Introduction: Degludec and Degludec/Aspart

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 8, 2012

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Division of Metabolism and Endocrinology Product
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

1. Regulatory requirements to file a marketing application for an injectable insulin product
2. Benefits and risks associated with insulin use
3. Insulin and cardiovascular risk
4. Regulatory requirements for CV risk assessment in type-2 diabetes products
5. Regulatory requirements for CV risk assessment in insulin products
6. Purpose of the advisory committee meeting

Injectable Insulin
Clinical Requirements for Submission

Sponsors developing novel injectable insulin products are required to establish the clinical safety and efficacy of the new product

The development program may include clinical trials to specifically evaluate:

- The impact of a new method of use (e.g., novel injection schedule)
- The impact of a new product characteristic (i.e., a novel formulation strength)

Characteristics of Insulin Development Programs

Patients with type 1 and patients with type 2 diabetes mellitus are studied

Trials are active comparator controlled and not placebo controlled

Doses of investigational insulin and comparator are individually titrated to target a specific glycemic goal

Trials are open-label

Long term safety is assessed by use of controlled extensions

Insulin Benefit and Risk

Benefit:

Improvement in glucose control using insulin reduces the onset and progression of microvascular disease.

- **Type 1 diabetes:** Diabetes Control and Complications Trial
- **Type 2 diabetes:** Kumamoto and United Kingdom Prospective Diabetes Study

Risk:

Improvement in glucose control using insulin is associated with

- Weight gain
- Increased risk of hypoglycemia

Endogenous Insulin and CV Risk

Based on observed associations between high <u>endogenous</u> insulin and CV risk in small clinical studies and large epidemiological studies mostly based on populations of subjects without diabetes

Robert W. Stout, MD, DSc, FRCP

Insulin and Atheroma
20-Yr Perspective

Many clinical studies have shown an increased insulin response to oral glucose in patients with ischemia of the heart, lower limbs, or brain. Hyperinsulinemia also occurs in patients with angiographically proved atherosclerosis without ischemia and thus appears to be related to arterial disease and not to be a nonspecific response to tissue injury. Fasting insulin levels and insulin responses to intravenous stimuli, including glucose, tolbutamide, and arginine, are normal, suggesting a gastrointestinal factor may be involved in the increased insulin response to oral glucose. In patients with atherosclerosis, insulin sensitivity appears to be normal or enhanced with respect to both glucose and lipid metabolism. Five population studies have shown that insulin responses to glucose are higher in populations at greater risk of cardiovascular disease. Many of the hyperinsulinemic populations also had upper-body obesity, hypertriglyceridemia, lower high-density lipoprotein (HDL) levels, and hypertension. These prospective studies support an independent association between hyperinsulinemia and ischemic heart disease, although their results differ in detail. Hyperinsulinemia is associated with raised triglyceride and decreased HDL cholesterol levels. Total and low-density lipoprotein (LDL) cholesterol is less closely related to hyperinsulinemia. Upper-body adiposity is associated (in separate studies) with coronary heart disease, diabetes, hyperinsulinemia, and hypertriglyceridemia. Insulin and blood pressure are closely related in both normotensive and hypertensive people. Although obesity and diabetes are often found in hypertensive people, hyperinsulinemia also occurs in nonobese nondiabetic hypertensive people. Thus, hyperinsulinemia is closely associated with a cluster of cardiovascular risk factors, i.e., hypertriglyceridemia, low HDL levels, hypertension, hyperglycemia, and upper-body obesity. There is a possibility that insulin has a role in the sex differences in ischemic heart disease incidence and their absence in diabetes, but additional work is required for its clarification. Long-term treatment with insulin results in lipid-containing lesions and thickening of the arterial wall in experimental animals. Insulin also inhibits regression of diet-induced experimental atherosclerosis, and insulin deficiency inhibits the development of arterial lesions. Insulin stimulates lipid synthesis in arterial tissue; the effect of insulin is influenced by hemodynamic factors and may be localized to certain parts of the artery. In physiological concentrations, insulin stimulates proliferation and migration of cultured arterial smooth muscle cells but has no effect on endothelial cells cultured from large vessels. Insulin also stimulates cholesterol synthesis and LDL binding in both arterial smooth muscle cells and monocyte macrophages. The multiple effects of insulin provide evidence of a potential direct role for this hormone in the development of atherosclerosis. The combination of clinical, epidemiological, and experimental evidence favors a direct role of insulin in the development of atherosclerosis. Insulin may also promote atherogenesis by its effects on lipids and blood pressure. If hyperinsulinemia has a role in atherogenesis, regular physical exercise and avoidance of obesity should be effective in preventing atherosclerosis. *Diabetes Care* 13:631–54, 1990

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The idea that excessive concentrations of insulin might contribute to the development of atherosclerosis appeared in the mid-1960s, and the evidence was first reviewed in an article published in 1969 (1). Since then, clinical and experimental data

Based on animal data of unknown or limited relevance to humans

Exogenous Insulin and CV Risk: Type 1 DM

Use of exogenous insulin to control glycemia in type 1 diabetes has not been associated with increased CV risk

- In DCCT improvement in glucose control over 6.5 years achieved by intensification of insulin therapy was associated with:
  - Non significant reduction in CV events
  - Improvement in lipid parameters
  - No increase in hypertension
- The EDIC study followed 93% of DCCT participants for an additional 10 years after intervention had stopped.
- After 17 years of follow-up subjects who had been randomized to intensive insulin therapy in DCCT had:
  - -A 42% (95% CI: 9-63) reduction in the risk of total cardiovascular events
  - -A 57% (95% CI: 12-79) reduction in the risk of nonfatal myocardial infarction, stroke or death from CV disease

Exogenous Insulin and CV Risk: Type 2 DM

Use of exogenous insulin to control glycemia in type 2 diabetes has not been associated with increased CV risk

- In the UKPDS study excess CV harm was not seen in the subgroup of individuals randomized to insulin to achieve tight glucose control
- In the first DIGAMI study (DIGAMI-1) randomization to intensive glucose control with insulin immediately post-myocardial infarction in subjects with type 2 diabetes was observed to reduce mortality
- This initial finding was not confirmed in the similarly designed DIGAMI 2 study
- Neither study suggested excess CV harm with insulin use in this high risk population
- A published report for the ORIGIN study showed that normalization of plasma glucose using insulin glargine in 12,537 subjects with dysglycemia at high risk of CV events was reported to not be associated with either a beneficial or harmful effect on major adverse cardiovascular events over a mean follow-up time of 6.5 years compared to standard of care therapy [Hazard Ratio for MACE 1.02 (95% CI: 0.94-1.11)]

Cardiovascular Risk Assessment

- Patients with diabetes are at increased risk of cardiovascular disease
- In December 2008, FDA issued a guidance outlining an approach to cardiovascular risk assessment for investigational new drugs intended for the treatment of type 2 diabetes
  - Pre-market CV safety analysis should demonstrate a "reassuring" point estimate of risk
  - Pre-market CV safety analysis should definitively exclude an 80% risk
  - Post-market CV safety analysis should definitively exclude a 30% risk increase

Cardiovascular Risk Assessment

Applicants developing novel injectable insulins were not required to exclude a pre-defined level of risk in the Guidance document

During development, applicants are asked to prospectively define, collect, adjudicate and analyze CV events throughout development

Novo Nordisk was given the following advice at the End of Phase 2 meeting which took place in January 2009.

FDA Response: At the present time, we are not holding inhaled or injectable insulins to the 95% confidence interval upper bound values of 1.8 and 1.3 described in the December 2008 guidance document. Nonetheless, you should still collect and analyze the cardiovascular data from your clinical trials as outlined in that guidance document, perform statistical testing on your cardiovascular data, and report the values in your NDA submission. We recommend that you submit with your phase 3 protocols, a detailed plan describing how you will capture and analyze cardiovascular adverse events of interest in each trial and across your development programs.

Purpose of the Meeting

Novo Nordisk agreed with FDA recommendations

A detailed protocol outlining the planned statistical analyses of cardiovascular data across the degludec program was received and reviewed in early 2010

Cardiovascular safety analyses submitted with the NDA were based on 5444 patient-years of exposure

A signal suggesting degludec was associated with cardiovascular harm was observed in analyses performed by FDA on the original dataset

Data for most of the planned long-term controlled extensions of Phase 3 trials were not available in the original dataset

The applicant was asked to update the original cardiovascular analysis with these additional data in April 2012

Purpose of the Meeting

An analysis based 7716 patient-years of exposure was repeated on updated data received in May 2012

The signal of harm suggesting degludec could increase the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and unstable angina relative to comparators was again seen in this analysis

The uncertainty around the risk estimate suggested the risk could be as high as 93% or alternatively that degludec could reduce the risk by 12%

We have convened an advisory committee meeting today to discuss these findings

I want to thank all the members of the advisory committee meeting for agreeing to participate and look forward to a productive advisory committee meeting

Endocrinologic and Metabolic Drugs Advisory Committee

Insulin Degludec
Insulin Degludec/Insulin Aspart

Clinical Safety

Karim Anton Calis, Pharm.D., M.P.H.
Clinical Reviewer

Division of Metabolism and Endocrinology Products

November 8, 2012
Silver Spring, Maryland

Outline

- Introduction
- Safety Database
- Trial Population
- Major Safety Findings
- CV Meta-analysis
- Assessment of CV Safety Methodology

Introduction

- Insulin degludec is a long-acting human insulin analog produced by recombinant DNA technology
- Two other long-acting insulin analog products—insulin glargine (Lantus) and insulin detemir (Levemir)—are currently approved for use in the United States

Introduction

- Important **safety considerations** with insulin products include:
  - Hypoglycemia
  - Weight gain
  - Immunogenicity and allergic reactions
  - Injection-site reactions
  - Cancer risk (theoretical)
    - Based on observational studies
    - Evidence is inconclusive due to methodological limitations
    - No definitive data to suggest actual risk

Insulin Abbreviations

IDeg	Insulin Degludec
IDegAsp	Insulin Degludec/Insulin Aspart
IDeg + IDegAsp	Pooled data across both programs
IGlar	Insulin Glargine
IDet	Insulin Detemir
IAsp	Insulin Aspart

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Safety Database

STUDY TYPE	IDeg*	IDegAsp#	IDeg + IDegAsp
Clinical Pharmacology	25	13	38
Therapeutic Exploratory	3	3	6
Therapeutic Confirmatory (Phase 3)	**11**	**5**	**16**
Other	2	-	2
TOTAL	41	21	62

* 6 trials were still ongoing at NDA submission (5 were extensions)
\# 2 trials were still ongoing at NDA submission (1 was an extension)

Safety Database: Phase 3 Trials

- Safety evaluation was based largely on the therapeutic confirmatory trials:
  - Accounted for majority of exposure
  - Randomized and controlled
  - Had longest duration of controlled exposure
  - Evaluated the to-be-commercialized formulations
- Non-inferiority, open-label, treat-to-target design
- IGlar was most commonly used comparator (> 70%)

Safety Database: Phase 3 Trials

Trial Number	Treatment Arms	Ratio	N	Population	Duration (weeks)
3579 + 3643	**IDeg** vs. IGlar	3:	1,030	**T2DM**	52 + **52**
3580	**IDeg**	1:	458	**T2DM**	26
3582 + 3667	**IDeg** vs. IGlar	3:	1,006	**T2DM**	52 + **26**
3583 + 3644	**IDeg** vs. IGlar	3:	629	T1DM	52 + **52**
3585 + 3725	**IDeg** vs. IDet	2:	456	T1DM	26 + **26**
3586	**IDeg** vs. IGlar	2:	435	**T2DM**	26
3668	**IDeg**, **IDeg Flex**	1:1:1	687	**T2DM**	26
3672	**IDeg** vs. IGlar	1:	460	**T2DM**	26
3718	**IDeg** vs. IGlar	1:	467	**T2DM**	26
3724	**IDeg** vs. IGlar	1:	460	**T2DM**	26
3770 + Ext.	**IDeg**, **IDeg Flex**	1:1:1	493	T1DM	26 + **26**
3590 + 3726	**IDegAsp** vs. IGlar	1:1	530	**T2DM**	26 + **26**
3592	**IDegAsp** vs. BIAsp	1:1	447	**T2DM**	26
3593	**IDegAsp** vs. IGlar	1:1	465	**T2DM**	26
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	T1DM	26 + **26**
3597	**IDegAsp** vs. BIAsp	2:1	424	**T2DM**	26

Safety Database: Exposure

TYPE OF EXPOSURE	IDeg N (%)	IDegAsp N (%)	IDeg + IDegAsp N
All Exposures	5624	2031	7510*
Phase 3 Exposure T2DM *Insulin-naïve*	**4275** 3173 (74%) 1964 (61%)	**1360** 998 (73%) 265 (27%)	**5647#** 4171 (74%) 2229 (53%)
≥ 6 months	3758 (88%)	1181 (87%)	4939
≥ 12 months	1635 (38%)	235 (17%)	1870

*A few subjects in crossover clinical pharmacology studies were exposed to both IDeg and IDegAsp
#Safety analysis set

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Trial Population: Characteristics

	IDeg + IDegAsp N = 5647	COMPARATORS N = 3312
Male Sex	56%	55%
Mean Age (y)	54 + 13 20%	55 + 12 20%
Race White Black Asian Other	 70% 5% 23% 2%	 69% 5% 24% 2%
Ethnicity Hispanic/Latino	 8.7%	 9.8%
Type 2 Diabetes Insulin naïve	74% 53%	80% 59%
Mean BMI (kg/m^2)	29 +	30 + 5
Mean Duration of Diabetes (y)	13	12
Mean HbA1c (%)	8.2	8.3
U.S. Region	31%	30%

Trial Population: Characteristics

	IDeg + IDegAsp N = 5647	COMPARATORS N =3312	T2DM Only N = 6834
Prior Cardiovascular Disease	16.0%	15.0%	18.8%
Hypertension	59.6%	62.5%	70.2%
Lipid Disorders			
Dyslipidemia	18.1%	19.7%	21.6%
Hypercholesterolemia	11.9%	12.3%	12.5%
Hyperlipidemia	25.6%	25.2%	28.2%
Renal Insufficiency			
Mild (CrCl > 50-80 mL/min) or Moderate (CrCl > 30-50 mL/min)	15.9%	15.3%	17.2%
Concomitant Medications			
Aspirin	31.0%	33.2%	36.0%
Beta-blocker	17.8%	17.5%	21.5%
Lipid-lowering drugs	52.3%	55.1%	59.7%
R/A system inhibitors	53.8%	55.8%	62.1%

R/A = renin-angiotensin

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Major Safety Findings

Safety Findings				
	IDeg N = 4275	**Comparator N = 2269**	**IDegAsp N = 1360**	**Comparator N = 1037**
Death	**14**	**7**	**4**	**2**
Rate (per 100 PYE)	0.6	0.6	—	—
T1DM / T2DM	3 / 11	1 / 6	0 / 4	0 / 2
Male / Female	11 / 3	6 / 1	3 / 1	2 / 0
Age Range (y)	46 - 72	26 - 73	41 - 85	59 - 71
SAE	**337 (7.9%)**	**147 (6.5%)**	**115 (8.5%)**	**80 (7.7%)**
Rate (per 100 PYE)	15.1	13.5	19.9	18.7
Rate T1DM	15.5	14.9	24.3	19.2
Rate T2DM	14.9	13.1	17.0	18.6
Dropouts Due to AE	**99 (2.3%)**	**30 (1.3%)**	**25 (1.8%)**	**16 (1.5%)**
Rate (per 100 PYE)	4.7	2.4	2.8*	2.4*
Rate T1DM	5.2	1.4	—	—
Rate T2DM	4.5	2.7	—	—

•Rates presented are for SAEs, which accounted for the majority of withdrawals due to AEs in IDegAsp program
PYE = patient years of exposure

Major Safety Findings

SAE & Dropouts Due to AEs

- Hypoglycemia, Cardiac disorders, and Infections were most common SAEs
- Within the Cardiac disorders SOC, splitting of preferred terms may have obscured potential differences in CV events
- Hypoglycemia accounted for the most dropouts due to AEs
- Types and rates of SAEs and AEs leading to withdrawal were generally similar across trials and between IDeg or IDegAsp and comparators

CV-Related Safety Parameters

- Lipids
  - Total-C, LDL-C, HDL-C, Triglycerides
- Cardiovascular Biomarkers
  - hs-CRP and brain natriuretic peptide (NT proBNP)
    (measured in *two* Phase 3 IDeg trials in subjects with T2DM)
- Biochemistry
  - Electrolytes, creatinine, liver parameters
- Vital Signs
  - HR, BP
- 12-lead ECG
  - QTc interval was measured in *one* Phase 3 trial
- Body Weight

CV-Related Safety Parameters: Body Weight

Body Weight (kg)				
	IDeg N = 4275	**Comparator N = 2269**	**IDegAsp N = 1360**	**Comparator N = 1037**
Baseline Body Weight*				
Mean (SD)	84.2 (19)	85.8 (19.2)	78.2 (17.7)	79.4 (18.0)
Body Weight Change from Baseline (Week 26)				
N	3746	1998	1179	907
Mean (SD)	2.0 (3.6)	1.4 (3.6)	2.0 (3.4)	1.6 (3.3)
Body Weight Change from Baseline (Week 52; LOCF)				
N	1991	662	362	180
Mean (SD)	2.7 (4.5)	2.7 (4.4)	2.8 (4.2)	1.2 (4.1)

*Baseline mean body weight of 75.9 kg and 87.5 kg for all subjects with T1DM and T2DM, respectively

CV-Related Safety Parameters

- No substantial on-treatment changes or categorical shifts from baseline
- No major differences between IDeg or IDegAsp and comparators
- No important differences noted across age, race, ethnicity, BMI, duration of diabetes, or study region

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CV Meta-Analysis

- **Objective:** Assess CV risk potential of IDeg and IDegAsp
- **Plan:** Evaluate CV safety data from pooled IDeg and IDegAsp Phase 3 trials and their controlled extensions
- **Goal:** Demonstrate that these new insulin products are not associated with an increased risk of major adverse CV events (MACE) compared to active controls

CV Meta-Analysis

- Primary Endpoint
- Definition of MACE
- Event Capture and Review
- Adjudication
- Data Quality
- Trials Included

Primary Endpoint

- The primary endpoint was a pre-defined **MACE**, which was analyzed in the primary analysis as the time in days from first trial drug administration to ***first*** adjudicated MACE
- The analysis of MACE was defined as events with an onset on or after the first day of exposure to randomized treatment but **not later than 7 days** after the last study day

Definition of MACE

- The applicant defined MACE as a **composite endpoint** including the following:
  - Unstable angina pectoris (UAP)
  - Nonfatal myocardial infarction (MI)*
  - Nonfatal stroke
  - CV death

FDA defines strict MACE as excluding UAP and will refer to **"MACE"** *for the strict MACE definition which* **excludes** *UAP and to* **"MACE+"** *for the applicant's original definition which* **includes** *UAP*

* Thygesen K, et al. "Universal definition of myocardial infarction." *J Am Coll Cardiol* 2007 Nov 27;50(22):2173-95. All trial protocols included a list of diagnoses (international classification of diseases [ICD]-10 codes), that were expected to be linked to ACS, stroke, or cardiovascular death.

