

Insulin Degludec

Insulin Degludec/Insulin Aspart

Treatment of Type 1 and 2 Diabetes

FDA Advisory Committee Presentation

November 8, 2012

Introduction

Robert Clark
Vice President
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Candidates for Approval and Proposed Indication

- Insulin degludec or “IDeg”
 - Long-acting insulin
- Insulin degludec/insulin aspart or “IDegAsp”
 - Soluble co-formulation of insulin degludec and insulin aspart
- *“...to improve glycemic control in adult patients with diabetes mellitus.”*

IDeg Regulatory Status

- IDeg and IDegAsp NDAs filed in Sept, 2011
- 10,000 patients across spectrum of diabetes
- Data cut-off from orig NDA = Jan 31, 2011
 - Referred to as "**NDA Dataset**"
- Updated dataset to capture additional exposure up to May 1, 2012
 - Referred to as "**May 1 Dataset**"
- IDeg approved in Japan (9/12) and IDeg and IDegAsp recommended for approval in Europe (10/12)

Insulin Treatment of Diabetes

- Insulin is an essential therapy for all patients with T1DM and many with T2DM
- Challenges of current insulin therapy
 - Narrow therapeutic window
 - Peak-to-trough levels important
 - Patients' fear of hypoglycemia, weight gain
 - Strict regimens negatively impact adherence

IDeg – Continued Evolution of Insulin Analogs

- Replicates all of insulin's biological effects
- Optimizing PK and PD properties
 - Long-acting insulin
 - Stable, predictable, flat action profile
 - Low day-to-day within-subject variability
- Vary daily injection time from day to day
- Low-volume formulation (U200)
- Allow soluble co-formulation with insulin aspart

IDeg – Benefit/Risk Considerations

- Efficacy non-inferior to comparators
- Addresses unmet needs
 - Low risk of hypoglycemia
 - Flexibility if a patient misses/delays a dose
 - Low-volume formulation (U200)
- Overall safety profile consistent with insulin
- Prespecified CV meta-analysis similar to comparators
- Post-approval CV outcome trial
- IDeg has a positive benefit/risk profile

Agenda

Defining the Rationale for an Improved Insulin

Bernard Zinman, CM, MD

Director, Leadership Sinai Centre for Diabetes
Professor of Medicine, University of Toronto
Mount Sinai Hospital

Design of Insulin Degludec

Peter Kurtzhals, PhD

Senior Vice President, Novo Nordisk

Efficacy, Hypoglycemia and General Safety

Alan Moses, MD

Chief Medical Officer, Novo Nordisk

Cardiovascular Safety of IDeg and IDegAsp

Anne Phillips, MD

Corporate Vice President, Novo Nordisk

Insulin Degludec – Assessing Cardiovascular Risk

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University of Missouri, Kansas City
Consulting Cardiologist
St. Luke's Cardiovascular Consultants

Overall Benefit/Risk

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Defining the Rationale for an Improved Insulin

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Director, Leadership Sinai Centre for Diabetes
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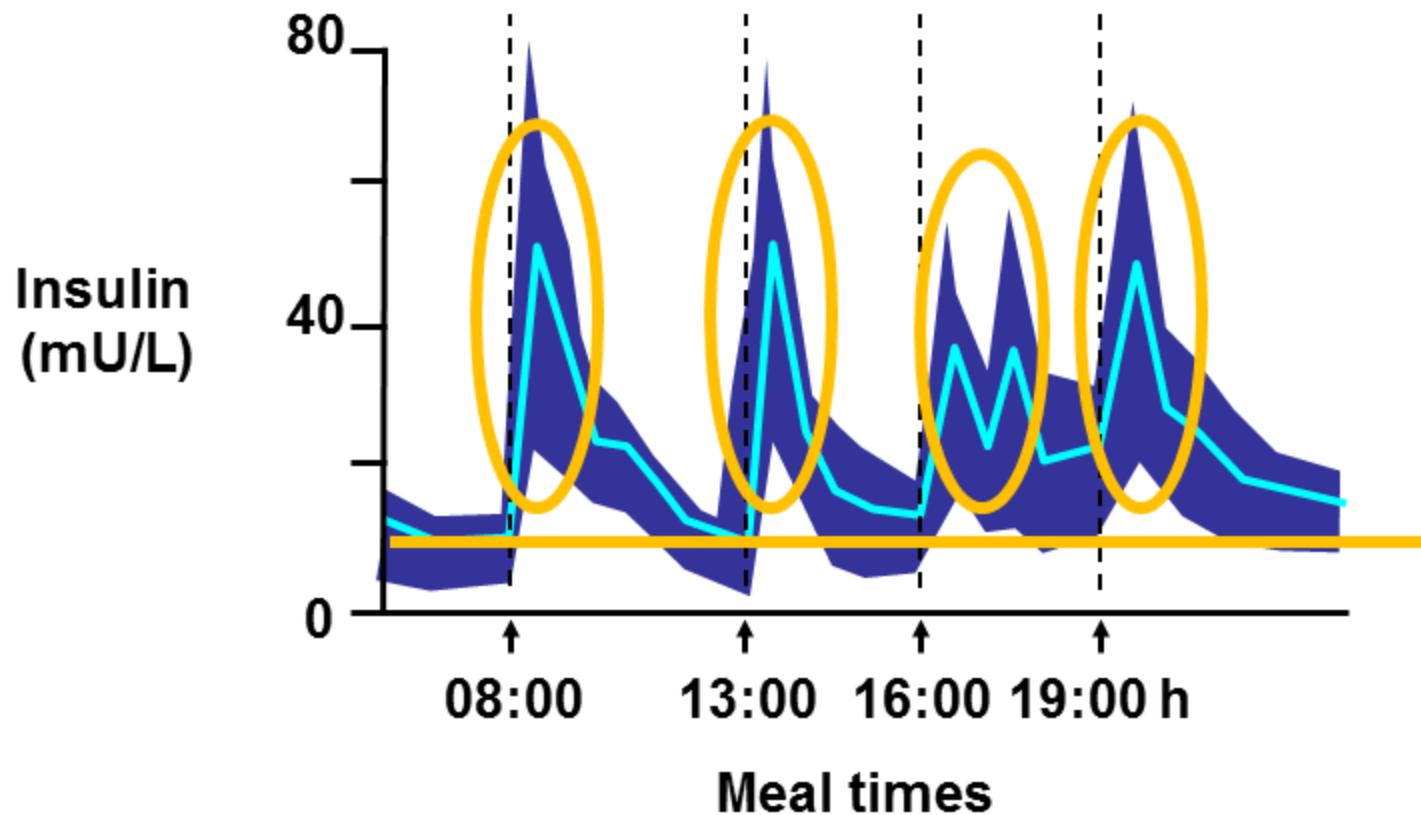
Presentation Overview

- Normal physiology of insulin secretion
- Challenges of administering insulin
 - Hypoglycemia
 - Rigid administration schedules

