4818	-0.6100	-0.3537	3697
3697	Female	Lira	-0.5802	-0.7088	-0.4515	3697
3697	Male	IDeg	-0.4912	-0.6223	-0.3600	3697
3697	Male	Lira	-0.6273	-0.7606	-0.4940	3697
3851	Female	GLP-1	-1.0122	-1.1995	-0.8249	3851
3851	Male	GLP-1	-0.8180	-1.0205	-0.6154	3851
3912	Female	IDeg	-1.1499	-1.4132	-0.8867	3912
3912	Male	IDeg	-0.76	-1.19	-0.32	3912
3951	Female	Placebo	-1.1635	-1.5321	-0.8	3951
3951	Male	Placebo	-0.9474	-1.1386	-0.7562	3951
3952	Female	IGlar	-0.5716	-0.7464	-0.3968	3952
3952	Male	IGlar	-0.7031	-0.8786	-0.5277	3952

Table 24. Subgroup analyses BMI

study	BMI category	Comparator	Estimate	Lower	Upper
3697	[0;25[	IDeg	-0.6369	-0.9223	-0.3514
3697	[0;25[	Lira	-1.0339	-1.3511	-0.7166
3697	[25;30[	IDeg	-0.5288	-0.6941	-0.3635
3697	[25;30[	Lira	-0.4932	-0.6600	-0.3264
3697	[30;35[	IDeg	-0.5223	-0.6850	-0.3595
3697	[30;35[	Lira	-0.6617	-0.8221	-0.5014
3697	[35;[	IDeg	-0.3437	-0.5134	-0.1741
3697	[35;[	Lira	-0.5147	-0.6850	-0.3444
3851	[0;25[	GLP-1	-0.09511	-1.2136	1.0233
3851	[25;30[	GLP-1	-0.8088	-1.0858	-0.5317
3851	[30;35[	GLP-1	-0.6649	-0.9078	-0.4219
3851	[35;[	GLP-1	-1.0590	-1.2679	-0.8500
3912	[25;30[	IDeg	-0.970	-1.3421	-0.593
3912	[30;35[	IDeg	-1.3695	-1.6263	-1.1126
3912	[35;[	IDeg	-0.5941	-0.9035	-0.2847
3951	[0;25[	Placebo	-0.8992	-1.5890	-0.2094
3951	[25;30[	Placebo	-0.8412	-1.0893	-0.5931
3951	[30;35[	Placebo	-1.0661	-1.2762	-0.8559
3951	[35;[	Placebo	-0.9752	-1.2291	-0.7213
3952	[0;25[	IGlar	-0.8350	-1.4582	-0.2119
3952	[25;30[	IGlar	-0.7350	-0.9540	-0.5161
3952	[30;35[	IGlar	-0.5656	-0.7700	-0.3611
3952	[35;[	IGlar	-0.5649	-0.7908	-0.3389

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

/s/

ANNA E KETTERMANN
06/15/2016

MARK D ROTHMANN
06/15/2016
I concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208583 **Applicant:** Novo Nordisk Inc. **Stamp Date:** 9/12/2015

Drug Name: insulin degludec and liraglutide [rDNA origin] injection **NDA/BLA Type:** Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			The sponsor is planning to use LOCF as a primary analysis and MMRM as a sensitivity
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.	✓			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			✓	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		✓		

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Comments for the 74-day letter:

1. We could not get the MMRM models specified in the documentation and SAS codes provided by the sponsor to function properly. It does not seem that these were the codes and datasets that were used to produce the results. Please clarify. If these are not the codes and datasets used to produce the results, please provide the codes that would reproduce your findings. Please include comments and clarifications in the codes.

2. Please clarify whether post-rescue data were collected on HbA1c and if those data were included in the submitted datasets.

Reviewing Statistician	Date
Team Leader	Date

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

/s/

ANNA E KETTERMANN
11/02/2015

MARK D ROTHMANN
11/02/2015
Concur