Event Capture and Review

- MACE were required to be reported as medical events of special interest (MESI)
- A thorough collection procedure was established for all CV MESI
- Events reported as potential CV adverse events but not initially classified as MESI were also evaluated through a pre-defined, standardized process
- The applicant planned to capture additional event information whether or not assessed as SAE

Event Capture and Review

- An internal CV Events Evaluation Group (CEEG) assessed all potential events and communicated directly with investigators
- All verified MESI were sent for adjudication
- 39 of the 185 total events sent for adjudication were not initially reported as MESI but were identified by CEEG using other extensive screening mechanisms
- Events not initially appearing to meet the established criteria were subsequently evaluated by an M.D. from Novo Nordisk Global Safety

Adjudication

- All collected CV MESI and suspected CV MESI were adjudicated in accordance with a pre-defined set of diagnostic criteria
- This was accomplished by an external, blinded independent adjudication group referred to as the Cardiovascular Event Committee (CEC)
- CEC adjudicated events based on pre-defined definitions and classifications detailed in a charter describing the adjudication process
- CEC was composed of a cardiologist as the chair, two additional cardiologist members, and one neurologist

Adjudication

- Two primary adjudicators reviewed each case
- Reviews were independent and ongoing
- CEC chair served as tie breaker if necessary
- The outcome of the adjudication process was a list of MACE

Data Quality

- CEEG reviewed source documents from study sites to verify their accuracy and completeness
- All CEC reviews and assessments were captured and audited in compliance with the ICH guidelines for Good Clinical Practice (GCP) and 21 CFR Part 11

Trials Included

- As per the statistical analysis plan, the applicant intended to include all completed **Phase 3 trials** and their ***controlled*** **extensions**
- At the time of NDA submission, only one extension trial (Trial 3645) had been completed

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Assessment of CV Safety Methodology

- The original and updated analyses of CV risk with IDeg and IDegAsp have raised concern because the data consistently trended toward harm
- A plausible mechanism and potential risk factors have not been identified
- No baseline or on-treatment differences were noted in key characteristics or parameters known to potentially influence CV safety
- CV safety data were not derived from a dedicated CV outcomes trial (i.e., one in which CV outcomes are the primary endpoints)

Assessment of CV Safety Methodology

- Validity of the CV safety data is supported by the following:
  - CV risk evaluation was pre-planned, and detailed procedures were developed and strictly followed
  - Applicant used consistent, pre-specified methods; and endpoints were objective, valid, and pre-defined
  - A data analysis plan was pre-specified
  - Data were collected prospectively
  - Trials were large and controlled

Assessment of CV Safety Methodology

- Validity of the CV safety data is supported by the following:
  - Extensions were ***controlled*** and applied the same methodology and rigor as the main trials and served to augment the safety database and inform long-term safety
  - Retention rate into the controlled extensions was high
  - Events were well-defined a priori
  - MACE were considered events of special interest
  - Detailed methods were developed for capturing and assessing MACE
  - Events were adjudicated by an independent, blinded experts

Summary

- A CV safety signal of increased risk of MACE has been detected in the degludec development programs
- The signal appears to be credible and consistently points to the potential for harm with degludec over comparators

IDeg/IDegAsp Cardiovascular Meta-Analysis

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 8, 2012

Bo Li, PhD

Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

- **Trial Databases**
- Statistical Methods
- Results
- Summary

Trial List in Original Database

Trial ID	Treatment Arms	Ratio	N	Population	Duration (weeks)
3579	**IDeg** vs. IGlar	3:1	1,030	T2DM	52
3580	**IDeg** vs. sitagliptin	1:1	447	T2DM	26
3582	**IDeg** vs. IGlar	3:1	992	T2DM	52
3583	**IDeg** vs. IGlar	3:1	629	T1DM	52
3585	**IDeg** vs. IDet	2:1	455	T1DM	26
3586	**IDeg** vs. IGlar	2:1	435	T2DM	26
3668	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	687	T2DM	26
3672	**IDeg** vs. IGlar	1:1	457	T2DM	26
3718	**IDeg** vs. IGlar	1:1	467	T2DM	26
3724	**IDeg** vs. IGlar	1:1	459	T2DM	26
3770	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	493	T1DM	26
3590	**IDegAsp** vs. IGlar	1:1	529	T2DM	26
3592	**IDegAsp** vs. BIAsp	1:1	446	T2DM	26
3593	**IDegAsp** vs. IGlar	1:1	463	T2DM	26
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	T1DM	26 + 26
3597	**IDegAsp** vs. BIAsp	2:1	422	T2DM	26

Trial List in Original Database

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3724	**IDeg** vs. IGlar	1:1	459	T2DM	26
3770	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	493	T1DM	26
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3592	**IDegAsp** vs. BIAsp	1:1	446	T2DM	26
3593	**IDegAsp** vs. IGlar	1:1	463	T2DM	26
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	T1DM	26 + 26
3597	**IDegAsp** vs. BIAsp	2:1	422	T2DM	26

Trial List Updated Database

Trial ID	Treatment Arms	Ratio	N	Population	Duration (weeks)
3579 + 3643	**IDeg** vs. IGlar	3:1	1,030	T2DM	52 + **52**
3580	**IDeg** vs. sitagliptin	1:1	447	T2DM	26
3582 + 3667	**IDeg** vs. IGlar	3:1	992	T2DM	52 + **26**
3583 + 3644	**IDeg** vs. IGlar	3:1	629	T1DM	52 + **52**
3585 + 3725	**IDeg** vs. IDet	2:1	455	T1DM	26 + **26**
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3718	**IDeg** vs. IGlar	1:1	467	T2DM	26
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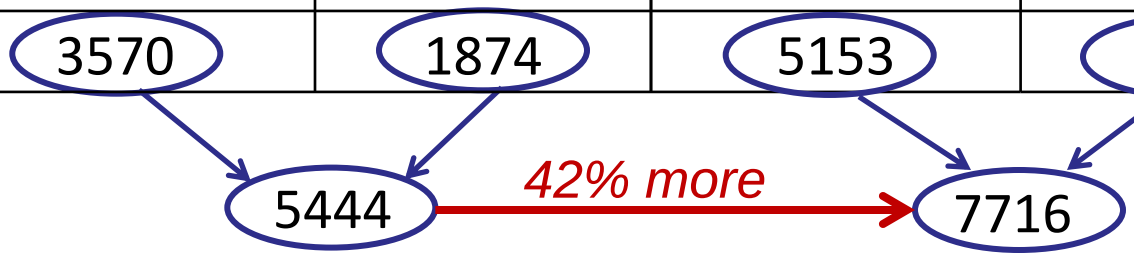
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	T1DM	26 + 26
3597	**IDegAsp** vs. BIAsp	2:1	422	T2DM	26
3896	**IDegAsp** vs. IGlar	1:1	296	T2DM	**26**

Original vs. Updated Database

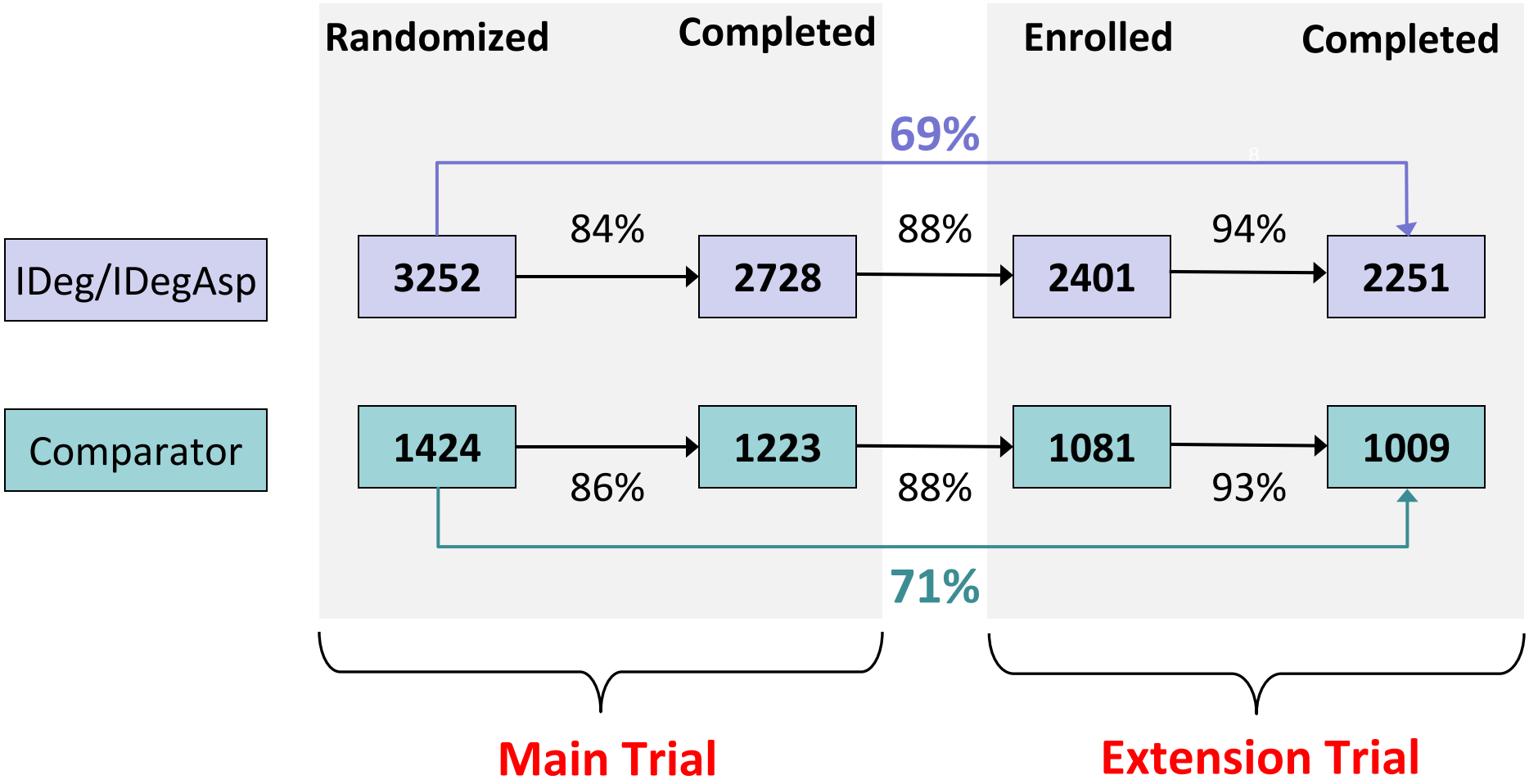
- **Updated database is robust and appropriate** for the evaluation of CV safety
  - **Pre-specification in SAP** to include extension trial data
  - Updated database provides **40% additional PYE**
  - Updated database provides **60% more CV events**
  - **High and balanced retention rates** in extension trials
  - **Baseline characteristics** for subjects that enrolled in extension trials are **similar** to those for subjects that enrolled in main trials

Trial Databases

	Original Database		Updated Database	
Cut-off date	Jan 31, 2011		May 1, 2012	
# of trials	16		17	
	IDeg/IDegAsp	**Comparator**	**IDeg/IDegAsp**	**Comparator**
N	5647	3312	5794	3461
PYE	3570	1874	5153	2563



Patient Retention in Trials w/ext



Demographics (Trials w/ext)

	Randomized (N = 4676)	Enrolled in extension (N = 3482)
Age, yrs	51	51
Sex, % Female	44%	43%
Race		
White	83%	83%
Black	5%	4%
Asian	10%	11%
Other	2%	2%
US	41%	39%

Baseline Characteristics (Trials w/ext)

	Randomized (N = 4676)	Enrolled in extension (N = 3482)
BMI, kg/m²	29	29
Duration of diabetes, yrs	13.8	13.6
HbA1c, %	8.2	8.1
Type I Diabetes	45%	45%
Hypertension	53%	54%
Prior CV disease	14%	14%
Renal impairment	11%	11%
Concomitant medications		
Lipid-lowering drug	47%	47%
Aspirin	29%	29%
Beta-blocker	16%	16%
Renin-angiotensin system inhibitors	49%	50%

Outline

- Trial Database
- **Statistical Methods**
- Results
- Summary

Pre-specified Analysis

- **Objective**
  - Investigate the CV profile of IDeg/IDegAsp
  - ***No formal requirement to rule out risk margin of 1.8***
- **Primary analysis population**
  - Full Analysis Set (FAS): ***All randomized patients*** excluding a small number of subjects (N=36)
- **Trial Set**
  - ***Main trials plus extensions***
- **Comparison**
  - ***IDeg/IDegAsp vs. All Comparators***

Composite Endpoints

- Definitions of Major Adverse Cardiovascular Event Endpoint
  - **MACE+**: ***pre-specified*** primary composite endpoint
    - *Cardiovascular death*
    - *Non-fatal myocardial infarction*
    - *Non-fatal stroke*
    - *Unstable Angina Pectoris (**UAP**)*
  - **MACE:** ***requested*** primary composite endpoint
    - *Excludes UAP*
- Event ascertainment: **7 days** or 30 days after treatment discontinuation
- All events prospectively adjudicated

Analysis Methods

- Pre-specified primary analysis
  - ***Time-to-event*** (Hazard Ratio, ***HR***): *Cox model stratified by trial*
- Secondary analysis
  - ***Risk Difference*** *(**RD**): Mantel-Haenszel stratified by trial*
  - ***Incidence Rate Difference*** (***IRD***):*Mantel-Haenszel stratified by trial*
- Trial-level subgroup analysis: **Time-to-event** (**HR**)
  - *by type of diabetes*
  - *by comparator (IGlar-controlled)*
  - *by IDeg treatment*

Outline

- Trial Database
- Statistical Methods
- **Results**
- Summary

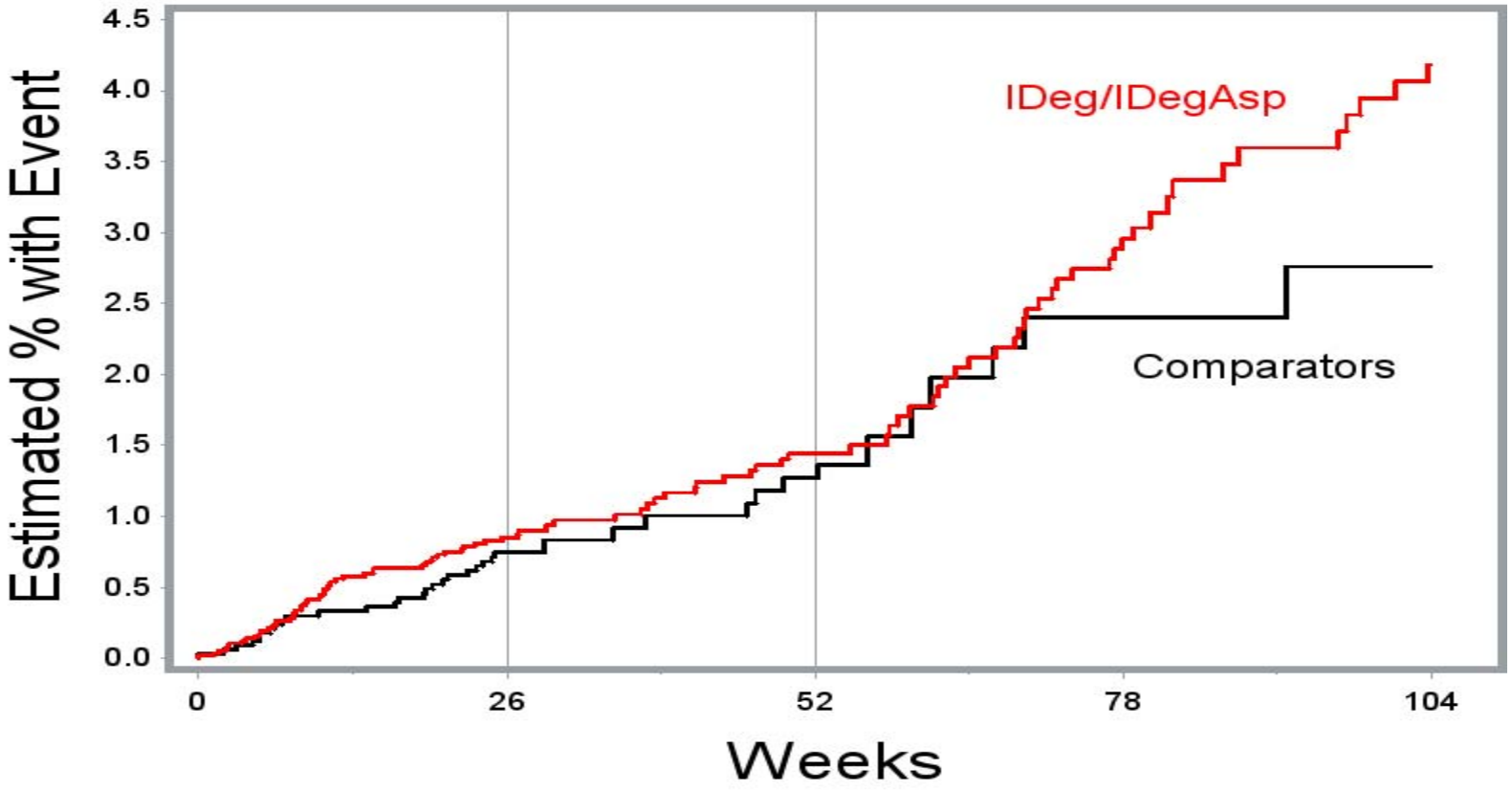
Summary Results of MACE+

	Original Database		Updated Database	
	IDeg/IDegAsp (N = 5647) [PYE = 3569.9]	Comparator (N = 3312) [PYE = 1873.9]	IDeg/IDegAsp (N = 5794) [PYE = 5153.6]	Comparator (N = 3461) [PYE = 2562.7]
MACE+	53 [14.8]	27 [14.4]	95 [18.4]	37 [14.4]
MI	20 [5.6]	7 [3.7]	34 [6.6]	9 [3.5]
Stroke	11 [3.1]	4 [2.1]	24 [4.6]	6 [2.3]
CV Death	8 [2.2]	4 [2.1]	12 [2.3]	6 [2.3]
UAP	14 [3.9]	12 [6.4]	25 [4.8]	16 [6.2]