Physiologic Insulin Secretion 24-Hour Profile

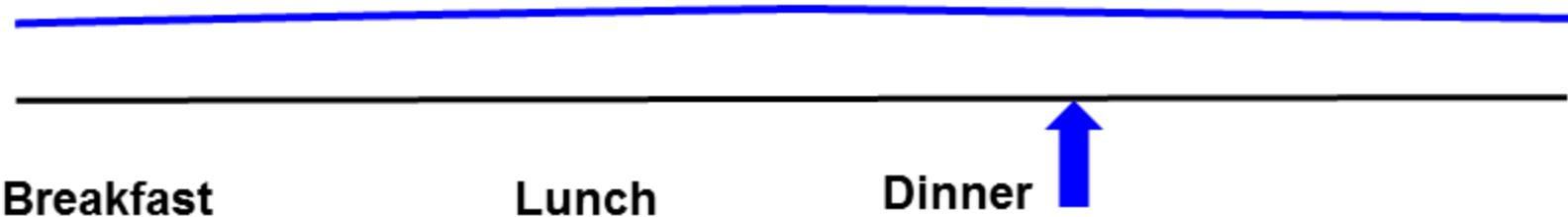
Glucose Homeostasis: *daytime profile*

Normal subjects *Mean levels with 95% CI*

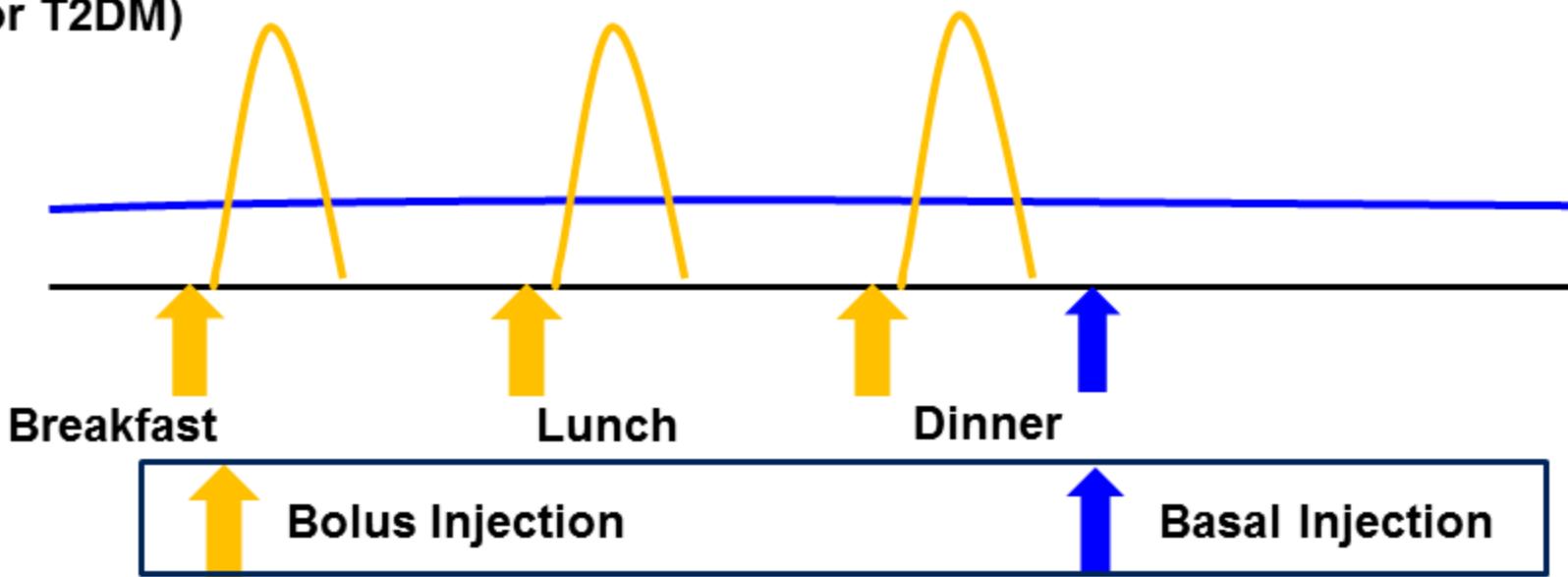


Translating Physiologic Insulin Secretion Principles to Insulin Therapy

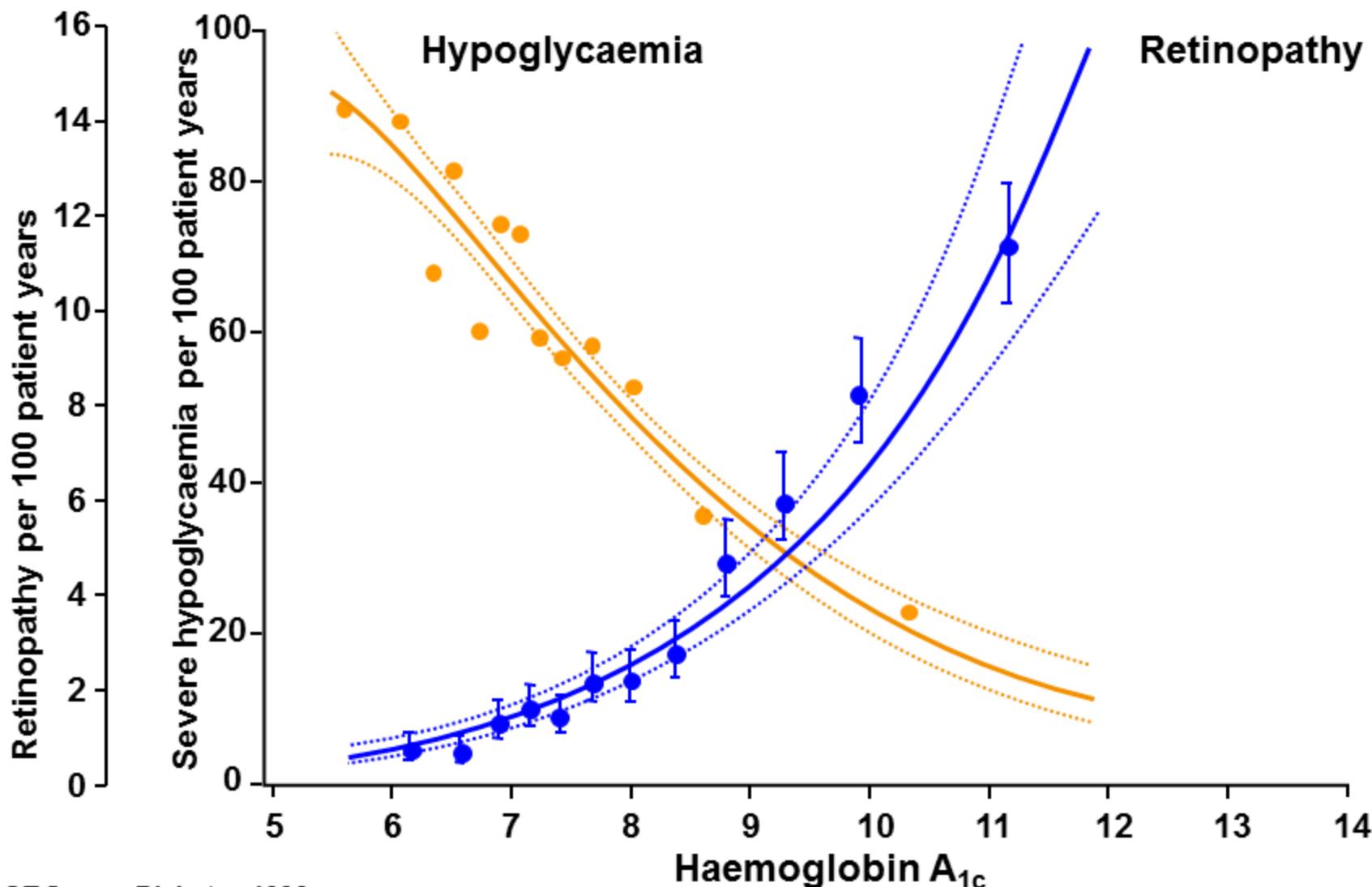
Basal Only Therapy (Only T2DM)



Basal-Bolus Therapy (T1DM or T2DM)



Intensive Therapy and Risk of Hypoglycemia in the DCCT (T1DM)



Multiple Presentations of Hypoglycemia

- Severe hypoglycemia – most medically significant
 - Requires assistance of 3rd party
 - Symptoms: confusion, loss of consciousness, coma, seizures
- Non-severe hypoglycemia
 - Patients generally able to self-treat
 - Often highly disruptive to patient
- Night-time or nocturnal hypoglycemia – often undetected
 - Can lead to serious consequences; falls, sleep disturbances, emergency department visits
 - May have consequences next day

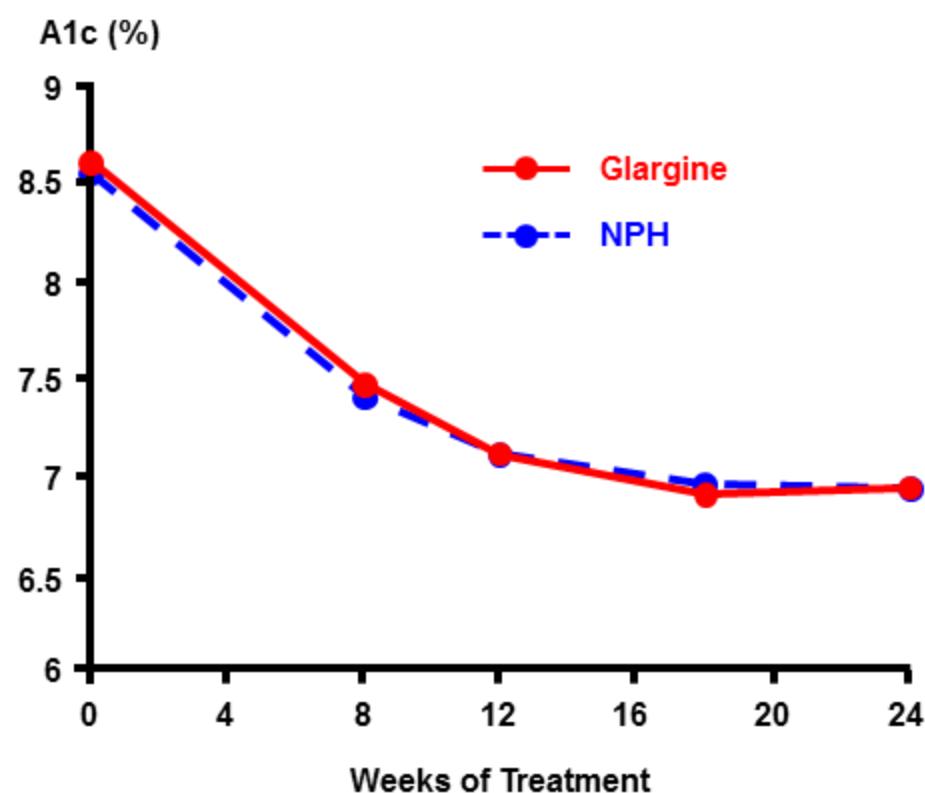
Hypoglycemia a Barrier to Optimal Glycemic Control

- Population based studies report rates of hypoglycemia in patients with T2DM using insulin
 - 1600 non-severe events per 100 patient years
 - 35 severe events per 100 patient years
- 84% physicians concerned about severe or nocturnal hypoglycemia

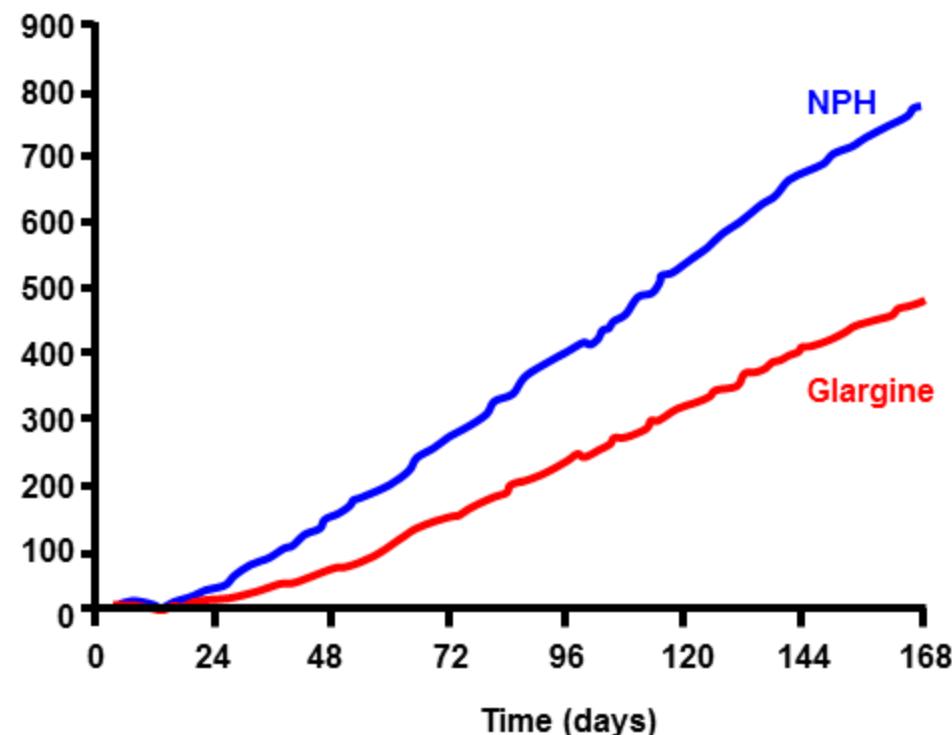
Nocturnal Hypoglycemia of Particular Concern to Patients and Physicians

- Symptoms
 - Nightmares/Night sweats
 - Altered mood/feeling of impending doom
 - Headache / Fatigue
 - Defective memory
- Potential danger to patients due to unawareness
- Primarily reflective of the Basal Insulin

NPH vs Glargine: HbA1c and Hypoglycemia



Cumulative Number of Events Documented
Glucose \leq 56 mg/dl (3.1 mmol/L)



Patient Challenges with Insulin Therapy

- 35% miss insulin dose, or don't take as prescribed
- On average, patients miss 3.4 doses/month
- No clear instructions on a delayed or missed dose

Unmet Needs Remain for Basal Insulin

Value of basal insulin with longer duration of action & less peak to trough variability

- Reduced risk of hypoglycemia, particularly nocturnal hypoglycemia
- Helps patients manage challenges of delayed or missed doses

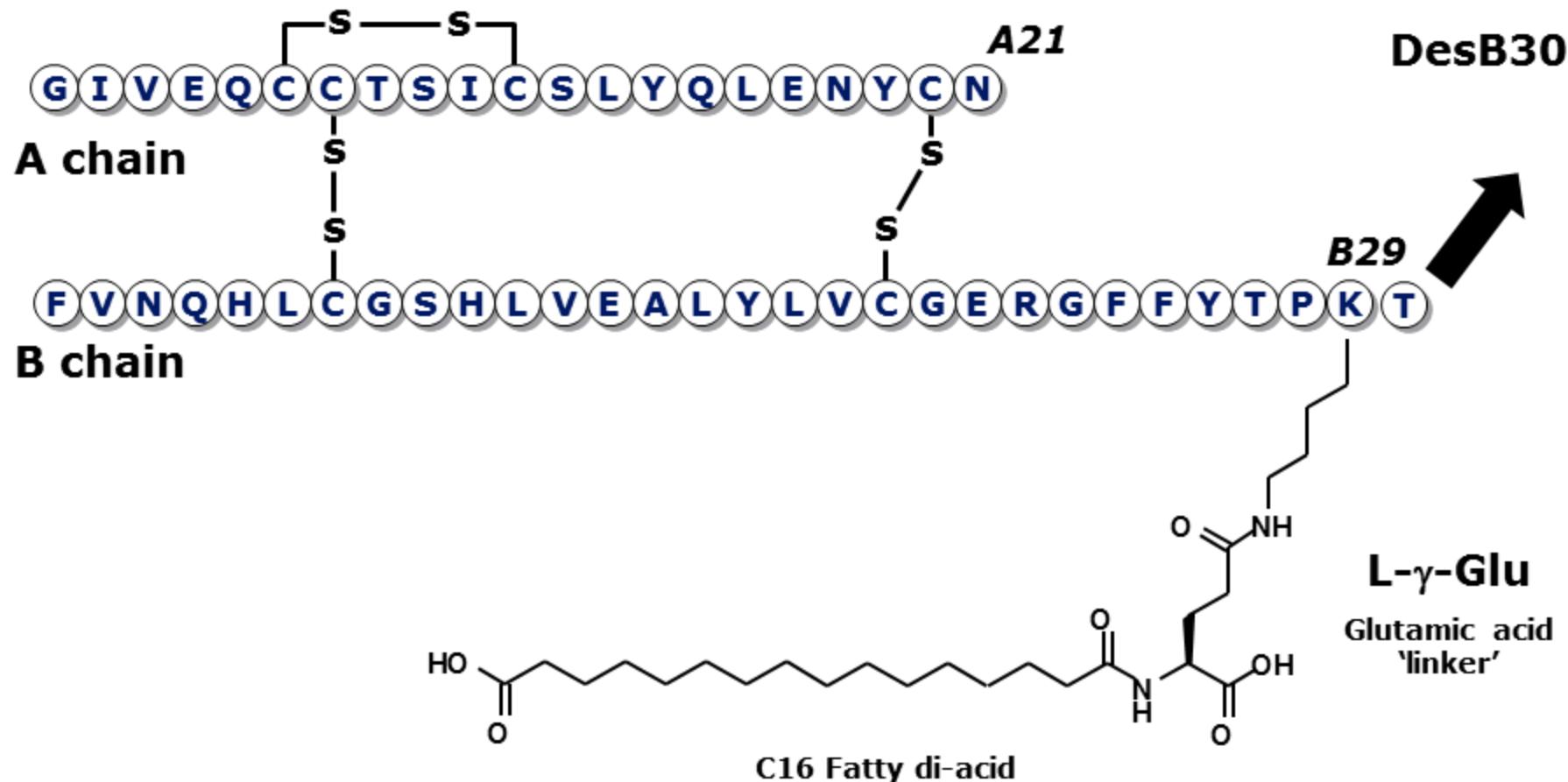
Design of Insulin Degludec

Peter Kurtzhals, PhD
Senior Vice President
Diabetes Research Unit
Novo Nordisk

Goals of Development of an Improved Basal Insulin

- Achieve target glycemic control with reduced risk of hypoglycemia
- Long and predictable action profile
- Low variability of action throughout day
- Retains biological profile, safety, efficacy of human insulin
- Soluble co-formulation with rapid-acting insulin aspart

Structure of IDeg is Based on Human Insulin



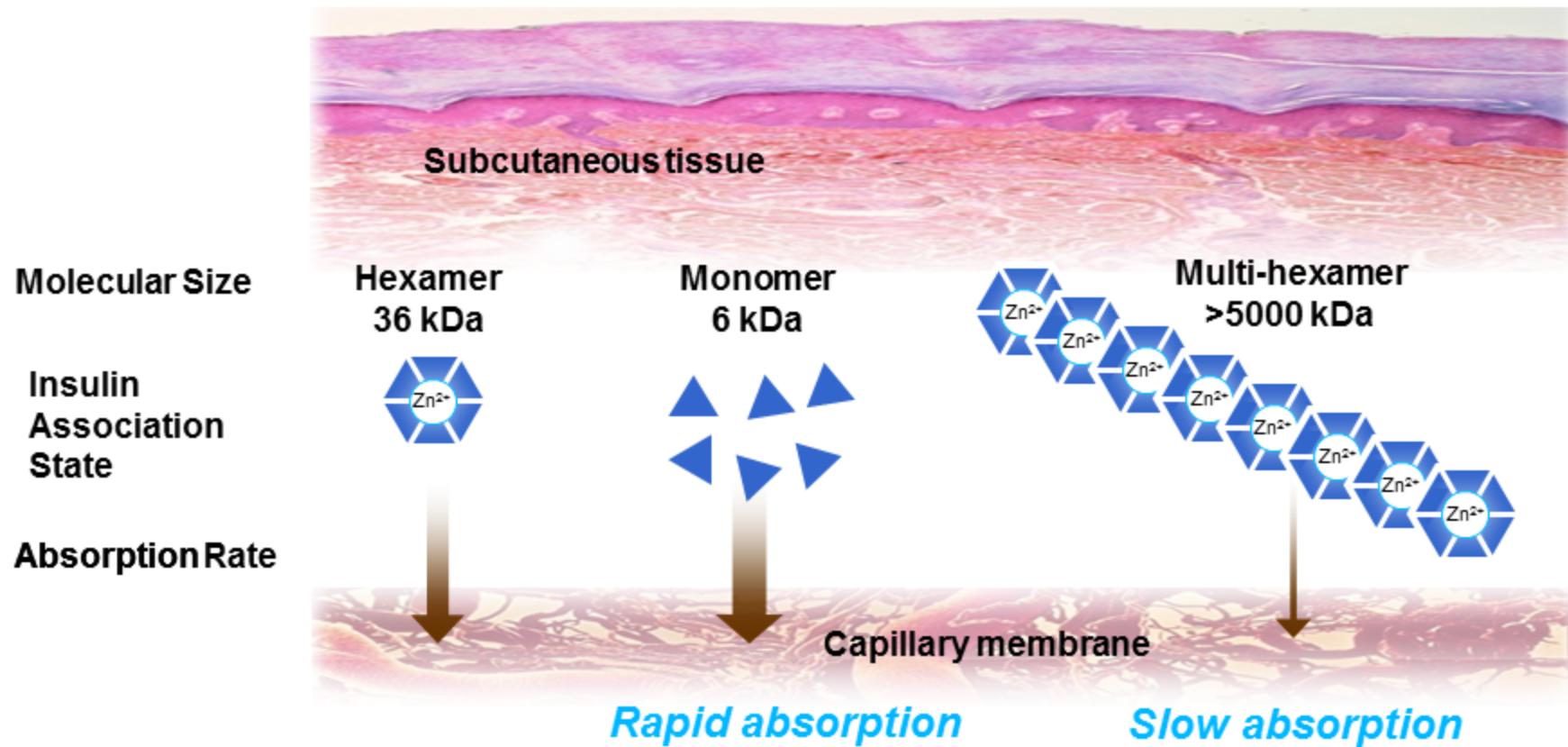
Molecular Pharmacology Equivalent to Human Insulin

- Effects mediated specifically via insulin receptor
- Intracellular signaling like human insulin
- Metabolic effects indistinguishable from human insulin
- Receptor-bound IDeg is internalized, degraded via same pathway as human insulin