Results are reported as counts [incident rate per 1,000 PYE]

Censor: 7 days

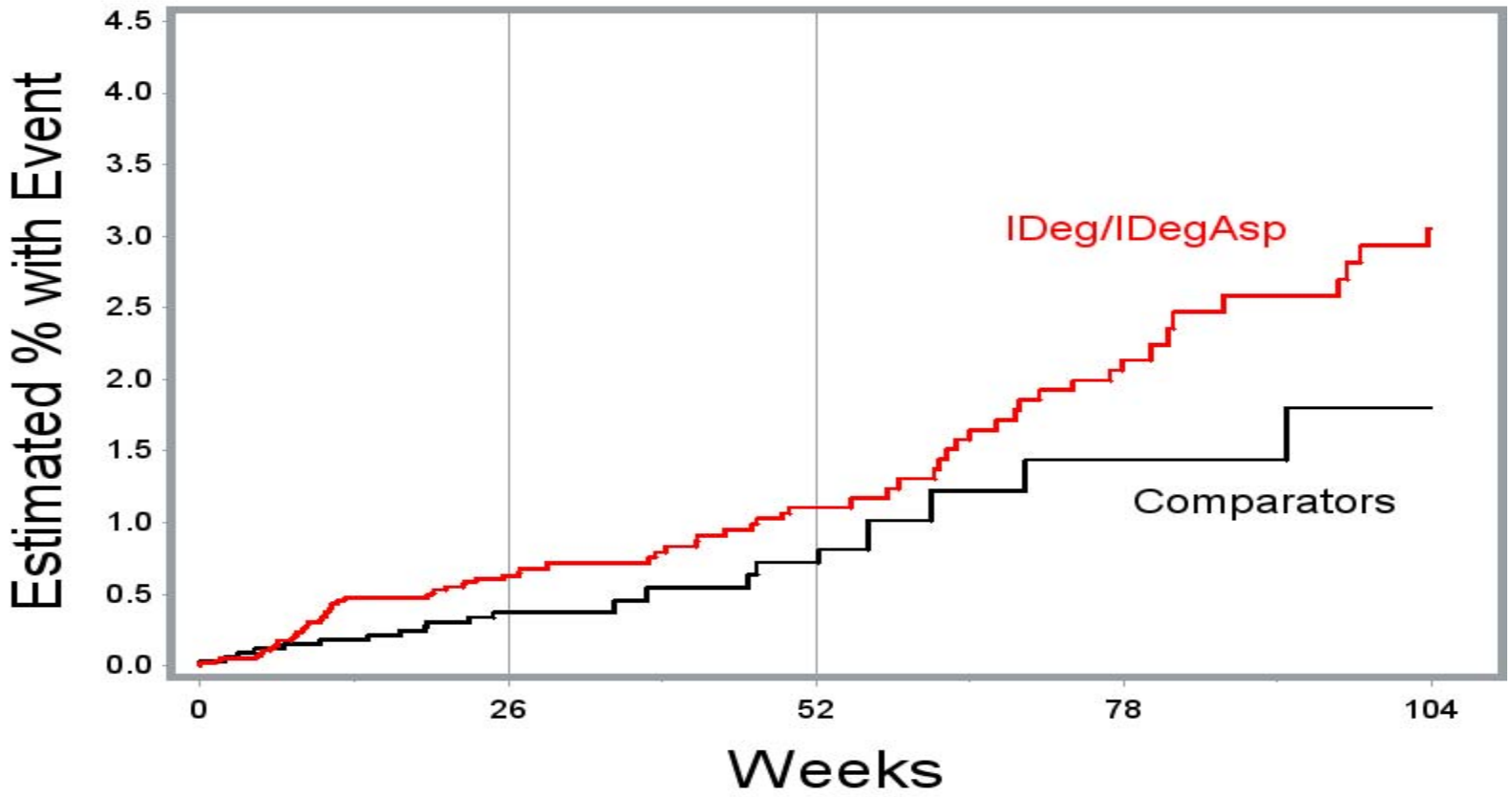
K-M Plot of MACE+



N at risk:					
IDeg/IDegAsp	5768	5056	2491	1378	811
Comparators	3446	3038	1107	458	265

Updated DB, Censor: 7 days

K-M Plot of MACE



N at risk:					
IDeg/IDegAsp	5768	5065	2500	1392	821
Comparators	3446	3048	1109	460	265

Updated DB, Censor: 7 days

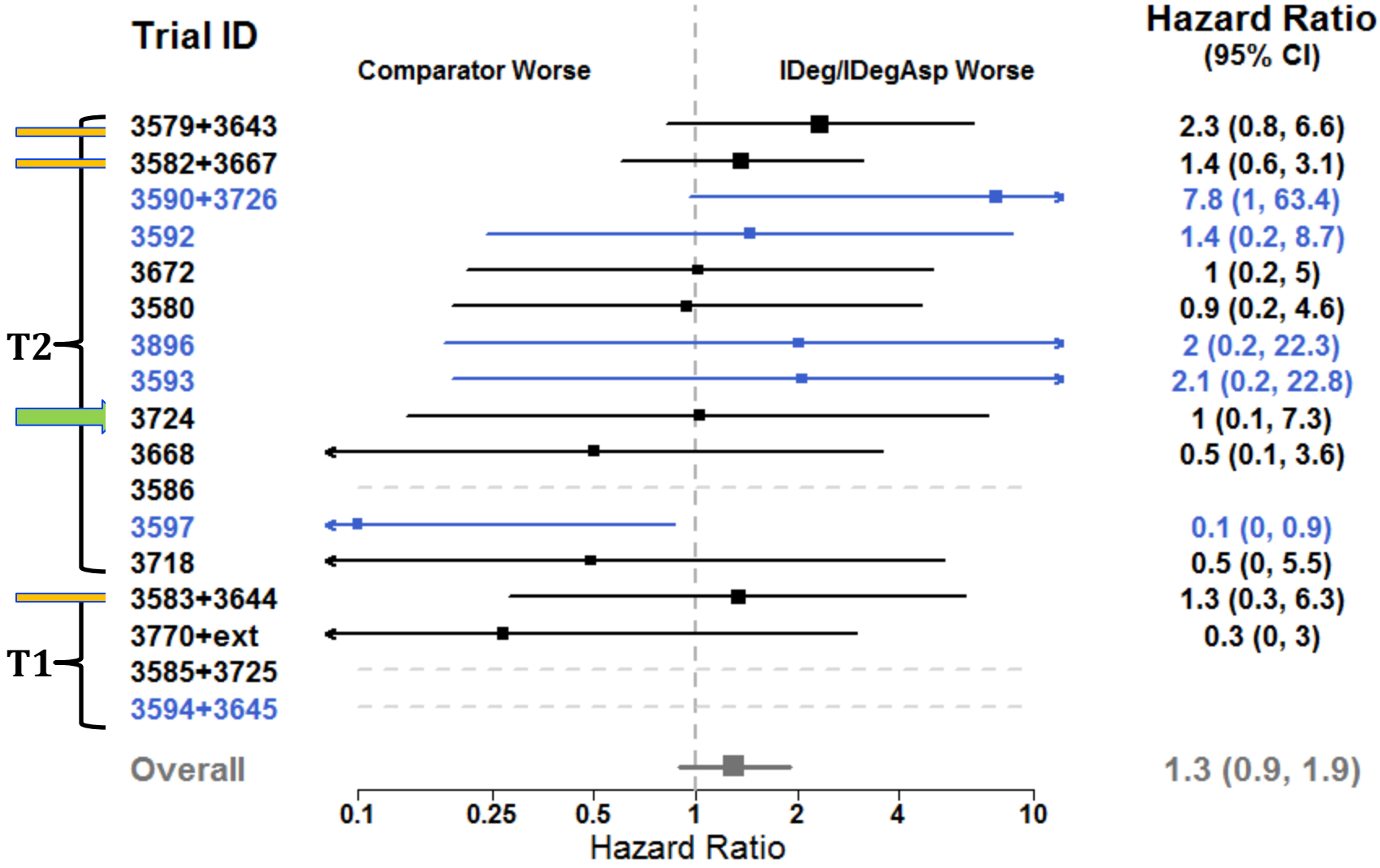
Primary Analysis Result

	IDeg/IDegAsp (*N* = 5794)	Comparator (*N* = 3461)
MACE+		
Events	95	37
HR (95% CI)	**1.30 (0.88, 1.93)**	
MACE		
Events	70	21
HR (95% CI)	**1.67 (1.01, 2.75)**	

Cox model stratified by trial

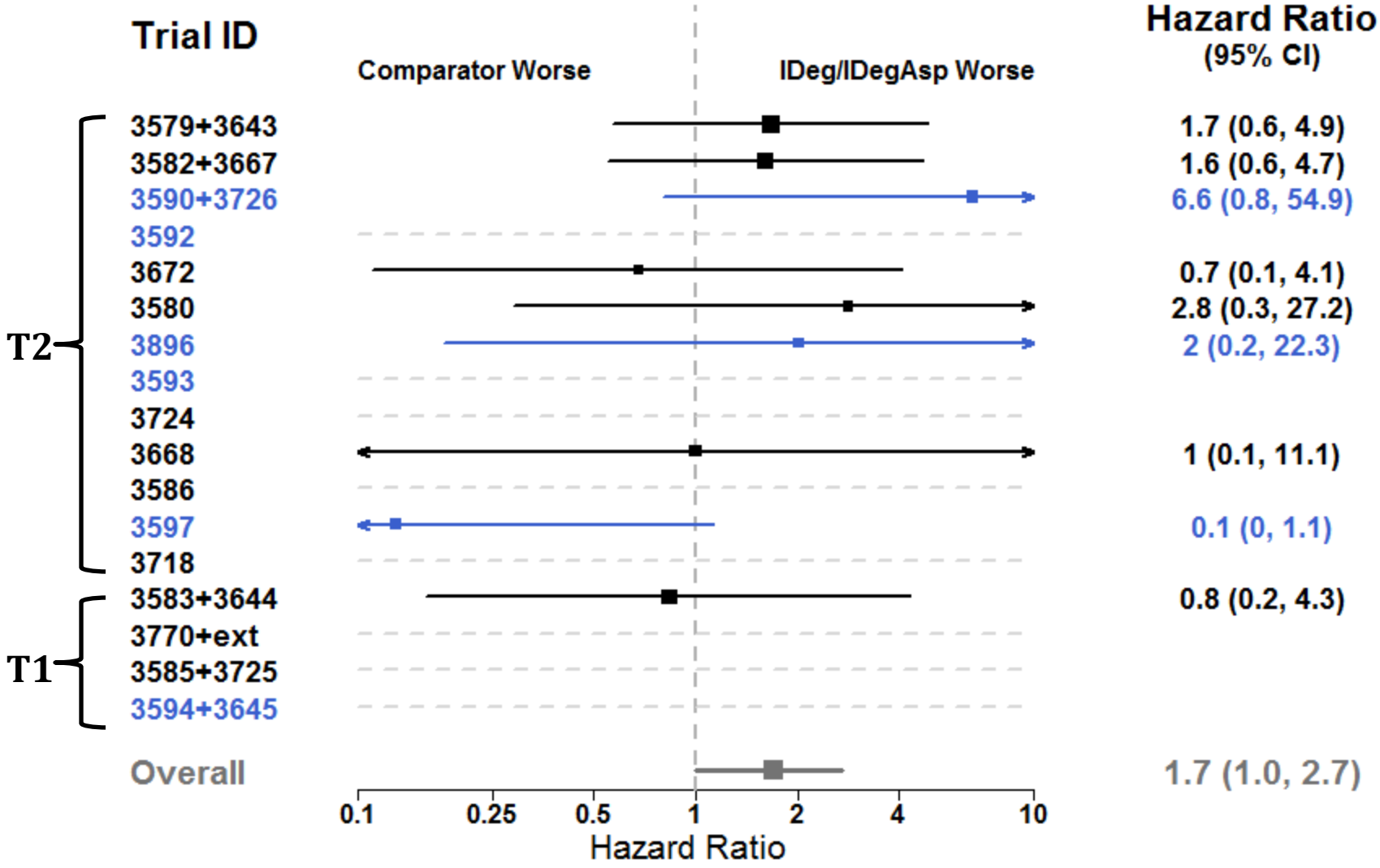
Updated DB, Censor: 7 days

Time-to-Event Forest Plot (MACE+)



days

Time-to-Event Forest Plot (MACE)



days

Secondary Analysis Results

- Primary analysis
  - **MACE+:** HR 1.30 (0.88, 1.89)
  - **MACE:** HR 1.67 (1.01, 2.75)
- **Secondary analysis**

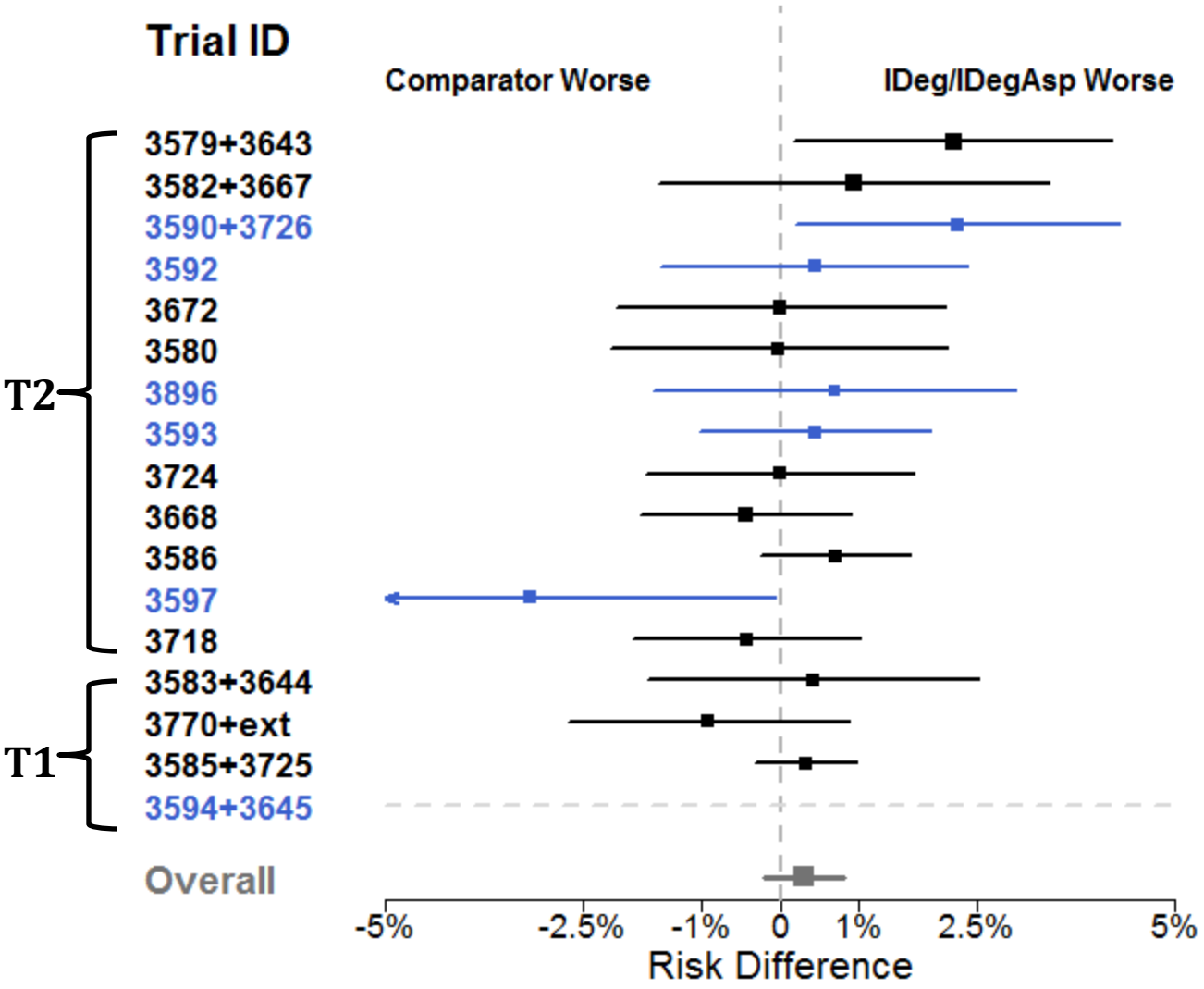
	Risk Difference (%)		Incidence Rate Difference *	
	Estimate	**95% CI**	**Estimate**	**95% CI**
MACE+	0.33	(-0.15, 0.81)	4.27	(-1.84, 10.4)
MACE	0.42	(0.03, 0.82)	5.41	(0.37, 10.5)