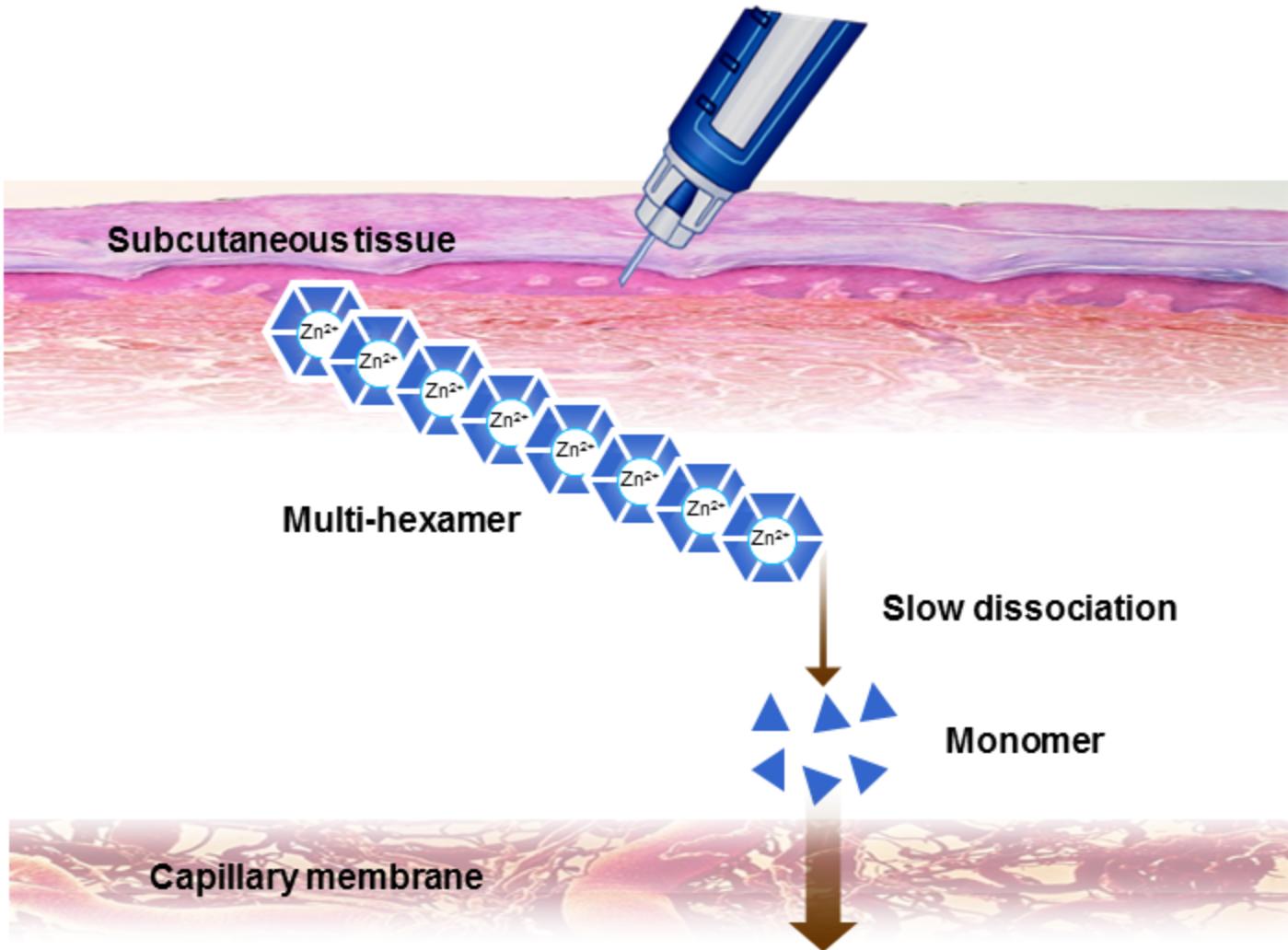
No Safety Signals Observed in Toxicology and Safety Pharmacology Studies

- No biological differences between IDeg and human insulin seen in all
 - Toxicology studies
 - Safety pharmacology studies

IDeg Engineered for Slower Absorption



IDeg Engineered for Slower Absorption



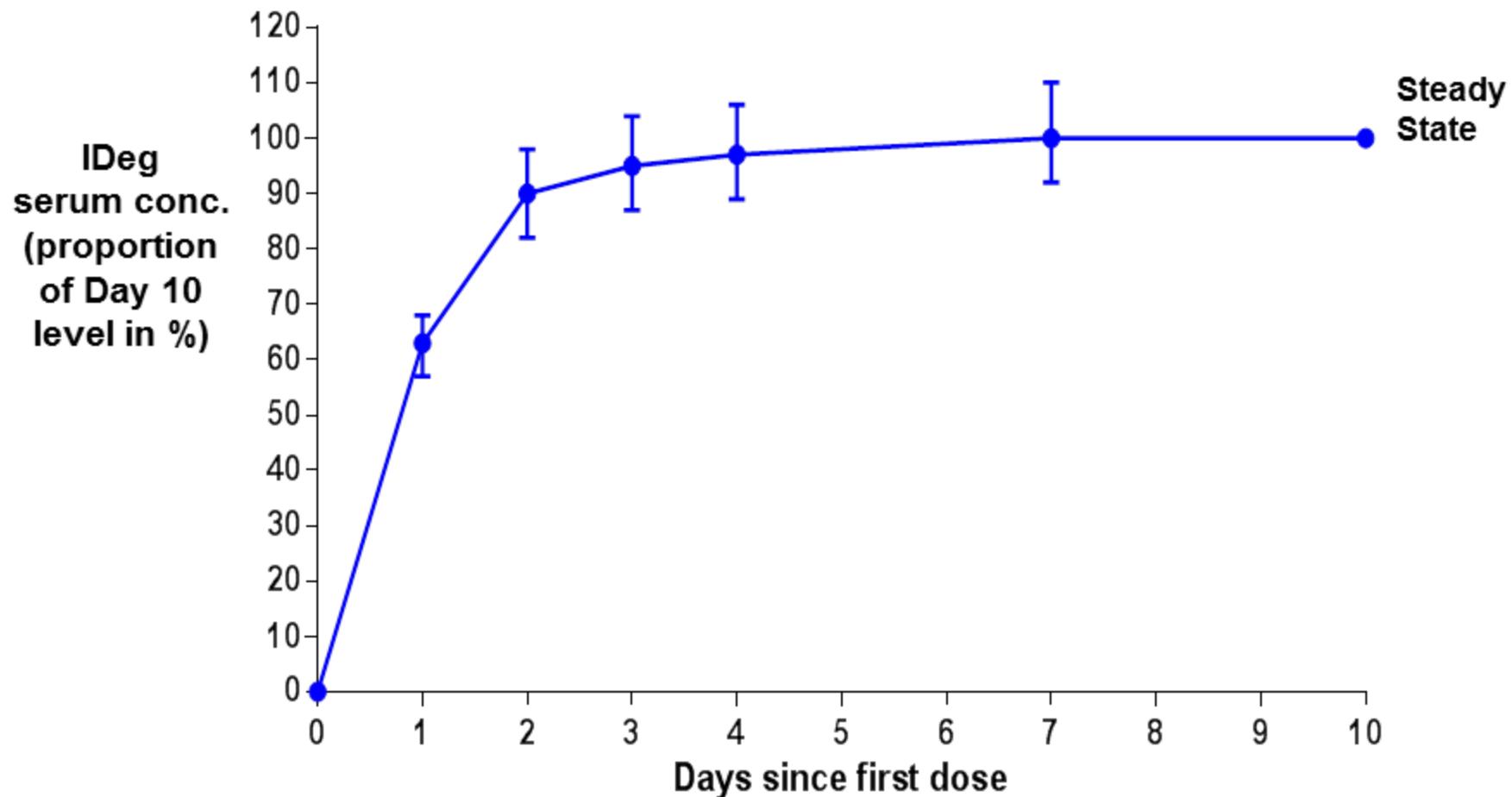
Longer Half-Life of IDeg After Subcutaneous Injection

	IDeg			Glargine		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-Life (hours)	25.9	27.0	23.6	11.5	12.9	11.9
Mean Half-Life	25.4 hours			12.1 hours		

Values are harmonic means

Trial 1993, T1DM, N (IDeg) = 21-22, N (Glargine) = 22

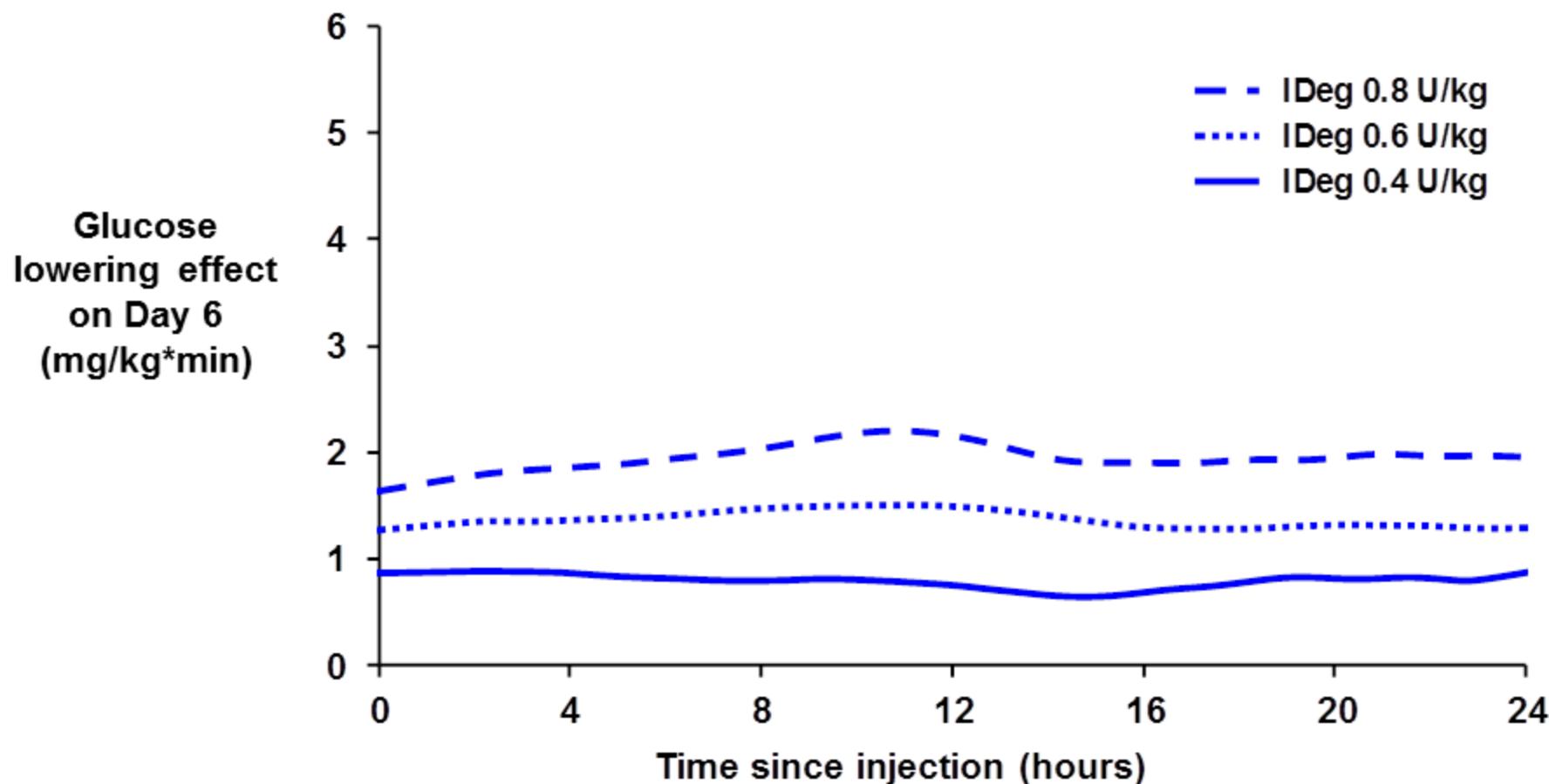
IDeg Steady State Is Reached Within 3 Days of Once-Daily Dosing



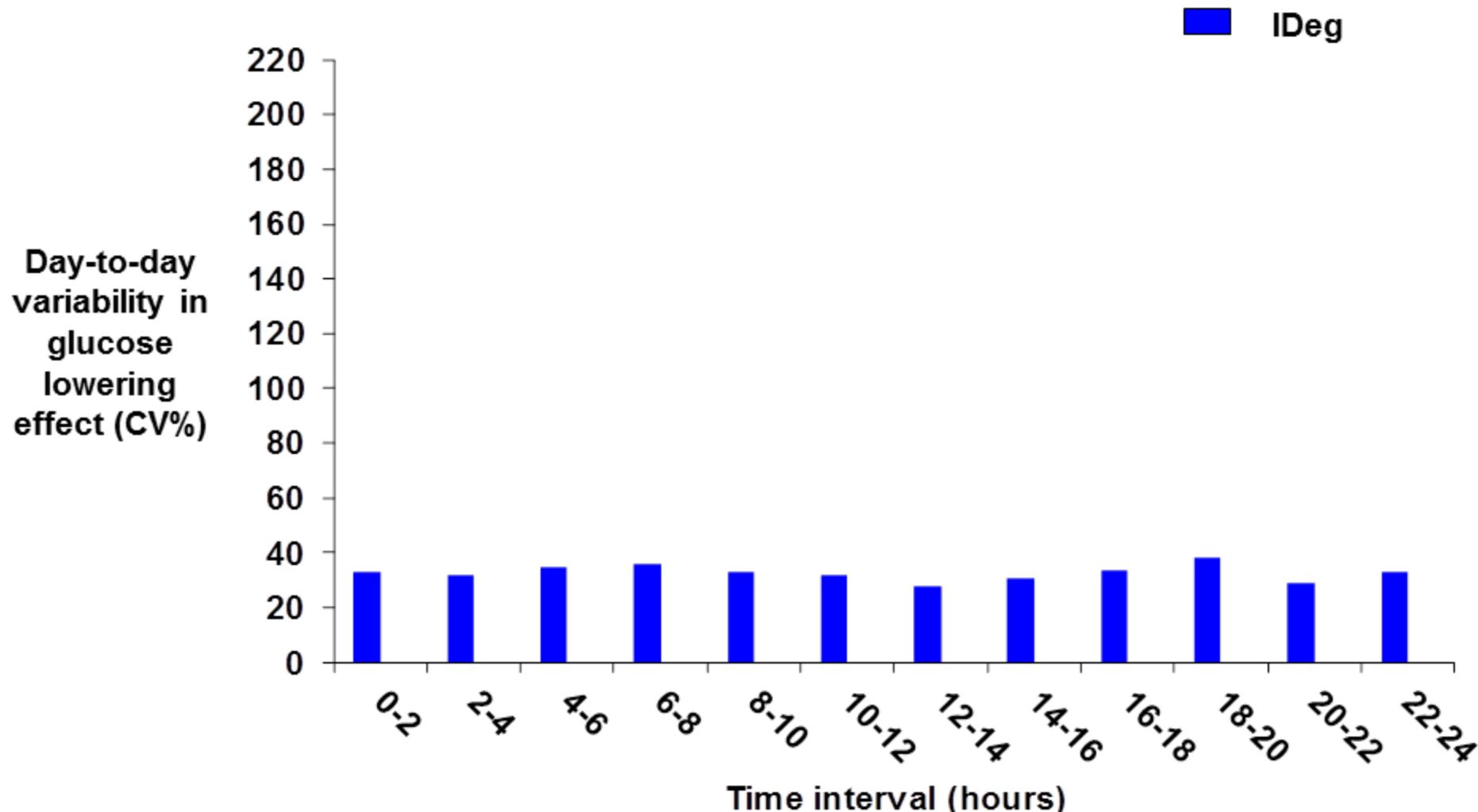
Values are estimated ratios and 95% CI relative to day 10

Trial 1991, T1DM, N=27, 0.4 U/kg

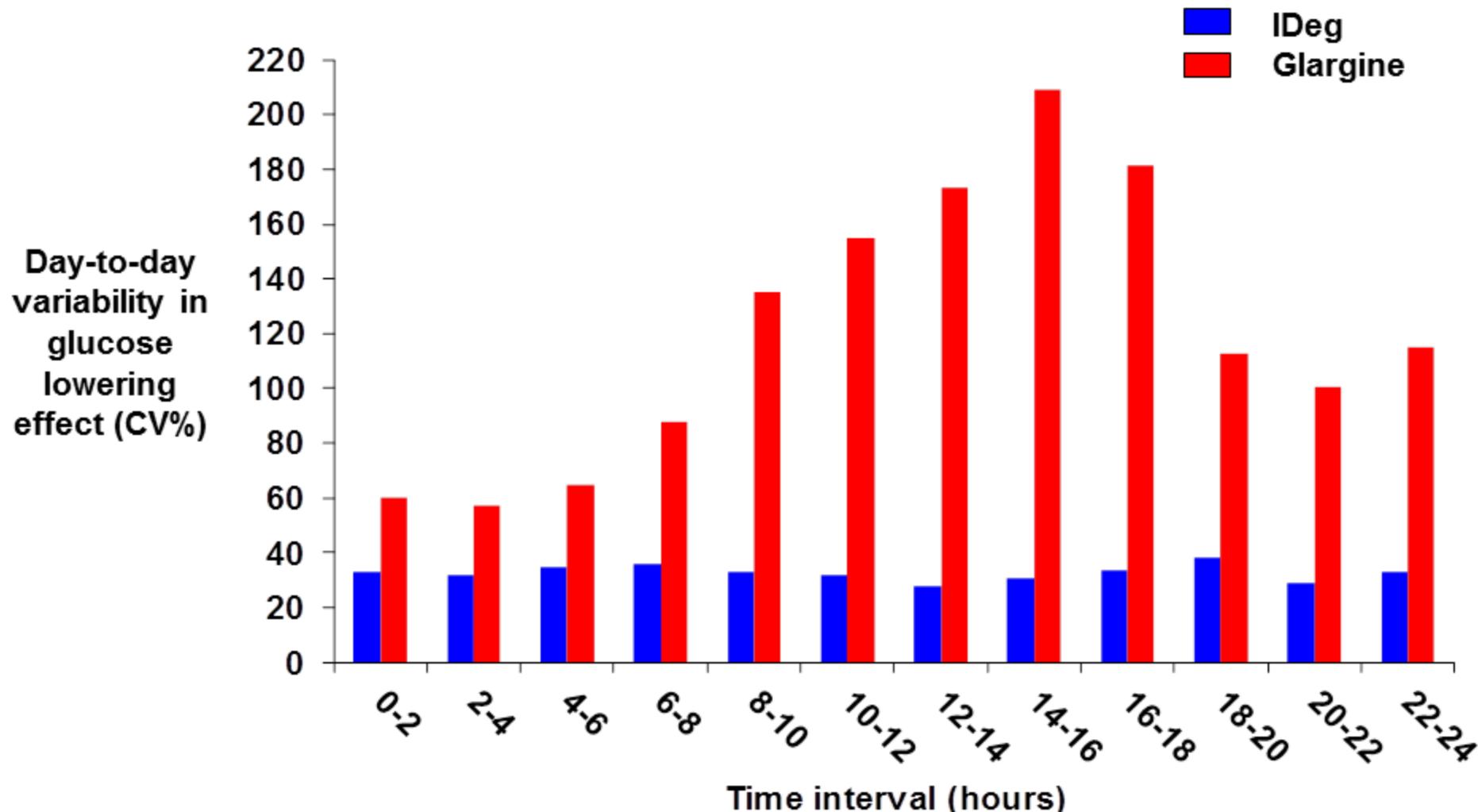
Long Half-Life Results in Flat, Stable PD Profile at Steady State