*: Per 1,000 PYE

Mantel-Haenszel

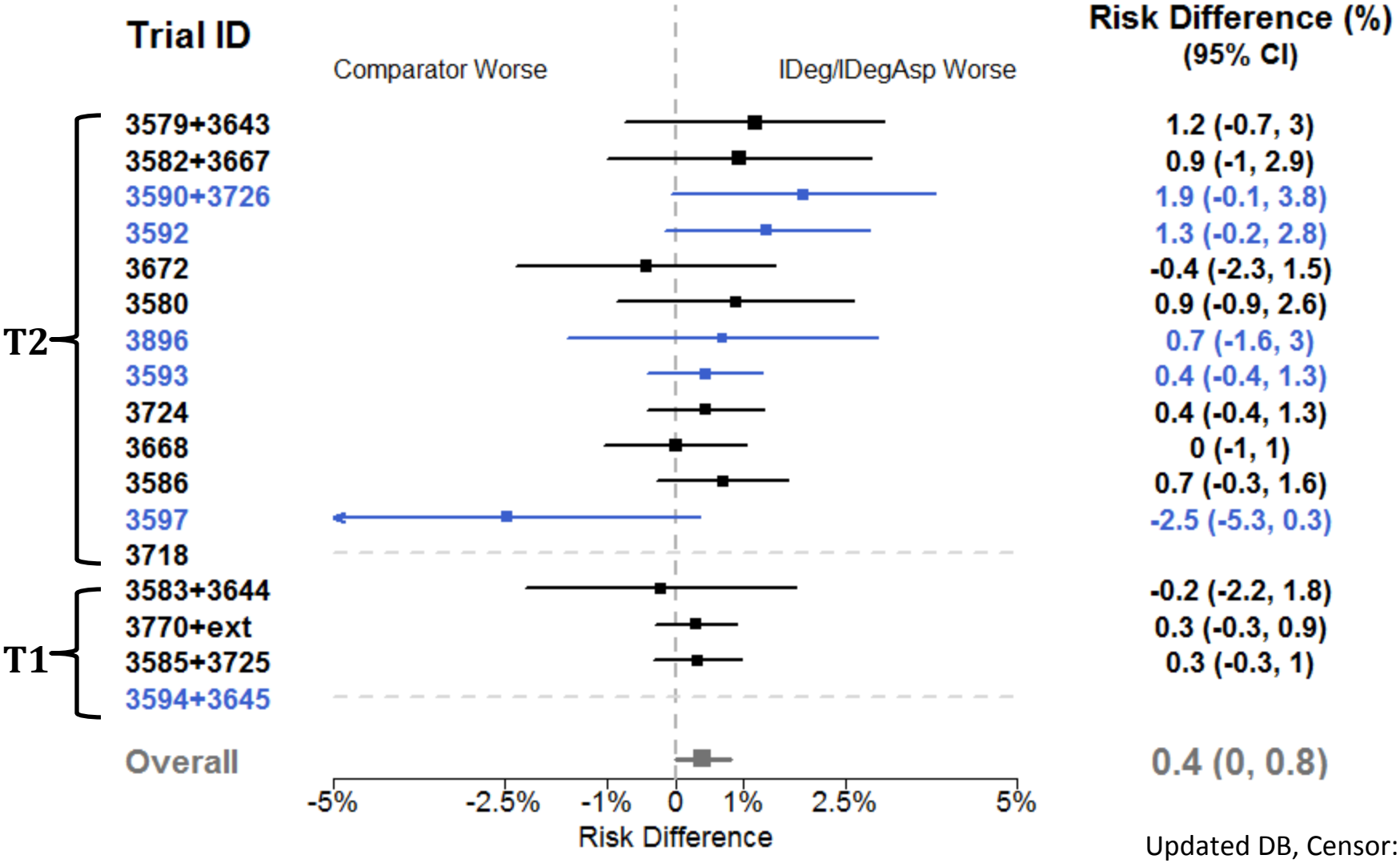
Updated DB, Censor: 7 days

RD Forest Plot (MACE+)



Updated DB, Censor: 7 days

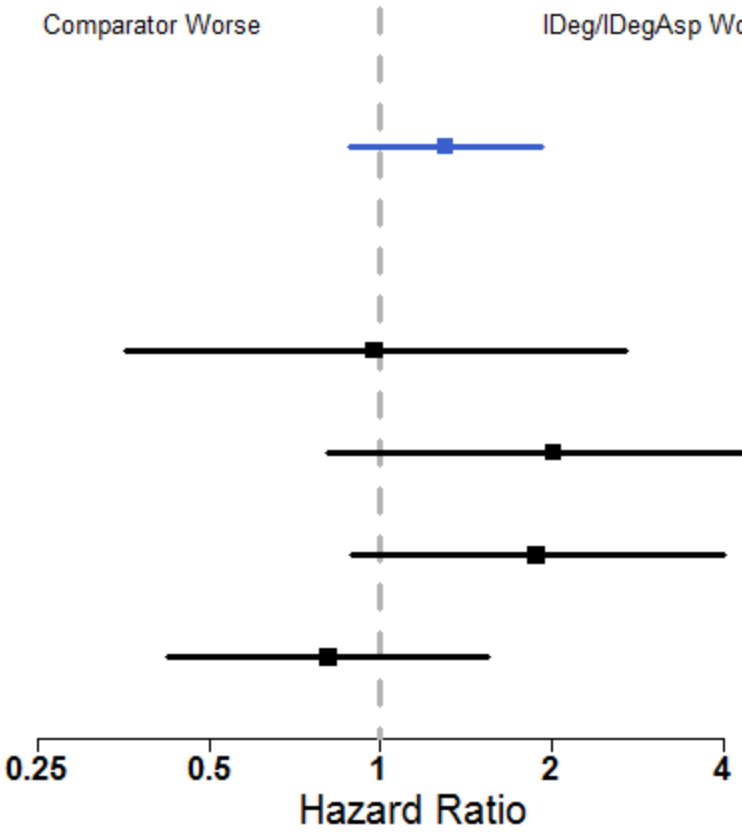
RD Forest Plot (MACE)



Updated DB, Censor: 7 days

MACE+ Components

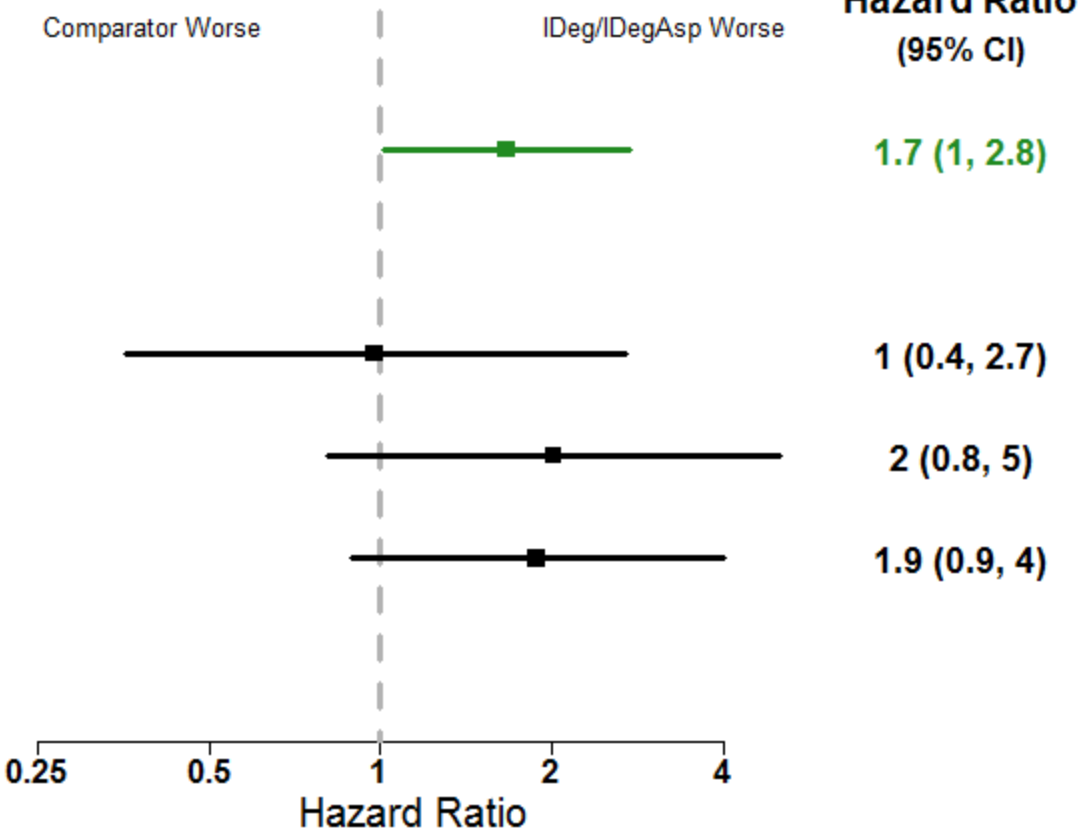
	IDeg/IDegAsp (N = 5794) Events (%)	Comparators (N = 3461) Events (%)	Hazard Ratio (95% CI)
MACE+	95 (1.6)	37 (1.1)	1.3 (0.9, 1.9)
CV Death	12 (0.2)	6 (0.2)	1 (0.4, 2.7)
Stroke	24 (0.4)	6 (0.2)	2 (0.8, 5)
MI	34 (0.6)	9 (0.3)	1.9 (0.9, 4)
UAP	25 (0.4)	16 (0.5)	0.8 (0.4, 1.5)



Updated DB, Censor: 7 days

MACE Components

	IDeg/IDegAsp (N = 5794) Events (%)	Comparators (N = 3461) Events (%)	Hazard Ratio (95% CI)
MACE	70 (1.2)	21 (0.6)	1.7 (1, 2.8)
CV Death	12 (0.2)	6 (0.2)	1 (0.4, 2.7)
Stroke	24 (0.4)	6 (0.2)	2 (0.8, 5)
MI	34 (0.6)	9 (0.3)	1.9 (0.9, 4)



Updated DB, Censor: 7 days

Trials by Type of Diabetes

Trial ID	Treatment Arms	Ratio	N	Population	Duration (weeks)
3579 + 3643	**IDeg** vs. IGlar	3:1	1,030	T2DM	52 + 52
3580	**IDeg** vs. sitagliptin	1:1	447	T2DM	26
3582 + 3667	**IDeg** vs. IGlar	3:1	992	T2DM	52 + 26
3583 + 3644	**IDeg** vs. IGlar	3:1	629	**T1DM**	52 + 52
3585 + 3725	**IDeg** vs. IDet	2:1	455	**T1DM**	26 + 26
3586	**IDeg** vs. IGlar	2:1	435	T2DM	26
3668	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	687	T2DM	26
3672	**IDeg** vs. IGlar	1:1	457	T2DM	26
3718	**IDeg** vs. IGlar	1:1	467	T2DM	26
3724	**IDeg** vs. IGlar	1:1	459	T2DM	26
3770 + Ext.	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	493	**T1DM**	26 + 26
3590 + 3726	**IDegAsp** vs. IGlar	1:1	529	T2DM	26 + 26
3592	**IDegAsp** vs. BIAsp	1:1	446	T2DM	26
3593	**IDegAsp** vs. IGlar	1:1	463	T2DM	26
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	**T1DM**	26 + 26
3597	**IDegAsp** vs. BIAsp	2:1	422	T2DM	26
3896	**IDegAsp** vs. IGlar	1:1	296	T2DM	26

Type 1 Diabetes (4 trials)

	MACE+		MACE	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
N	1469	656	1469	656
Events (%)	10 (0.7%)	4 (0.6%)	7 (0.5%)	2 (0.3%)
HR (95% CI)	**0.96 (0.30, 3.09)**		**1.30 (0.27, 6.29)**	

Cox model stratified by trial

Updated DB, Censor: 7 days

Type 2 Diabetes (13 trials)

	MACE+		MACE	
	IDeg/IDegAsp	**Comparator**	**IDeg/IDegAsp**	**Comparator**
N	4325	2805	4325	2805
Events (%)	85 (2.0%)	33 (1.2%)	63 (1.5%)	19 (0.7%)
HR (95% CI)	**1.35 (0.89, 2.04)**		**1.71 (1.01, 2.90)**	

Cox model stratified by trial

Updated DB, Censor: 7 days

IGlar-controlled (12 trials)

Trial ID	Treatment Arms	Ratio	N	Population	Duration (weeks)
3579 + 3643	**IDeg** vs. IGlar	3:1	1,030	T2DM	52 + 52
3580	**IDeg** vs. sitagliptin	1:1	447	T2DM	26
3582 + 3667	**IDeg** vs. IGlar	3:1	992	T2DM	52 + 26
3583 + 3644	**IDeg** vs. IGlar	3:1	629	T1DM	52 + 52
3585 + 3725	**IDeg** vs. IDet	2:1	455	T1DM	26 + 26
3586	**IDeg** vs. IGlar	2:1	435	T2DM	26
3668	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	687	T2DM	26
3672	**IDeg** vs. IGlar	1:1	457	T2DM	26
3718	**IDeg** vs. IGlar	1:1	467	T2DM	26
3724	**IDeg** vs. IGlar	1:1	459	T2DM	26
3770 + Ext.	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	493	T1DM	26 + 26
3590 + 3726	**IDegAsp** vs. IGlar	1:1	529	T2DM	26 + 26
3592	**IDegAsp** vs. BIAsp	1:1	446	T2DM	26
3593	**IDegAsp** vs. IGlar	1:1	463	T2DM	26
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	T1DM	26 + 26
3597	**IDegAsp** vs. BIAsp	2:1	422	T2DM	26
3896	**IDegAsp** vs. IGlar	1:1	296	T2DM	26

IGlar-controlled (12 trials)

	MACE+		MACE	
	IDeg/IDegAsp	**IGlar**	**IDeg/IDegAsp**	**IGlar**
N	4397	2540	4397	2540
Events (%)	87 (2.0%)	27 (1.1%)	62 (1.4%)	16 (0.6%)
HR (95% CI)	**1.54 (0.99, 2.40)**		**1.82 (1.03, 3.19)**	

Cox model stratified by trial

Updated DB, Censor: 7 days

IDeg Trials (no IAsp use)

Trial ID	Treatment Arms	Ratio	N	Population	Duration (weeks)
3579 + 3643	**IDeg** vs. IGlar	3:1	1,030	T2DM	52 + 52
3580	**IDeg** vs. sitagliptin	1:1	447	T2DM	26
3582 + 3667	**IDeg** vs. IGlar	3:1	992	T2DM	52 + 26
3583 + 3644	**IDeg** vs. IGlar	3:1	629	T1DM	52 + 52
3585 + 3725	**IDeg** vs. IDet	2:1	455	T1DM	26 + 26
3586	**IDeg** vs. IGlar	2:1	435	T2DM	26
3668	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	687	T2DM	26
3672	**IDeg** vs. IGlar	1:1	457	T2DM	26
3718	**IDeg** vs. IGlar	1:1	467	T2DM	26
3724	**IDeg** vs. IGlar	1:1	459	T2DM	26
3770 + Ext.	**IDeg**, **IDeg flex** vs. IGlar	1:1:1	493	T1DM	26 + 26
3590 + 3726	**IDegAsp** vs. IGlar	1:1	529	T2DM	26 + 26
3592	**IDegAsp** vs. BIAsp	1:1	446	T2DM	26
3593	**IDegAsp** vs. IGlar	1:1	463	T2DM	26
3594 + 3645	**IDegAsp** vs. IDet	2:1	548	T1DM	26 + 26
3597	**IDegAsp** vs. BIAsp	2:1	422	T2DM	26
3896	**IDegAsp** vs. IGlar	1:1	296	T2DM	26

IDeg Trials (no IAsp use)

	MACE+		MACE	
	IDeg	Comparator	IDeg	Comparator
N	2434	1548	2434	1548
Events (%)	42 (1.7%)	16 (1.0%)	31 (1.3%)	9 (0.6%)
HR (95% CI)	**1.35 (0.75, 2.44)**		**1.64 (0.77, 3.51)**	

Cox model stratified by trial

Updated DB, Censor: 7 days

Outline

- Trial Database
- Statistical Methods
- Results
- **Summary**

Summary

- Results of CV meta-analysis of original submission triggered information request for additional data
  - Includes data from **6 extension trials** and **one new trial** = "Updated database"
  - **Updated database is robust and appropriate** to evaluate the cardiovascular risk of IDeg/IDegAsp
- **Consistent trend of CV risk increase** associated with IDeg/IDegAsp across
  - Endpoints
  - Effect measures
  - Analysis methods
  - Subgroup analyses

Insulin Degludec Hypoglycemia Meta-Analysis

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 8, 2012

Eugenio Andraca-Carrera, PhD
Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Background

- Novo Nordisk conducted a meta-analysis of 7 RCTs comparing IDeg once daily (OD) vs. IGlar OD on the rate of **Novo confirmed hypoglycemia**
- The objective of the meta-analysis was to show **superiority** (lower rate) of **IDeg vs. IGlar**
- Primary Endpoint: **Novo Confirmed hypoglycemia**
  - glucose < 56 mg/dL or
  - requiring assistance from another person to actively administer carbohydrate, glucagons or resuscitative actions

Outline

- **Trial and Subject Characteristics**
- Descriptive Analysis Results
- Statistical Analyses
  - Primary Analysis
  - Analysis by Type of Diabetes
  - Subgroup Analyses
- Summary

Trial Design Features

Trial	Insulin use	Duration (Weeks)	Randomized IDeg:IGlar	Sample Size	
				IDeg	IGlar
3583	insulin-treated	52	3:1	472	157
3770	insulin-treated	26	1:1	165	164
3582	insulin-treated	52	3:1	744	248
3579	insulin naïve	52	3:1	773	257
3672	insulin naïve	26	1:1	228	229
3586	insulin naïve	26	2:1	289	146
3668	insulin-naïve / basal insulin	26	1:1	228	230

Trials in patients with T1DM

Source: "Meta-analysis of Hypoglycaemic Episodes." Table 4-1. Completed by Novo Nordisk on 26 August 2011

Baseline Characteristics

		IDeg	IGlar
Sample Size	T1DM	637	321
	T2DM	2262	1110
% Female	T1DM	41.6%	44.5%
	T2DM	45.1%	43.6%
Mean Age	T1DM	43.3	43.9
	T2DM	58.7	57.8
Mean BMI	T1DM	26.3	26.6
	T2DM	30.6	30.8
Mean diabetes duration (years)	T1DM	19.4	18.2
	T2DM	11.1	10.3
% White	T1DM	93.9%	96.6%
	T2DM	72.2%	69.0%
% United States	T1DM	65.3%	60.7%
	T2DM	34.8%	28.5%

Outline

- Trial and Subject Characteristics
- **Descriptive Analysis Results**
- Statistical Analyses
  - Primary Analysis
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- Summary

Annual Rates of Novo Confirmed Hypoglycemia

			Mean annual rate		Median annual rate	
		Trial	IDeg	IGlar	IDeg	IGlar
T1DM	insulin-treated	3583	41	39	29	27
		3770	87	75	72	62
T2DM	insulin-treated	3582	11	13	6	7
	insulin-naïve	3579	1.4	1.7	0	0
		3672	1.2	1.3	0	0
		3586	3.2	3.9	1.0	1.9
	insulin-naïve / basal insulin	3668	4.1	3.5	0	0

Proportion of Patients by Annual Rate of Novo Confirmed Hypoglycemia

	T1DM	T2DM
No events	**3.7%**	**44.5%**
1 ≤ events per year ≤ 90	75.4%	55.2%
90+ events per year	20.9%	0.3%

Outline

- Trial and Subject Characteristics
- Descriptive Analysis Results
- **Statistical Analyses**
  - **Primary Analysis**
  - **Analysis by Type of Diabetes**
  - **Subgroup Analyses**
- Summary

Statistical Analyses

- Statistical parameter of interest: **rate ratio** of Novo confirmed hypoglycemia (IDeg vs. IGlar)
- Primary analysis
  - Assumes the rate ratio is **the same** in T1DM and T2DM trials
- Secondary analysis
  - Allows the rate ratio **to be different** in T1DM and T2DM trials
- Subgroup analysis: gender, age, region of randomization

Primary Analysis Model

- Novo confirmed hypoglycemia events ~ **Negative Binomial**
- Fixed effects: trial, treatment, baseline insulin, gender, region of randomization, age
  - Offset: log(time)
- Sensitivity analyses:
  - **Zero-Inflated Negative Binomial model**
  - **Wilcoxon Rank Sum test**
  - Conclusions are consistent with primary Negative Binomial (results not shown)

Primary Analysis Results

Novo Confirmed Hypoglycemia Events

	IDeg	IGlar
Subjects randomized	2899	1431
Subjects used in analysis	2886	1421
Rate Ratio* (95% CI)	0.91 (0.83, 0.99)	

*Rate Ratio < 1.0 implies smaller rate of events associated with IDeg

Negative Binomial model

Source: "Meta-analysis of Hypoglycaemic Episodes." Table 7-2.

Secondary Analysis Model

- Novo confirmed hypoglycemia events ~ **Negative Binomial**
- Fixed effects: trial, treatment, baseline insulin, gender, region of randomization, age, **treatment x type of diabetes**.
  - Offset: log(time)

Secondary Analysis Results

Novo Confirmed Hypoglycemia Events

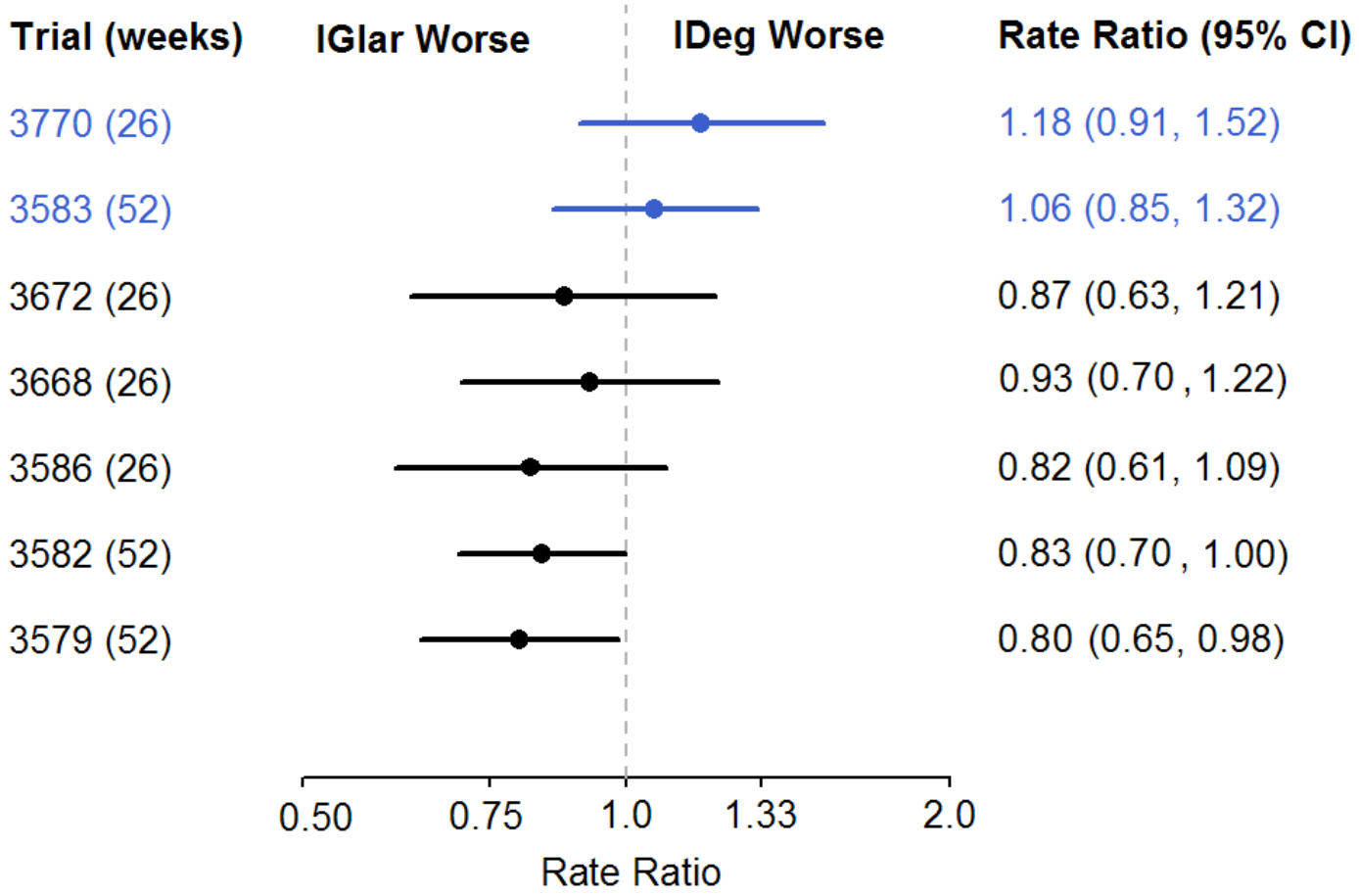
		Rate Ratio (95% CI)
Primary Analysis		**0.91 (0.83, 0.99)**
Secondary Analysis	**T1DM**	**1.11 (0.94, 1.31)**
	T2DM	**0.84 (0.76, 0.93)**

Treatment by type of diabetes interaction: ***p = 0.0057***

Negative Binomial model

Source: "Meta-analysis of Hypoglycaemic Episodes." Table 7-3.

Rate Ratios by Trial



*Trial-specific rate ratios were estimated with a negative binomial model adjusting for: trial, age, gender, insulin at baseline, Novo defined region, treatment and trial by treatment interaction.

Subgroup Analysis Results

Gender

	Overall	Females	Males
T1DM	1.11 (0.94, 1.31)	1.14 (0.90, 1.46)	1.07 (0.86, 1.35)
T2DM	0.84 (0.76, 0.93)	0.83 (0.71, 0.96)	0.84 (0.73, 0.97)

Age

	Overall	Age < 65	Age ≥ 65
T1DM	1.11 (0.94, 1.31)	1.09 (0.92, 1.30)	1.46 (0.75, 2.86)
T2DM	0.84 (0.76, 0.93)	0.86 (0.76, 0.97)	0.77 (0.62, 0.96)

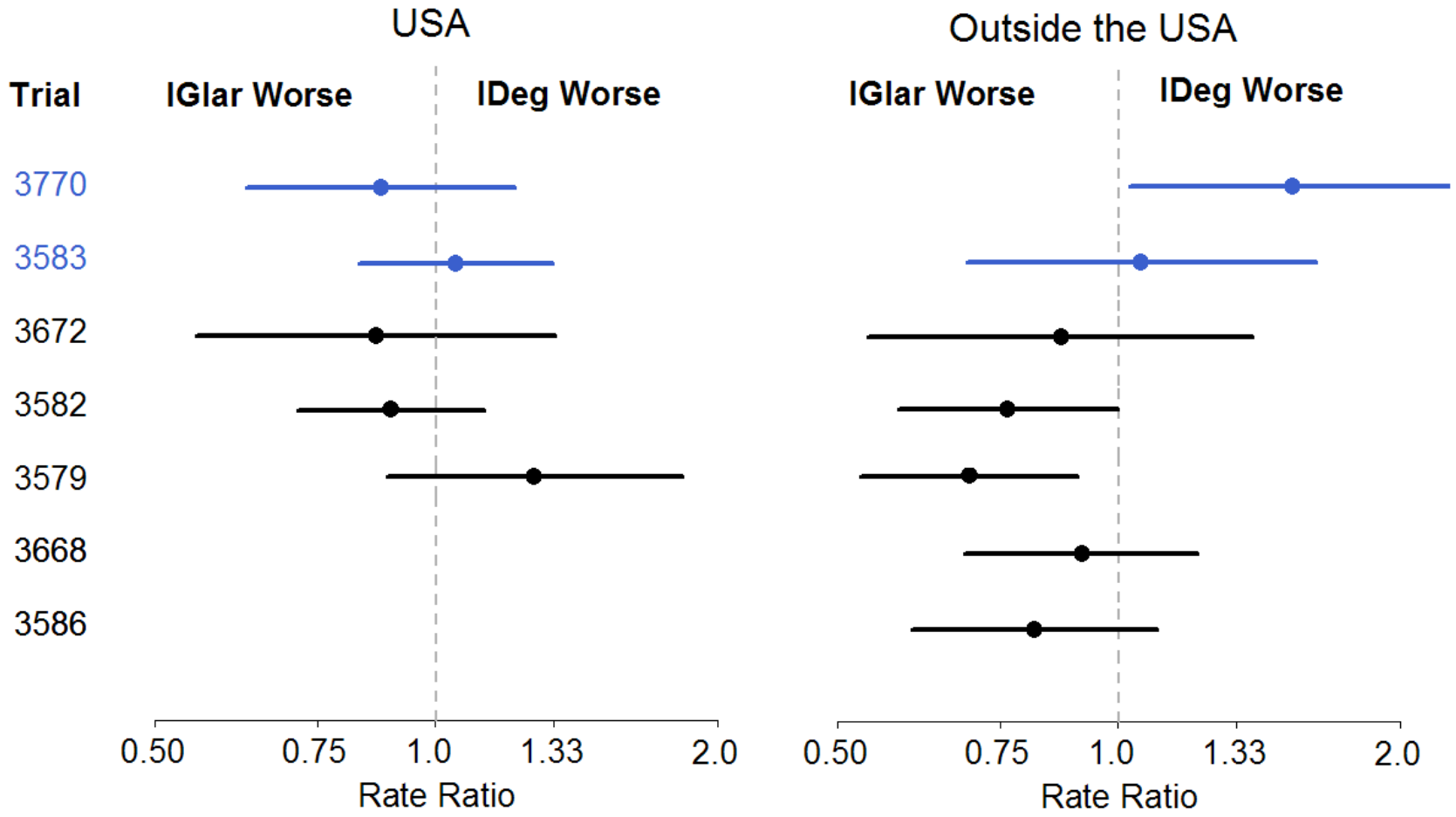
Subgroup Analysis Results (2)

Region of Randomization

	Overall	USA	Outside USA
T1DM	1.11 (0.94, 1.31)	0.99 (0.81, 1.20)	1.28 (0.96, 1.71)
T2DM	0.84 (0.76, 0.93)	**0.97 (0.81, 1.15)**	0.79 (0.69, 0.90)

*Rate ratios were estimated with a negative binomial model within each subgroup adjusting for: trial, age, gender, insulin at baseline, Novo defined region, treatment and treatment by type of diabetes interaction.

Rate Ratios by Trial & Region



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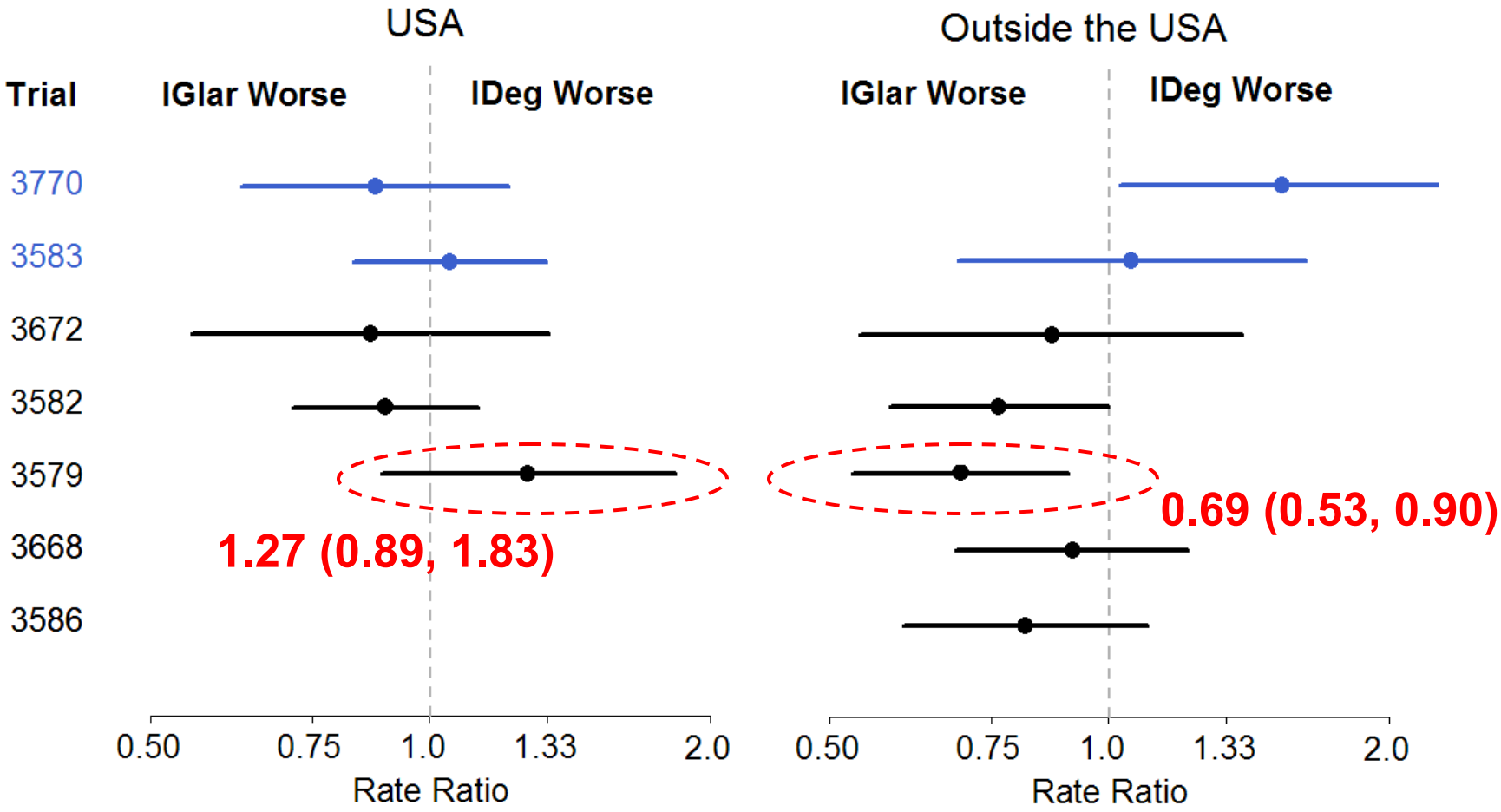
Rate Ratios by Trial & Region



*Trial-specific rate ratios were estimated with a negative binomial model within each subgroup adjusting for: trial, age, gender, insulin at baseline, treatment and trial by treatment interaction.