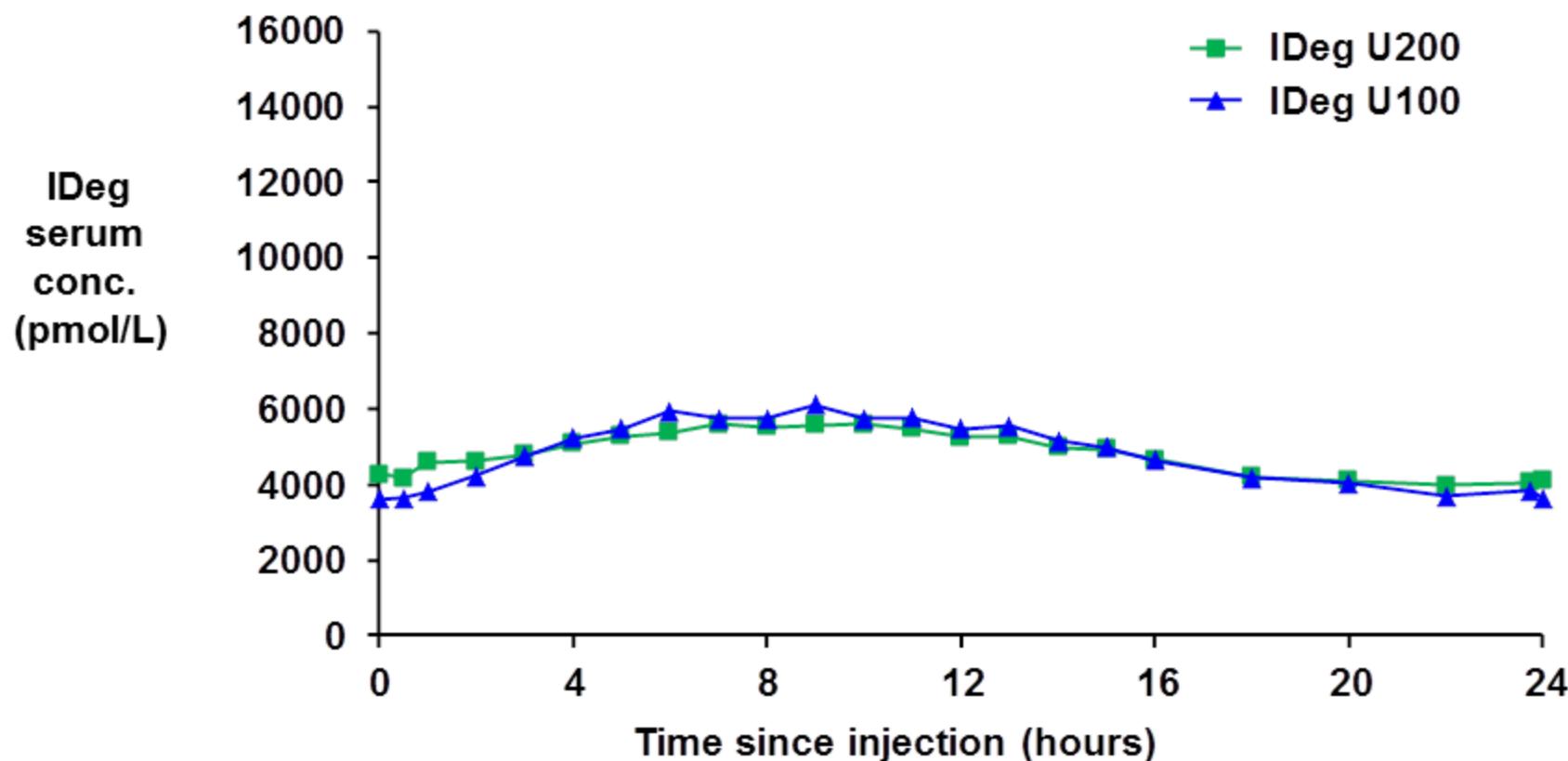
IDeg Demonstrates Low Day-to-Day Within-Subject Variability



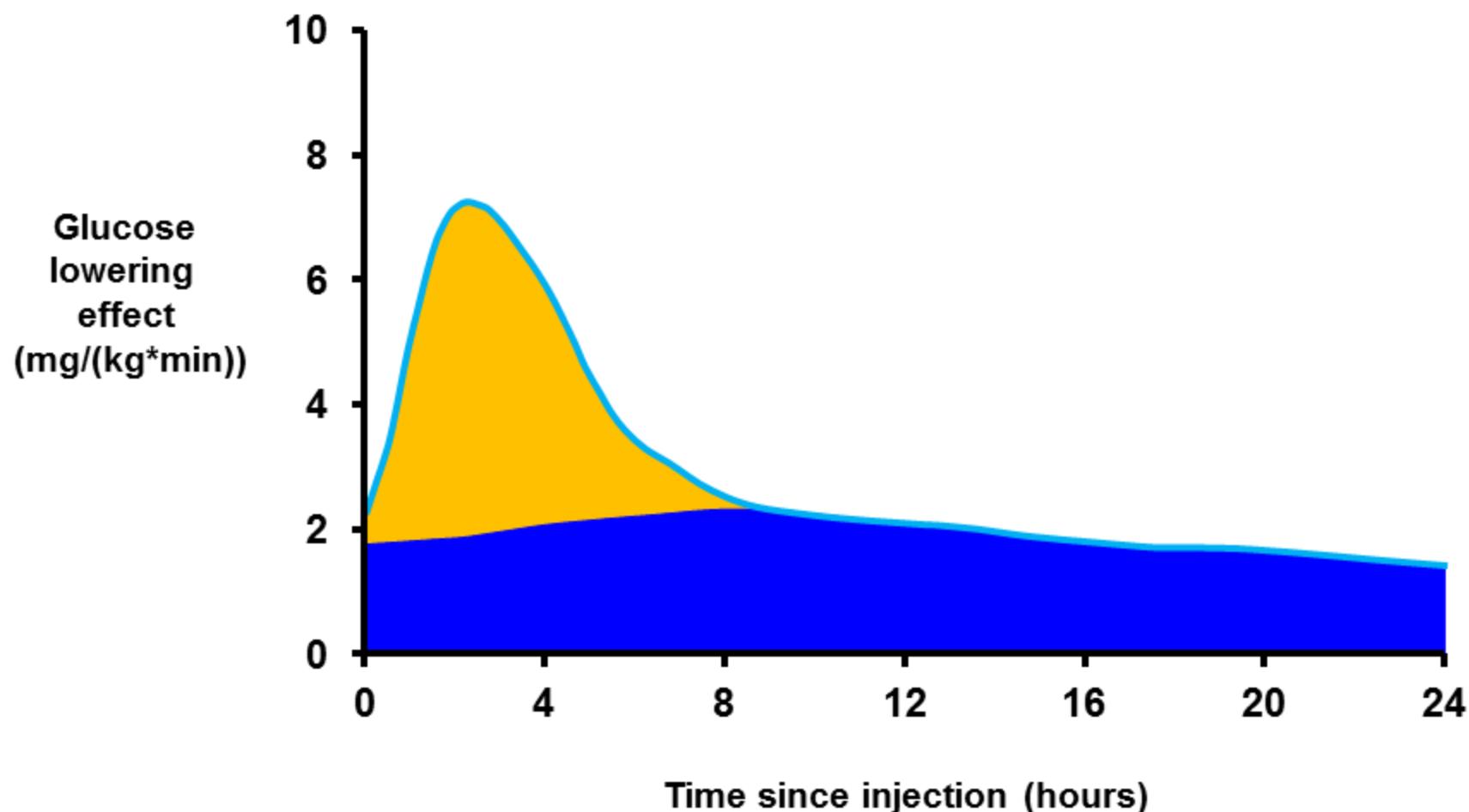
IDeg Demonstrates Low Day-to-Day Within-Subject Variability



Similar PK Profile at Steady State Between U100 and U200



Glucose-Lowering Effect Profile of IDegAsp at Steady State



IDeg – Retains Insulin Biology and Provides Unique Structure

- Stable, long action profile
- Once-daily dosing, preferably at the same time every day
- Low variability with potential to achieve target glycemic control with low risk of hypoglycemia
- Forgiving if patients inadvertently miss or delay a dose
- U200 formulation
- Soluble co-formulation with insulin aspart

Clinical Development Program and Efficacy of IDeg

Alan Moses, MD

Global Chief Medical Officer

Novo Nordisk

Clinical Program Covers Increasing Complexity of Insulin Treatment

Increasing complexity of insulin treatment

Insulin-Naïve T2DM

- Begin with basal insulin
- Relatively low rate of hypoglycemia

Insulin-Treated T2DM

- Basal-bolus insulin
- Higher rate of hypoglycemia

Insulin-Treated T1DM

- Full basal-bolus replacement
- Highest risk of overall and nocturnal hypoglycemia

Nearly 6,500 Patients in IDeg Program, ~40 Countries

Insulin-Naïve
T2DM
N = 3982

Insulin-Treated
T2DM
N = 992

Insulin-Treated
T1DM
N = 1577

52 wks vs. Glargine

26 wks vs. Glargine

26 wks vs. Glargine

26 wks vs. Sitagliptin

26 wks vs. Glargine

26 wks vs. Glargine

26 wks vs. Glargine

52 wks vs. Glargine

52 wks vs. Glargine

26 wks vs. Detemir

26 wks vs. Glargine

IDeg (once daily)

IDeg (3x weekly)

Key Phase 3 Baseline Demographics IDeg vs. Comparator

	IDeg N = 4281	Comparator N = 2270
Duration of Diabetes, years (mean)	12.3	11.1
Female – Gender, %	43.2%	44.2%
Age		
18–65 years, n (%)	3421 (79.9%)	1834 (80.8%)
> 65 years, n (%)	860 (20.1%)	436 (19.2%)
Race		
White, n (%)	3201 (74.8%)	1697 (74.8%)
Black or African American, n (%)	241 (5.6%)	131 (5.8%)
Ethnicity – Hispanic or Latino, n (%)	417 (9.7%)	242 (10.7%)

Key Inclusion/Exclusion Criteria for Phase 3 Trials

Inclusion Criteria	T2DM	T1DM
Diagnosed Clinically with Diabetes	≥ 6 months	≥ 12 months
BMI (kg/m ²)	≤ 40 ≤ 45 (U200)	≤ 35
HbA _{1c} (%)	7.0 – 10.0	≤ 10.0
Exclusion Criteria	T2DM	T1DM
History of Cardiovascular Disease	Within last 6 months prior to 1 st visit	
Severe Hypoglycemia	> 1 severe hypoglycemic episode in last 12 months or hypoglycemic unawareness	
Impaired Renal Function (serum creatinine)	Males ≥ 1.4 mg/dL Females ≥ 1.3 mg/dL	≥ 2.0 mg/dL

Development Program Based on Regulatory Guidance and Consultation with Experts

Study design considerations for insulin

- Achieve reductions in HbA_{1c} from baseline
- Similar glycemic control as approved insulin (i.e., treat to target)
- Non-inferior control of glycemia between insulin arms necessary to assess frequency, severity of hypoglycemia

Concept of Treat-to-Target Design

- Insulin is a fully titratable therapy
 - In clinical practice, target levels of glucose chosen for individual patient
 - In clinical trials, target goal set for population
- Regulatory expectation
 - All insulins can achieve same level of control, allowing assessment of hypoglycemia