Outline

- Trial and Subject Characteristics
- Descriptive Analysis Results
- Statistical Analyses
  - Primary Analysis
  - Analysis by Type of Diabetes
  - Subgroup Analyses
- **Summary**

Summary

- **Differences** between T1DM and T2DM trials
  - Population characteristics
  - Hypoglycemia experience

- IDeg had **lower rate** of Novo confirmed hypoglycemia than IGlar among patients with **T2DM only**:
  - T1DM : **1.11 (0.94, 1.31)**
  - T2DM: **0.84 (0.76, 0.93)**

- IDeg showed **significantly lower** rate of events in T2DM in subgroups by gender and age, but **not by region**
  - T2DM in the USA : **0.97 (0.81, 1.15)**
  - T2DM outside USA: **0.79 (0.69, 0.90)**

Clinical Perspective of Hypoglycemia Analyses and Results

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

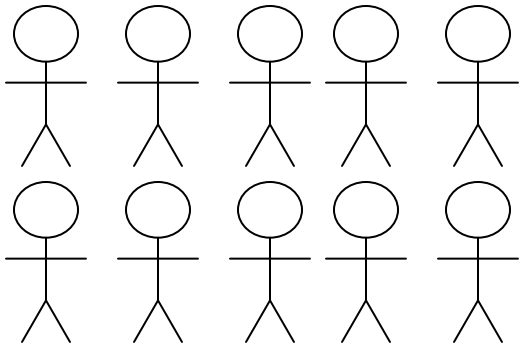
November 8, 2012

Jean-Marc Guettier, MDCM
Clinical Team Leader
Division of Metabolism and Endocrinology Product
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

1. Review the process of hypoglycemia data capture
2. Review factors important in assessing whether the results are generalizable
3. Review definitions of hypoglycemic episodes
4. Review endpoints used in analyses
5. Review trends in hypoglycemia data across definitions
6. Review hypoglycemia findings in light of efficacy results
7. Comment on nocturnal hypoglycemia analyses

Capture and Flow of Glucose Data Used in Hypoglycemia Analyses



- Glucose monitored by patients before breakfast, lunch, main evening meals and bedtime at least 3x per week
- CGMS devices used in subgroups in trials 3583, 3579 and 3668

Glucose measured by participants at point-of-care

Glucose value recorded by participant in dedicated glucose diary

Glucose data transferred into electronic case report form at site visit or telephone contact.
Measured value below 70 mg/dL triggers hypoglycemia questionnaire and questions related to symptoms were asked.
Hypoglycemia adverse event also triggers hypoglycemia questionnaire

To applicant/CRO for data analysis

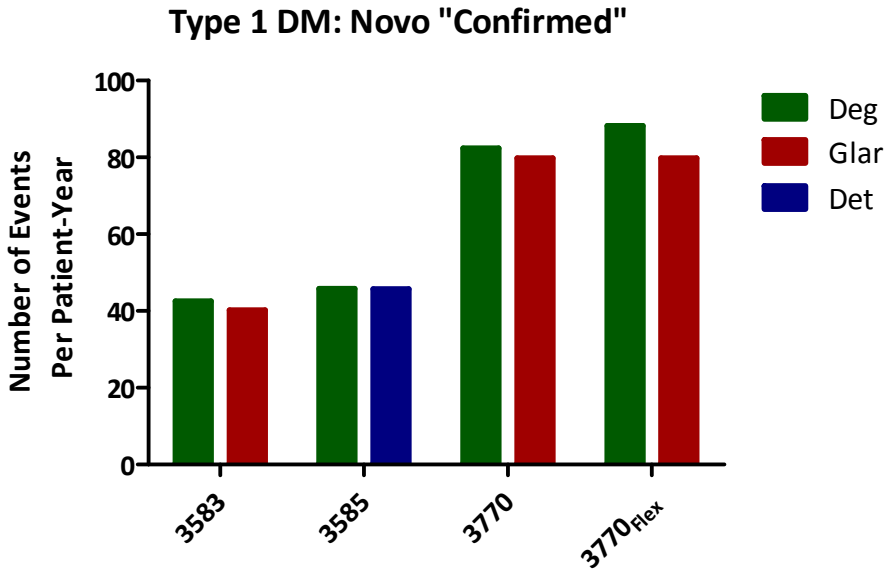
Hypoglycemia Risk Factors

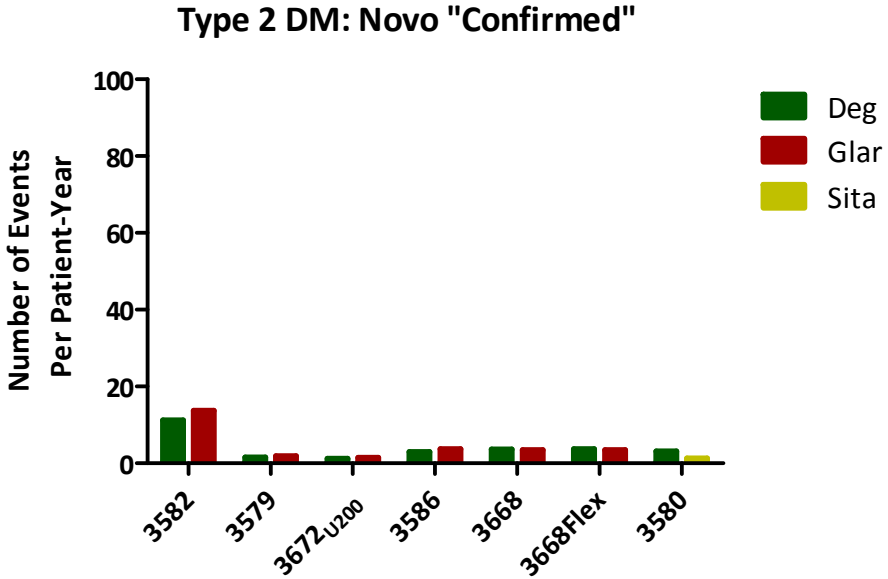
Characteristics of patients at greatest risk for hypoglycemia

- ✓Type of diabetes (type 1 DM >> 2 DM)
- ✓Use of multiple daily insulin injections to target tight glucose control (all type 1 trials and trial 3582 in type 2)
- ✓History of recurrent severe events
- ✓Hypoglycemic symptoms “unawareness”
- ✓Have significant end-organ dysfunction (e.g., renal failure)

Subjects with three of these characteristics were excluded from participating in the Degludec and Degludec/Aspart program

Type of Diabetes as Risk Factor in Degludec Program





Hypoglycemia
Clinical Presentation

Hypoglycemia can present in different ways

- As an acute life threatening event
- As a mild event with non-specific signs and symptoms

Capturing Hypoglycemic Episodes

Defining hypoglycemia based on a low glucose value alone can be misleading

- Point-of-care devices lack accuracy
- Glucose can be low due to normal physiology or can be falsely low

Defining hypoglycemia based on the presence of hypoglycemic symptoms alone can also be misleading

- Symptoms lack specificity

For mild hypoglycemic episodes, the most specific definitions rely on demonstrating the concurrent presence of low glucose and hypoglycemic symptoms

ADA Hypoglycemia Definitions

Least Specific

- **Probable:** Symptoms and no ***plasma*** glucose
- **Asymptomatic:** No Symptoms and low ***plasma*** glucose

≤ 70 mg/dL

- **Documented symptomatic**: Symptoms and low ***plasma*** glucose **30% REDUCTION**

- **Severe:** Third party assistance required to actively administer carbohydrate, glucagons, or other resuscitative actions. **10% REDUCTION**

Most Specific

Diabetes Care, Volume 28, Number 5, May 2005

Novo "Confirmed" Definition

Least Specific

≤ 56 mg/dL
or 50 mg/dL

Glucose Meter Derived
CGMS Derived

- **Asymptomatic:** No Symptoms and low ~~***plasma***~~ glucose
- **Documented symptomatic**: Symptoms and low ~~***plasma***~~ glucose

NOVO

MINOR EPISODE

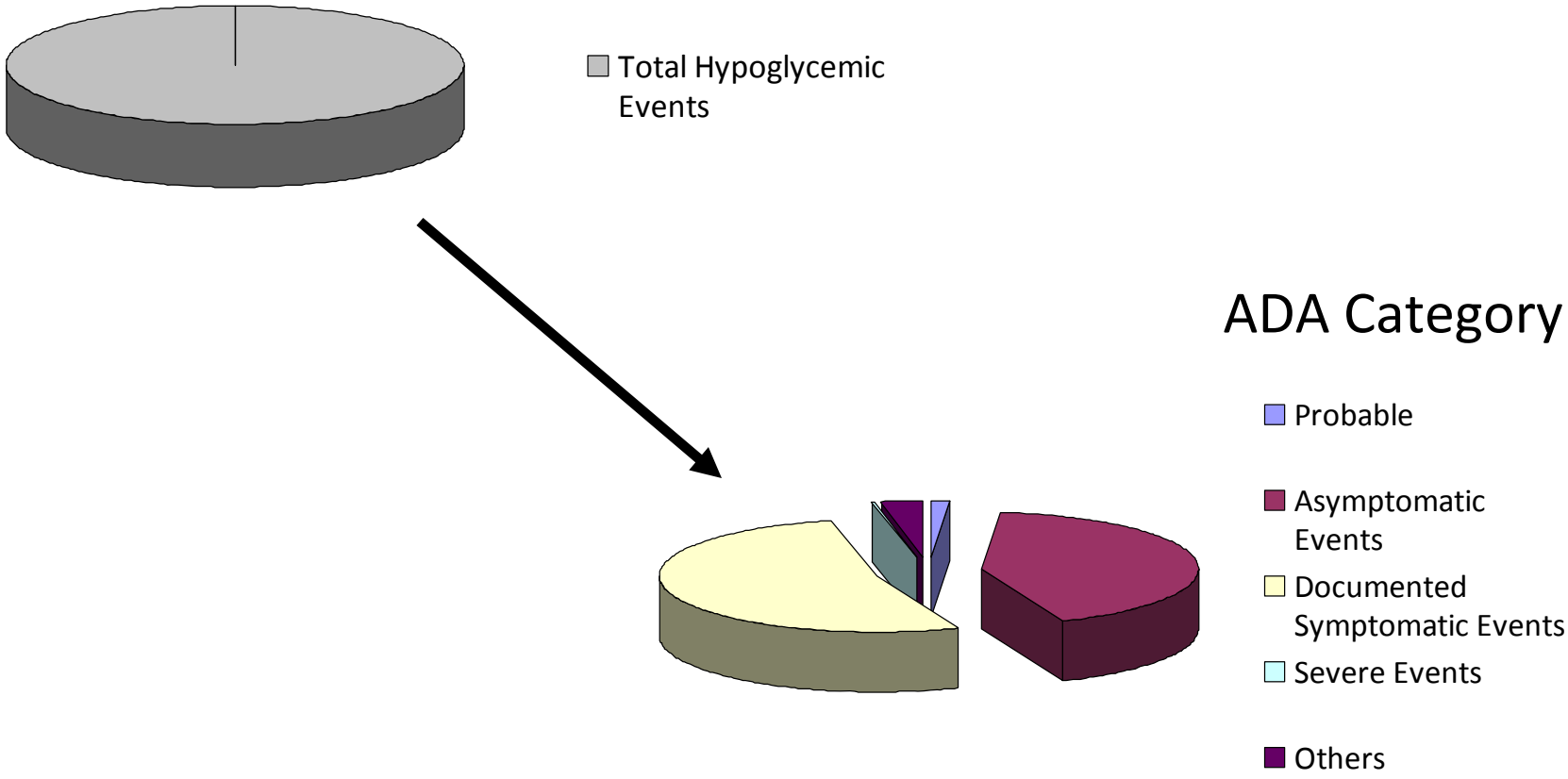
- **Severe Episodes:** Third party assistance required to actively administer carbohydrate, glucagons, or other resuscitative actions.

+

Most Specific

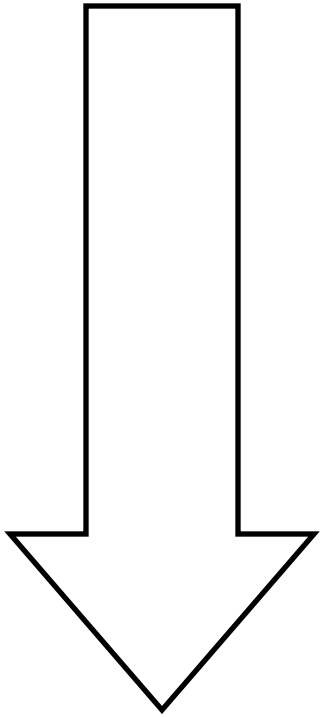
= Total Novo "Confirmed" Events

What Proportion of Total Events Were Specific Events in The Degludec Program?



Proportion Of Total Events by ADA Definitions in Degludec Program

Least Specific



Most Specific

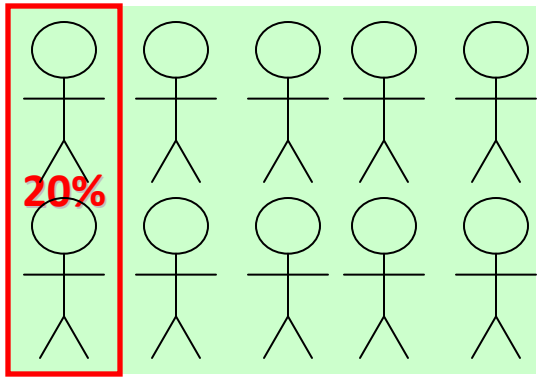
	Type-1 DM	Type 2 DM
PROBABLE	1.1%	1.6%
ASYMPTOMATIC	32.3%	53.4%
DOCUMENTED	65.8%	39.4%
SEVERE	0.27%	0.08%

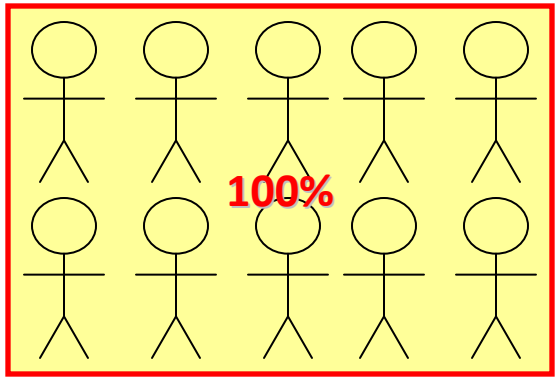
Source: ISE Tables 260-262 from NDA Submission

Hypoglycemia Endpoints

Endpoint based on event counts	10 EVENTS	=	10 EVENTS	Normalized to exposure to yield event rates

Endpoint based on proportion of subjects with at least one event

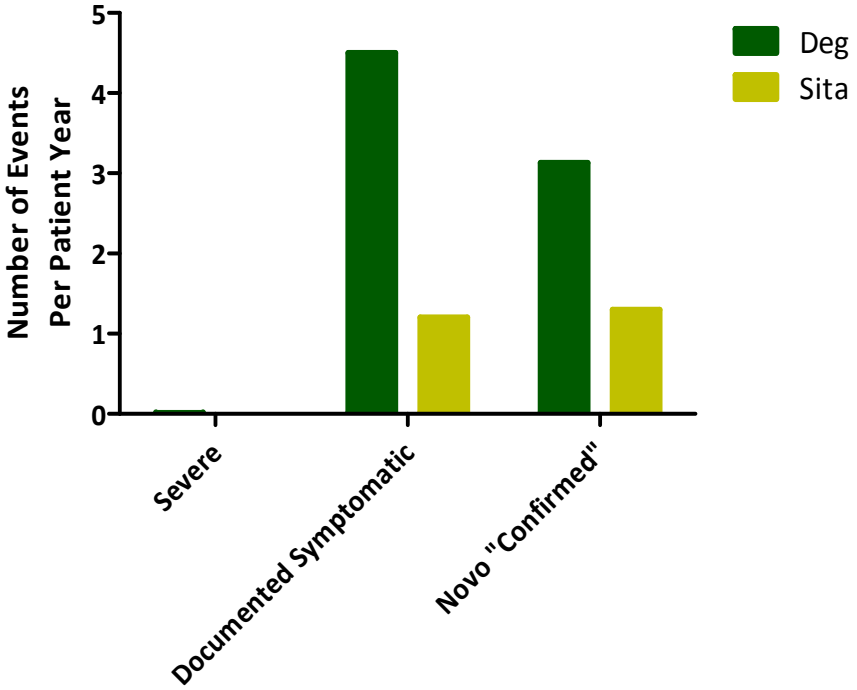


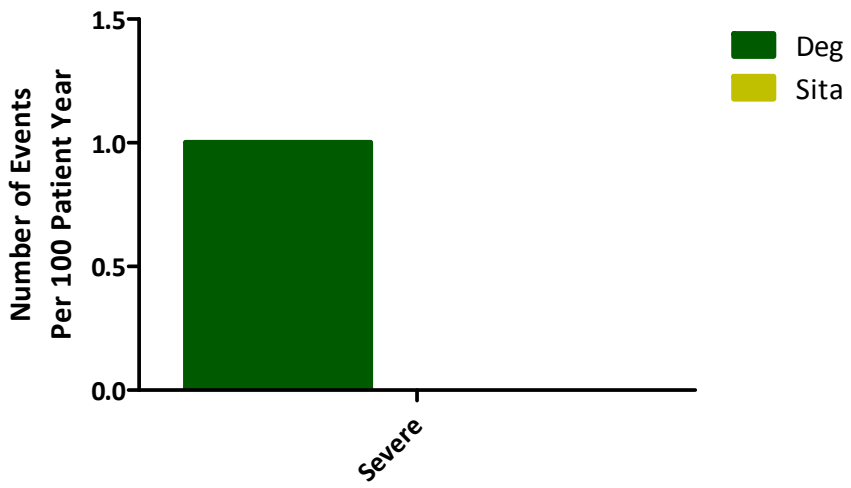


Normalized to exposure to yield incidence rates

Evaluating Hypoglycemia Data

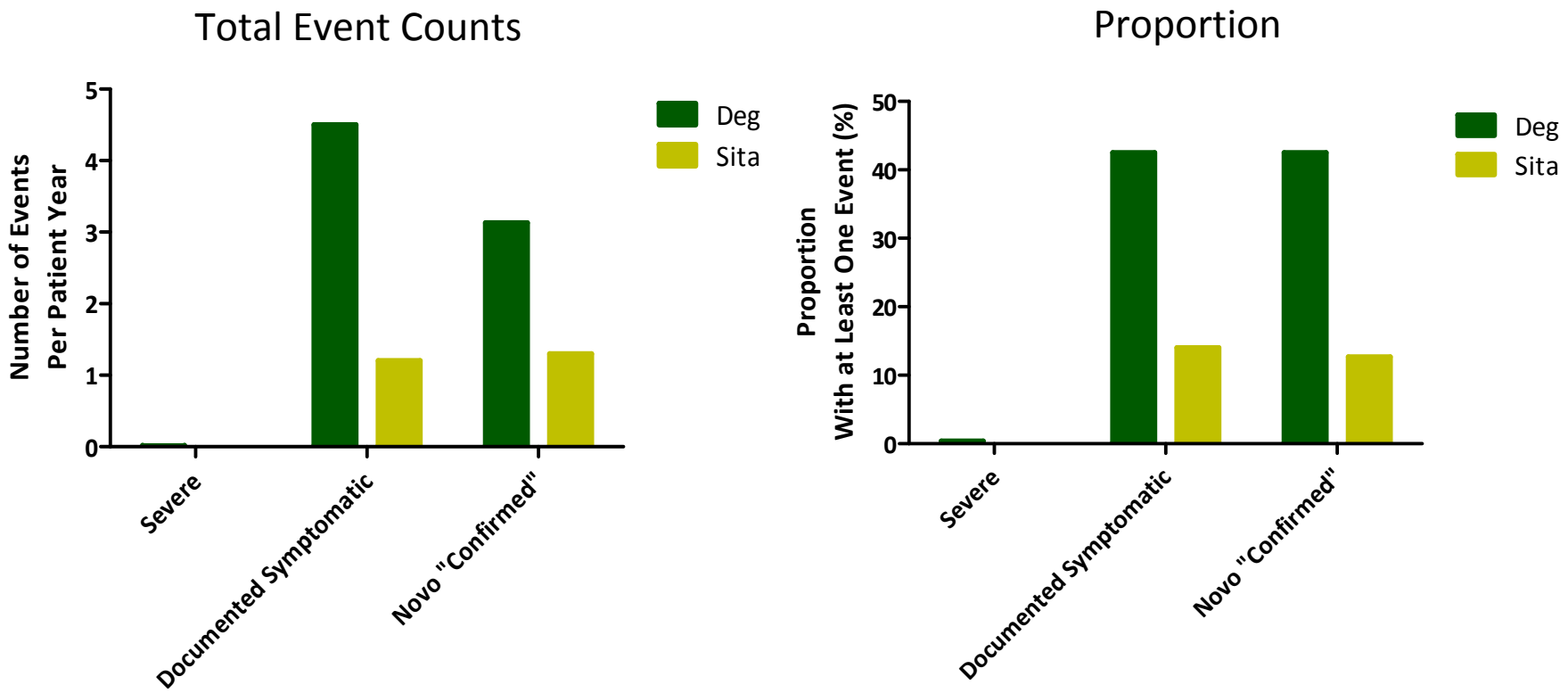
Within trial consistency across definitions of hypoglycemia





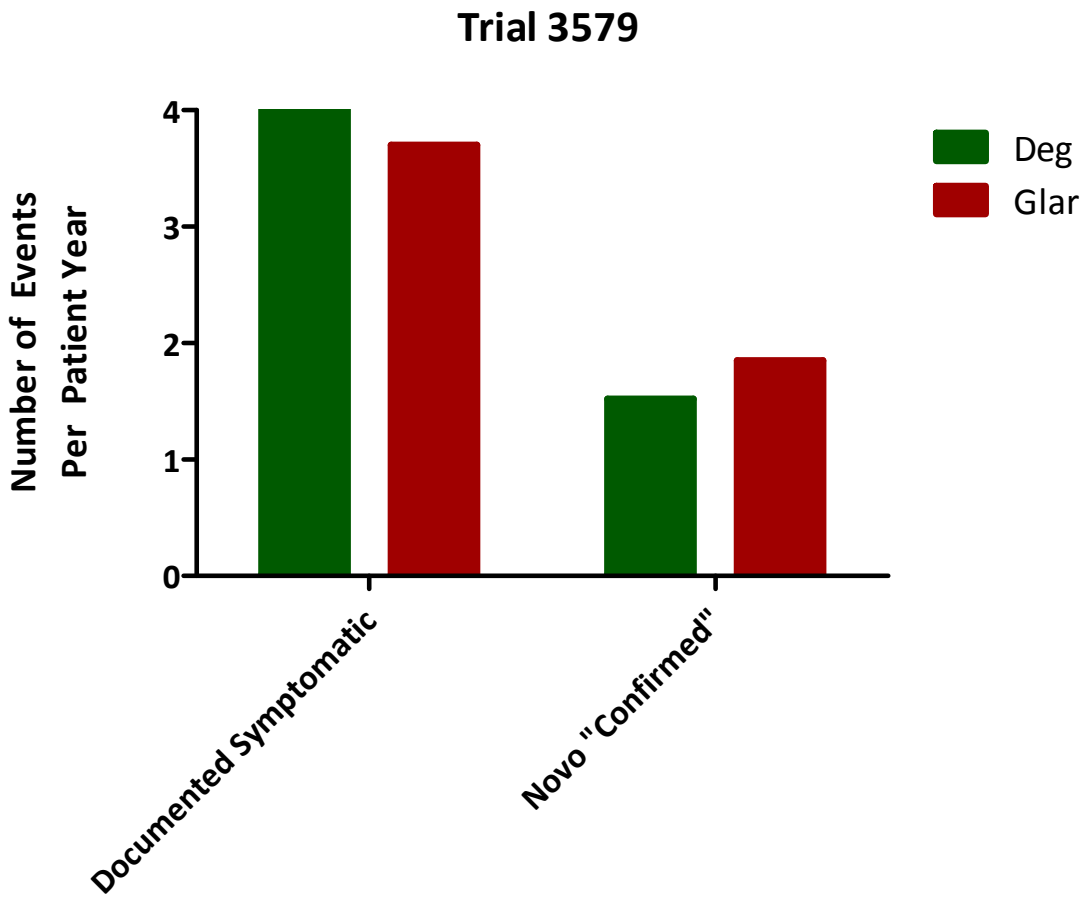
Evaluating Hypoglycemia Data

Within trial consistency across endpoints



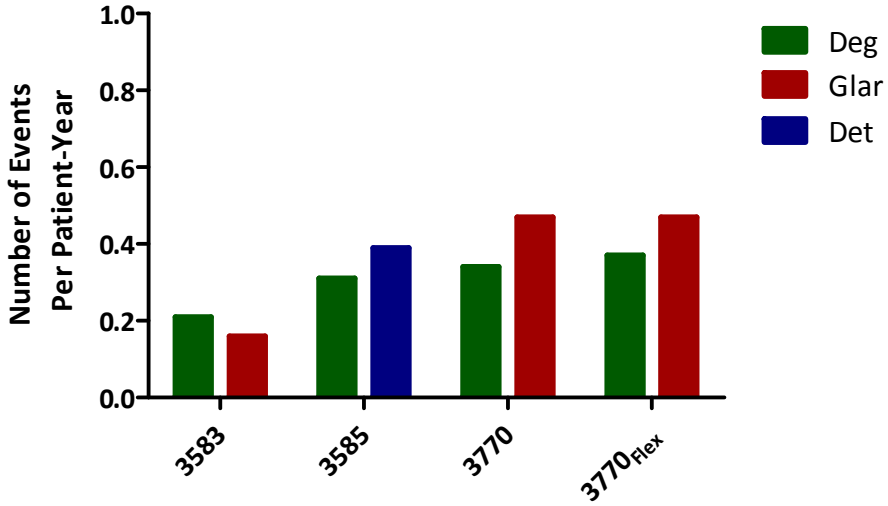
Evaluating Hypoglycemia Data

E.g., Inconsistency across definitions of hypoglycemia



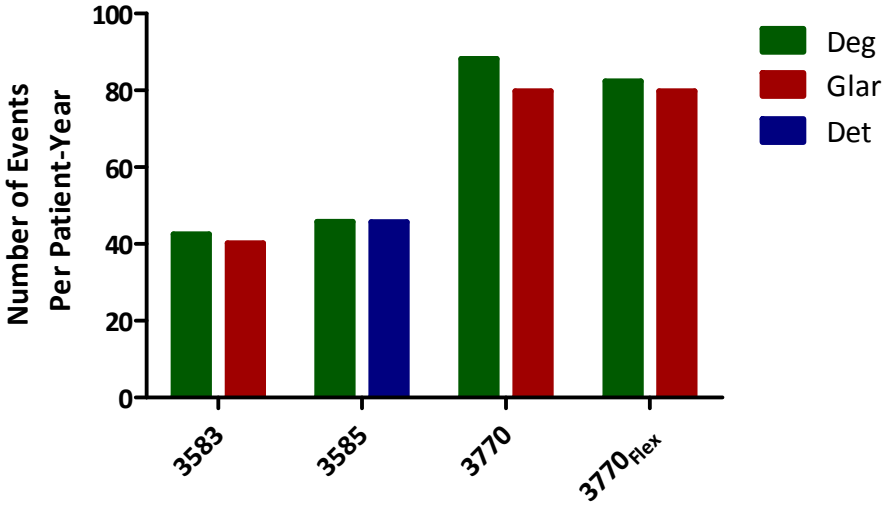
Hypoglycemic Episodes Type 1 DM

Type 1 DM: Severe



Relative Difference Degludec Versus Comparator	+31%	-20%	-21%	-28%

Type 1 DM: Novo "Confirmed"



Relative Difference Degludec Versus Comparator	+6%	0	+11%	+3%

+ = Higher Event Rates In Degludec Arm

Hypoglycemic Episodes Type 1 DM

Type 1 DM: Novo "Confirmed" versus Documented Symptomatic Definitions

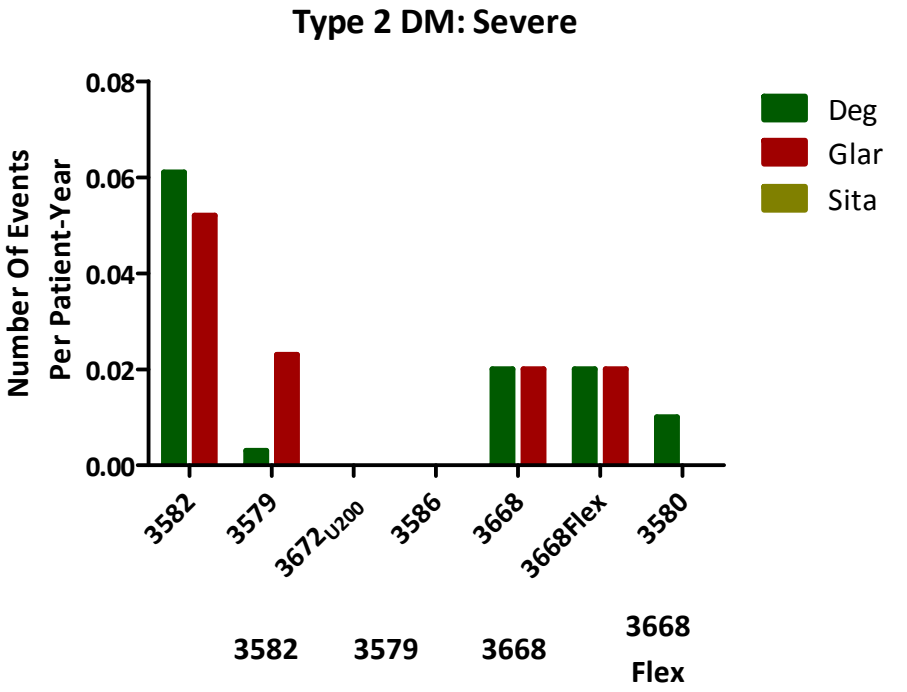
Novo "Confirmed" Definition

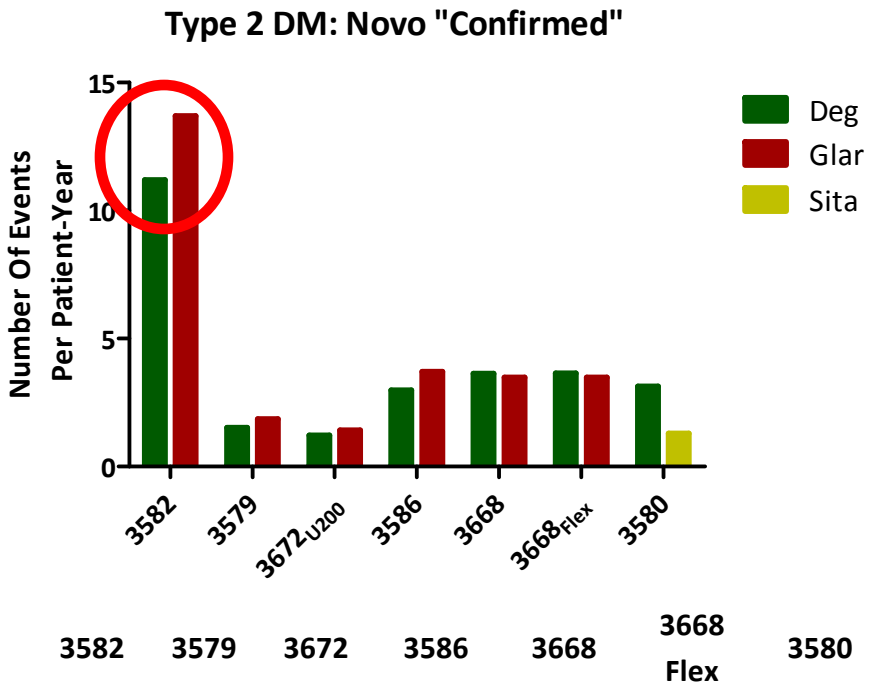
	3583	3585	3770	3770 Flex
Relative Difference Based on Rate Degludec Versus Comparator	+6%	0	+11%	+3%

ADA Documented Symptomatic Definition

	3583	3585	3770	3770 Flex
Relative Difference Based on Rate Degludec Versus Comparator	+4%	+11%	+22%	+1%

Hypoglycemia Data Type 2 DM





	3582	3579	3668	3668 Flex
Relative Difference Degludec Versus Comparator	+17%	-87%	0	0

	3582	3579	3672	3586	3668	3668 Flex	3580
Relative Difference Degludec Versus Comparator	-18%	-18%	-14%	-19%	+4%	+5%	+140%

+ = Higher Event Rate In Degludec Arm

Hypoglycemia Data Type 2 DM

Type 2 DM: Novo Confirmed versus Documented Symptomatic Definitions

Novo "Confirmed" Definition

	3582	3579	3672	3586	3668	3668 Flex	3580
Relative Difference Based on Rate Degludec Versus Comparator*	-18%	-18%	-14%	-19%	+4%	+5%	+140%

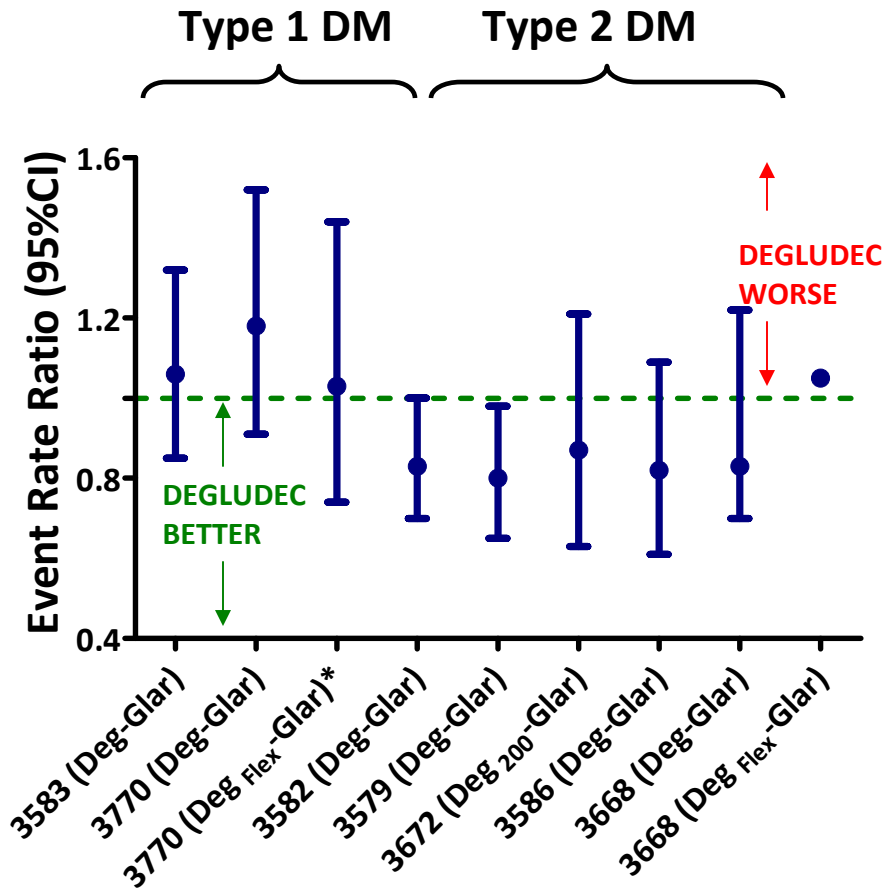
ADA Documented Symptomatic Definition

	3582	3579	3672	3586	3668	3668 Flex	3580
Relative Difference Based on Rate Degludec Versus Comparator*	-12%	+8%	-7%	+8%	-3%	+4%	+263%

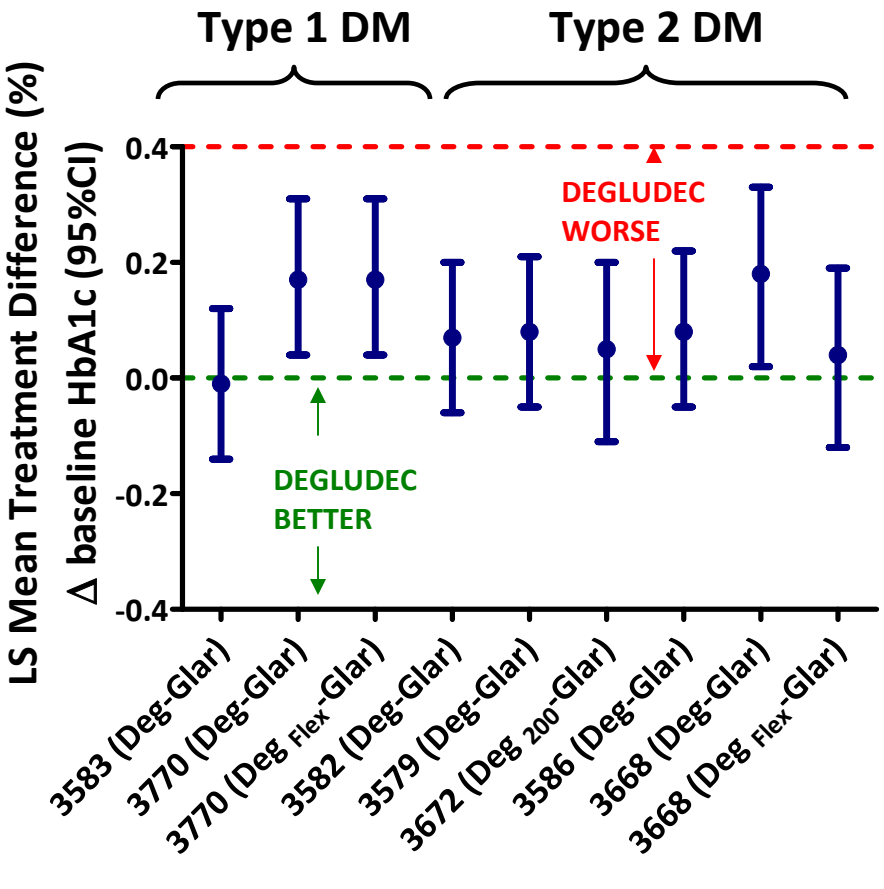
*Comparator = Glargine in all except 3580 (sitagliptin).