Rationale for Design of Phase 3 Trials

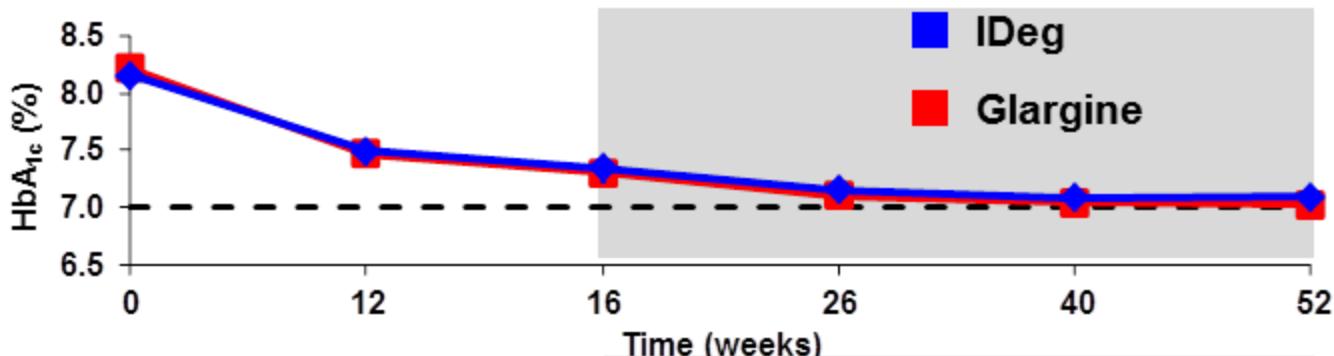
- Open-label design
- Doses individually titrated using protocol-designated algorithm
- Unequal randomization to increase exposure to IDeg

Efficacy Endpoints and Analysis

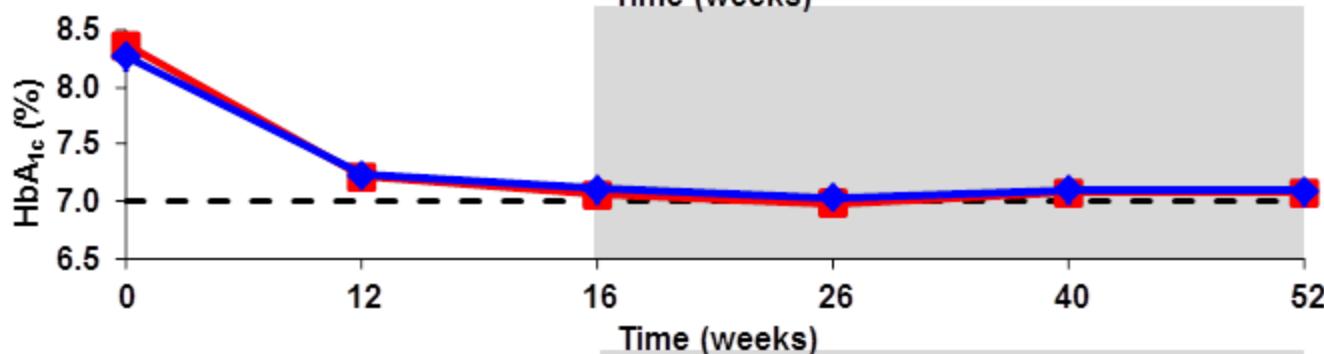
- Primary
 - Change from baseline in HbA_{1c}
 - Non-inferiority margin 0.4%
- Secondary
 - Fasting plasma glucose
 - Hypoglycemia

Change in HbA_{1c} over Time

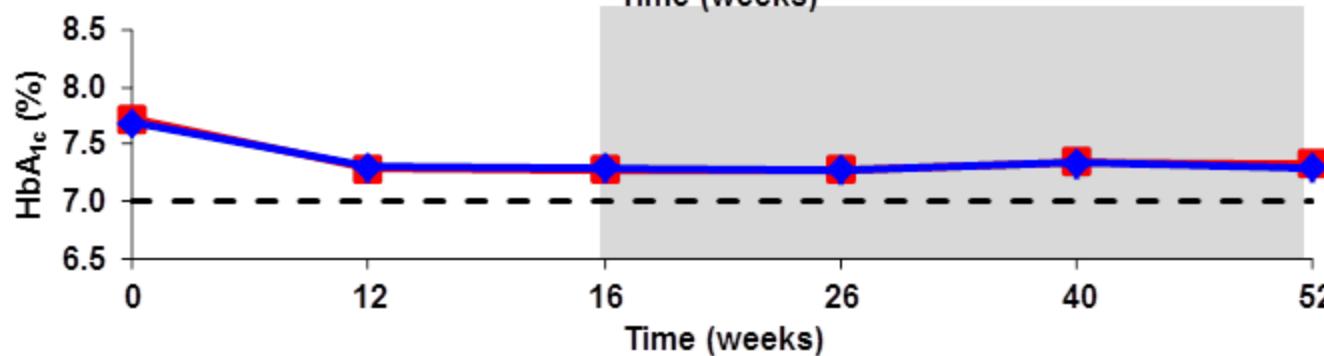
**Basal-Only
T2DM
Trial 3579**



**Basal-Bolus
T2DM
Trial 3582**



**Basal-Bolus
T1DM
Trial 3583**



HbA_{1c} Non-Inferiority Criteria Met in All IDeg Phase 3 Trials

	Trial		IDeg – Comparator (Difference)	[95% CI]
Basal-Only T2DM	52 wks vs. Glargine	(Trial 3579)	0.09	[-0.04; 0.22]
	26 wks vs. Glargine	(Trial 3672)†	0.04	[-0.11; 0.19]
	26 wks vs. Glargine	(Trial 3586)	0.11	[-0.03; 0.24]
	26 wks vs. Glargine	(Trial 3668)	0.04	[-0.12; 0.20]
	26 wks vs. Sitagliptin	(Trial 3580)	-0.43	[-0.61; -0.24]*
Basal-Bolus T2DM	52 wks vs. Glargine	(Trial 3582)	0.08	[-0.05; 0.21]
Basal-Bolus T1DM	52 wks vs. Glargine	(Trial 3583)	-0.01	[-0.14; 0.11]
	26 wks vs. Detemir	(Trial 3585)	-0.09	[-0.23; 0.05]
	26 wks vs. Glargine	(Trial 3770)	0.17	[0.04; 0.30]*

* p <0.05; † U200 IDeg vs. U100 Glargine

Fasting Plasma Glucose Reductions in All IDeg Phase 3 Trials

	Trial		IDeg – Comparator (Difference)	[95% CI]
Basal-Only T2DM	52 wks vs. Glargine	(Trial 3579)	-7.83	[-13.34; -2.31]*
	26 wks vs. Glargine	(Trial 3672)†	-7.59	[-14.09; -1.09]*
	26 wks vs. Glargine	(Trial 3586)	-1.57	[-7.31; 4.18]
	26 wks vs. Glargine	(Trial 3668)	-7.53	[-14.72;-0.35]*
	26 wks vs. Sitagliptin	(Trial 3580)	-39.07	[-46.75; -31.39]*
Basal-Bolus T2DM	52 wks vs. Glargine	(Trial 3582)	-5.24	[-11.62, 1.14]
Basal-Bolus T1DM	52 wks vs. Glargine	(Trial 3583)	-5.97	[-18.50, 6.56]
	26 wks vs. Detemir	(Trial 3585)	-29.84	[-42.64, -17.05]*
	26 wks vs. Glargine	(Trial 3770)	-0.83	[-15.35; 13.70]

* p <0.05; † U200 IDeg vs. U100 Glargine

Efficacy Established with Additional Clinical Benefits of IDeg

- Lower rates of hypoglycemia
- Vary daily injection time day to day if patient inadvertently misses, needs to delay dose
- U200 formulation
- Soluble co-formulation with insulin aspart (IDegAsp)

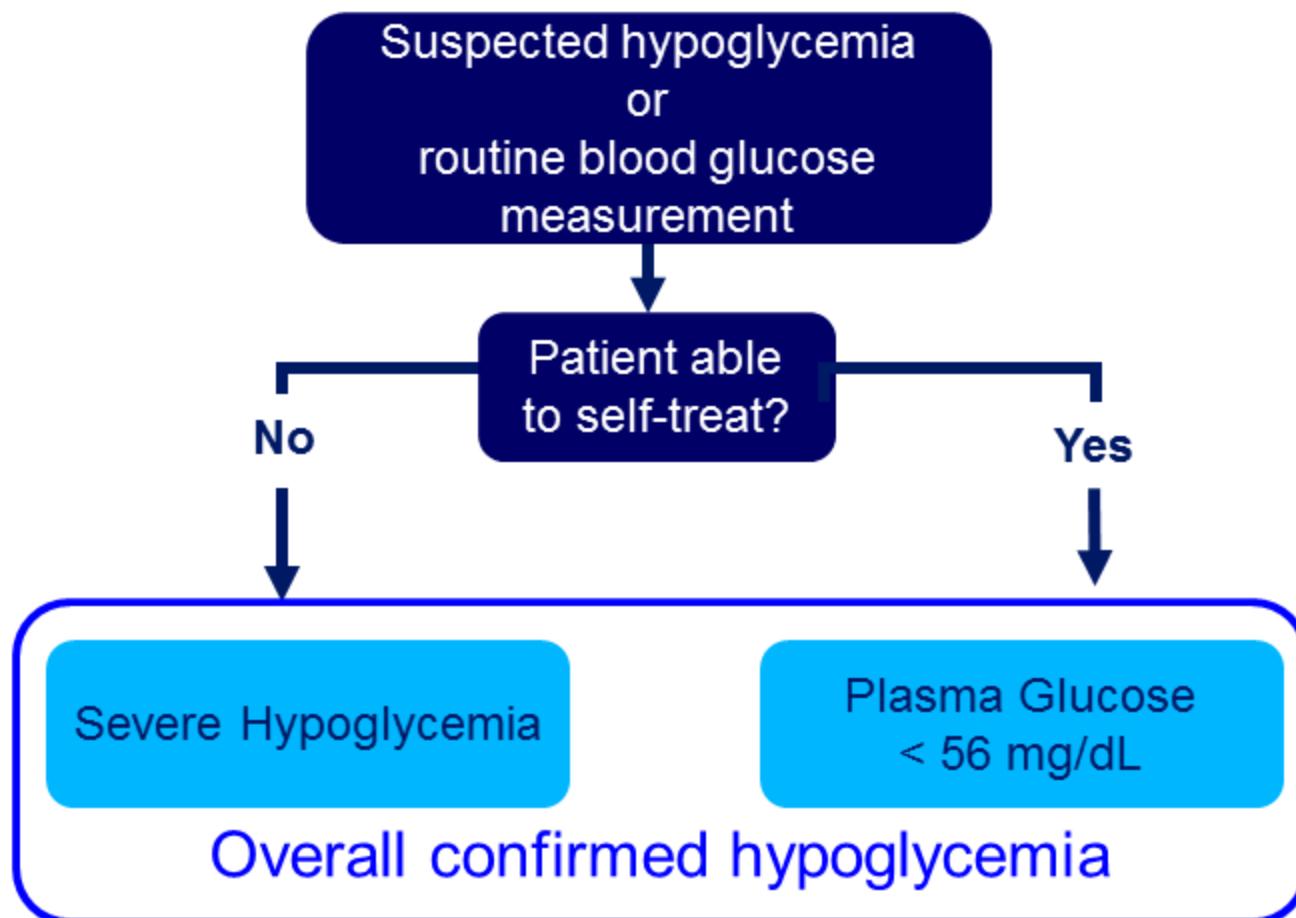
Further Differentiating IDeg from Available Basal Insulins