Hypoglycemia and Efficacy

Hypoglycemia*



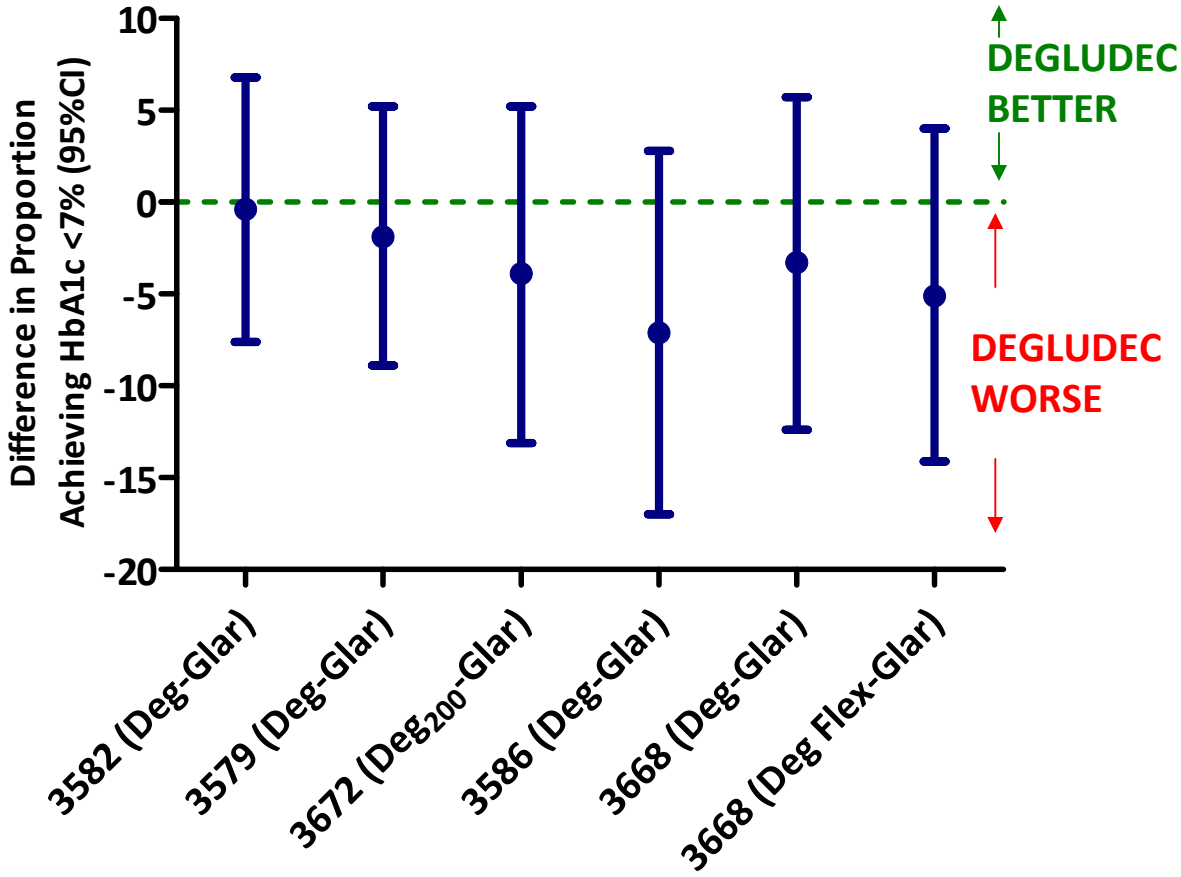
Efficacy



* Novo "Confirmed" Episodes

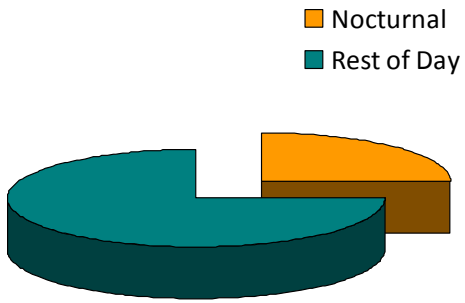
Hypoglycemia and Efficacy

Difference in proportion of Type 2 DM patients achieving ADA target glucose control at end of trial



Nocturnal Hypoglycemia Definition and Issues

- Hypoglycemic events occurring between 12:01 AM and 5.59 AM
- Analyses based on
  - ✓Novo "Confirmed" definition
  - ✓Event Count data



- Issues related to point of care data capture are amplified
  - ✓Nocturnal time period represent ¼ of 24 hours
  - ✓10 times fewer nocturnal events compared to events observed in the 24-hour time period

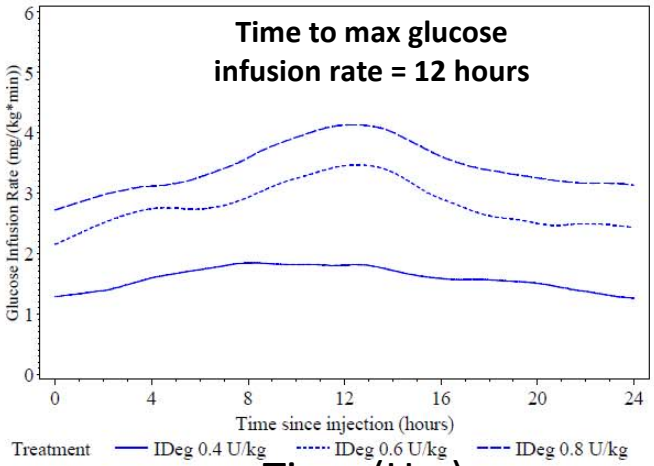
✓Inconsistencies between 24-hours and nocturnal analyses difficult to interpret

- Results confounded by between group differences in timing of basal insulin injection

Insulin Pharmacodynamic and Nocturnal Hypoglycemia

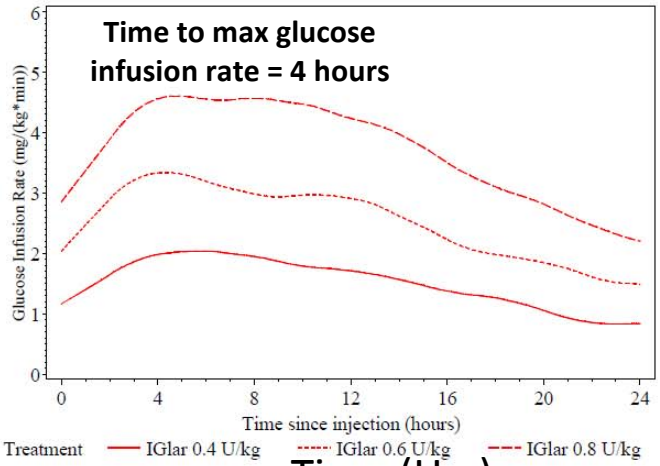
Steady State Pharmacodynamic Type 1 DM

Degludec



Trial 1993

Glargine



Glucose Infusion Rate

Time (Hrs)

Time (Hrs)

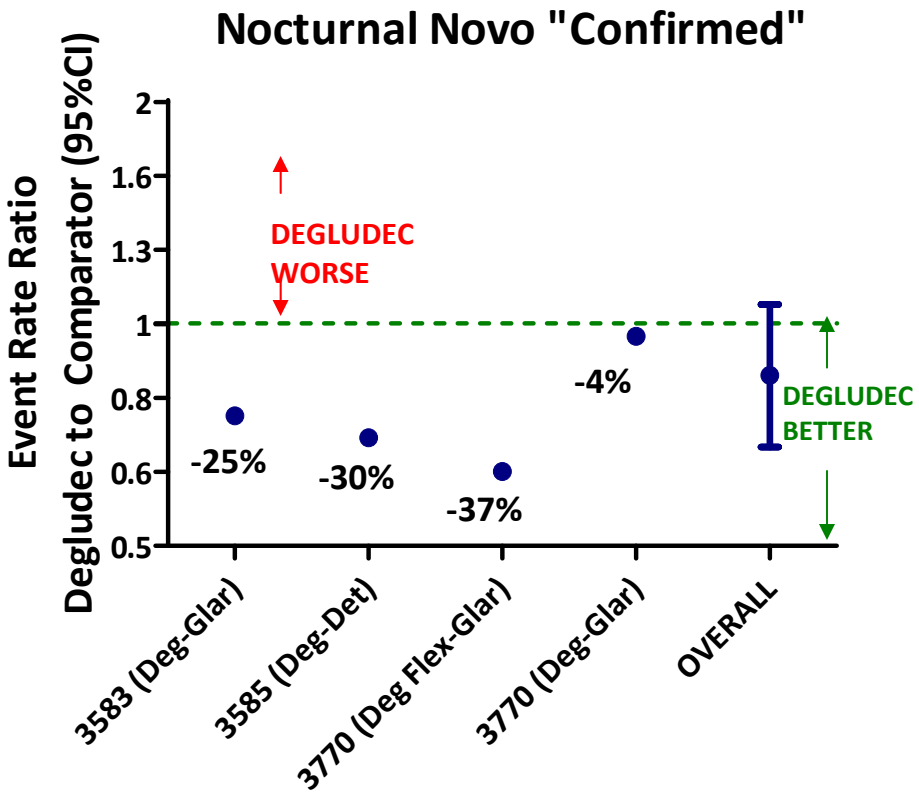
The time needed to reach maximal glucose lowering effect differs between degludec and glargine

In most trials degludec was injected in the evening and was expected to peak 12 hours after injection or in the morning

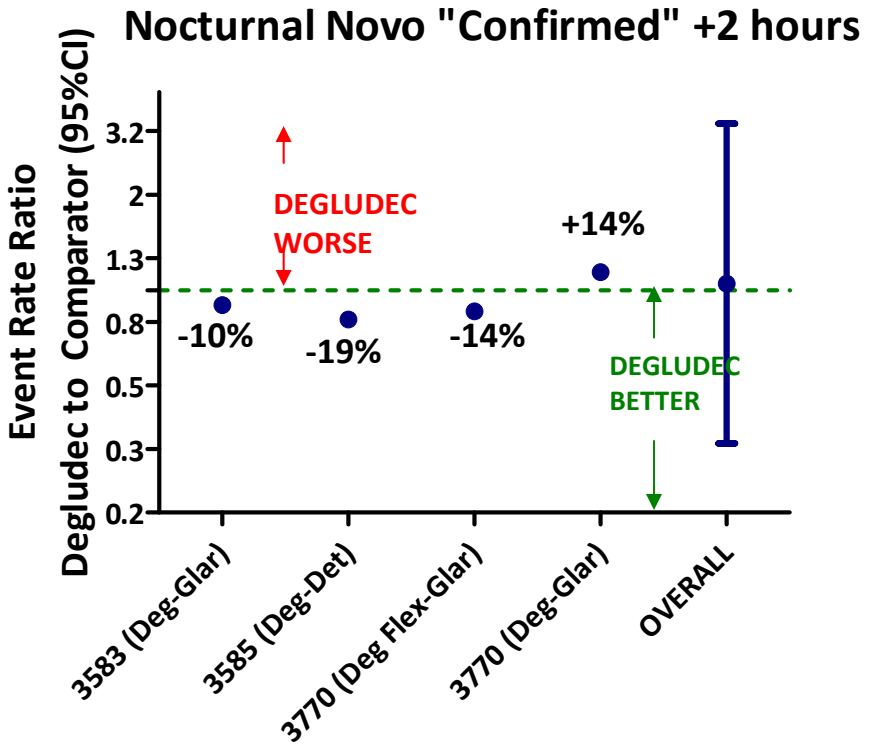
Glargine could be injected at any time of the day including in the evening

Timing of Basal Injection and Rate of Nocturnal Hypoglycemia: Type 1

When two hours are added to the nocturnal time period benefit disappears



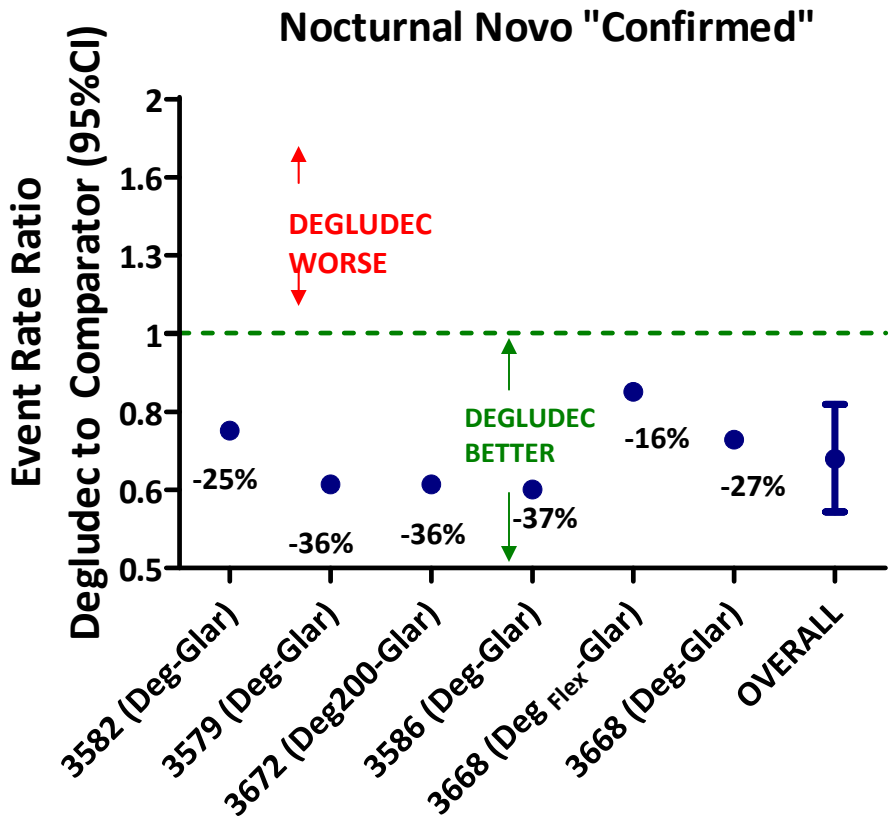
Overall Rate Ratio (95% CI): 0.85 (0.68, 1.06)

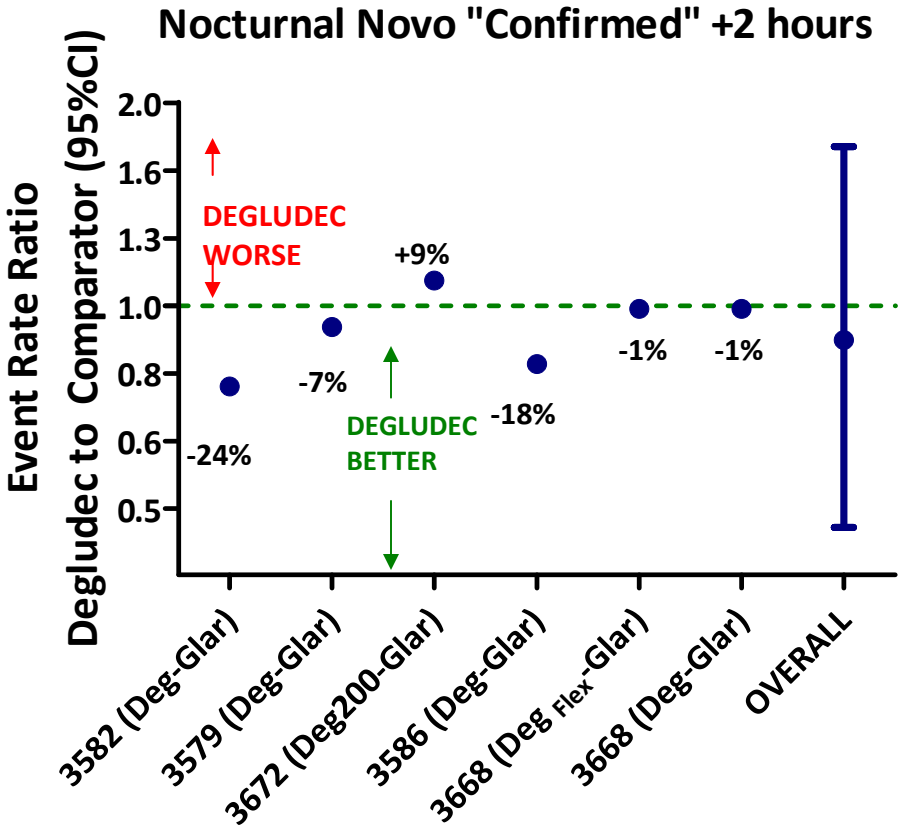


Overall Rate Ratio (95% CI): 1.05 (0.33, 3.35)

Timing of Basal Injection and Rate of Nocturnal Hypoglycemia: Type 2

When two hours are added to the nocturnal time period the benefit disappears





Overall Rate Ratio (95% CI): 0.69 (0.59, 0.81)

Overall Rate Ratio (95% CI): 0.89 (0.47, 1.72)

Hypoglycemia Summary

- In insulin programs interpretation of results of a purported hypoglycemic benefit is complicated by issues related to:
  - ✓ The secondary nature of hypoglycemia analyses
  - ✓ Generalizability of the findings to the population most at risk
  - ✓ The open-label nature of the trial
  - ✓ Questions surrounding the completeness of data capture
  - ✓ Questions surrounding the specificity of the definitions used in analyses
  - ✓ Questions surrounding the impact of slight efficacy or dose related differences observed in treat to target non-inferiority designs

Hypoglycemia Summary

- In the degludec program
  - ✓A **consistent** hypoglycemic benefit across **types of diabetes** and across **hypoglycemic episode definitions** and in particular across more objective hypoglycemia definitions **was not seen**
  - ✓**The safety advantage** based on the Novo "confirmed" hypoglycemia definition **did not translate into an efficacy advantage**
  - ✓Differences in **pharmacodynamic profiles** between comparators compounded by **inadequacy of data capture in the nocturnal time period** confound interpretability of reported differences in nocturnal event counts between comparators