Focus on Hypoglycemia

Outline of Hypoglycemia Presentation

- Trial-by-trial review
 - Severe hypoglycemia
 - Overall confirmed hypoglycemia
 - Nocturnal confirmed hypoglycemia
- Prespecified meta-analysis
- Additional analyses recommended by FDA

Hypoglycemia Defined Based on Clinically Relevant Criteria



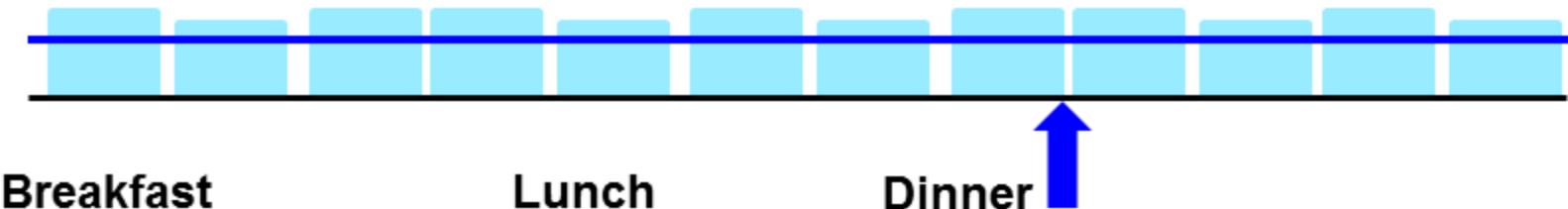
A nocturnal confirmed episode is any episode between midnight and 6:00 AM

Clinical Rationale for Prespecified Hypoglycemia Definition (PG < 56 mg/dL)

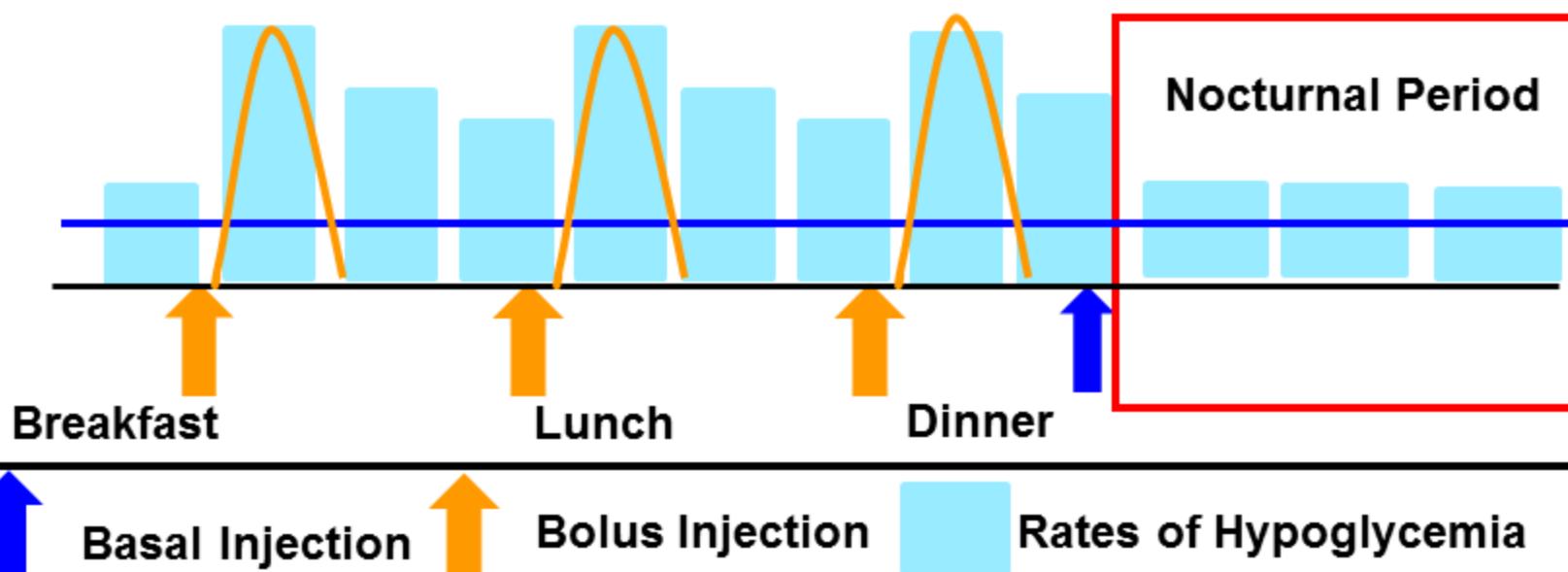
- Most patients experience clinical symptoms of hypoglycemia at PG < 56 mg/dL
- Increase specificity
- Clinical trial precedence

Effects of Basal-Only or Basal-Bolus Therapies on Timing of Hypoglycemia

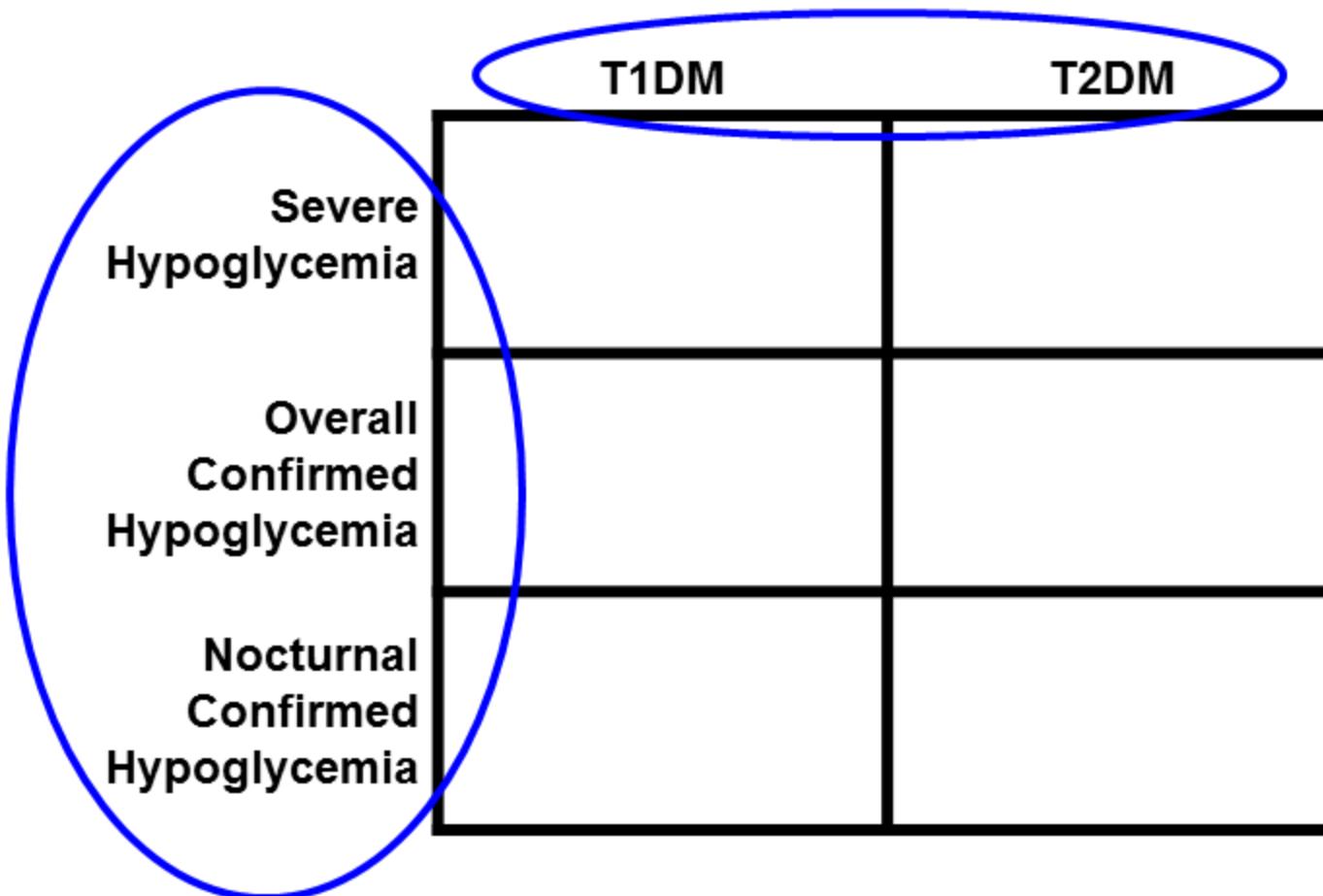
Basal-Only Therapy (Only T2DM)



Basal-Bolus Therapy (T1DM or T2DM)



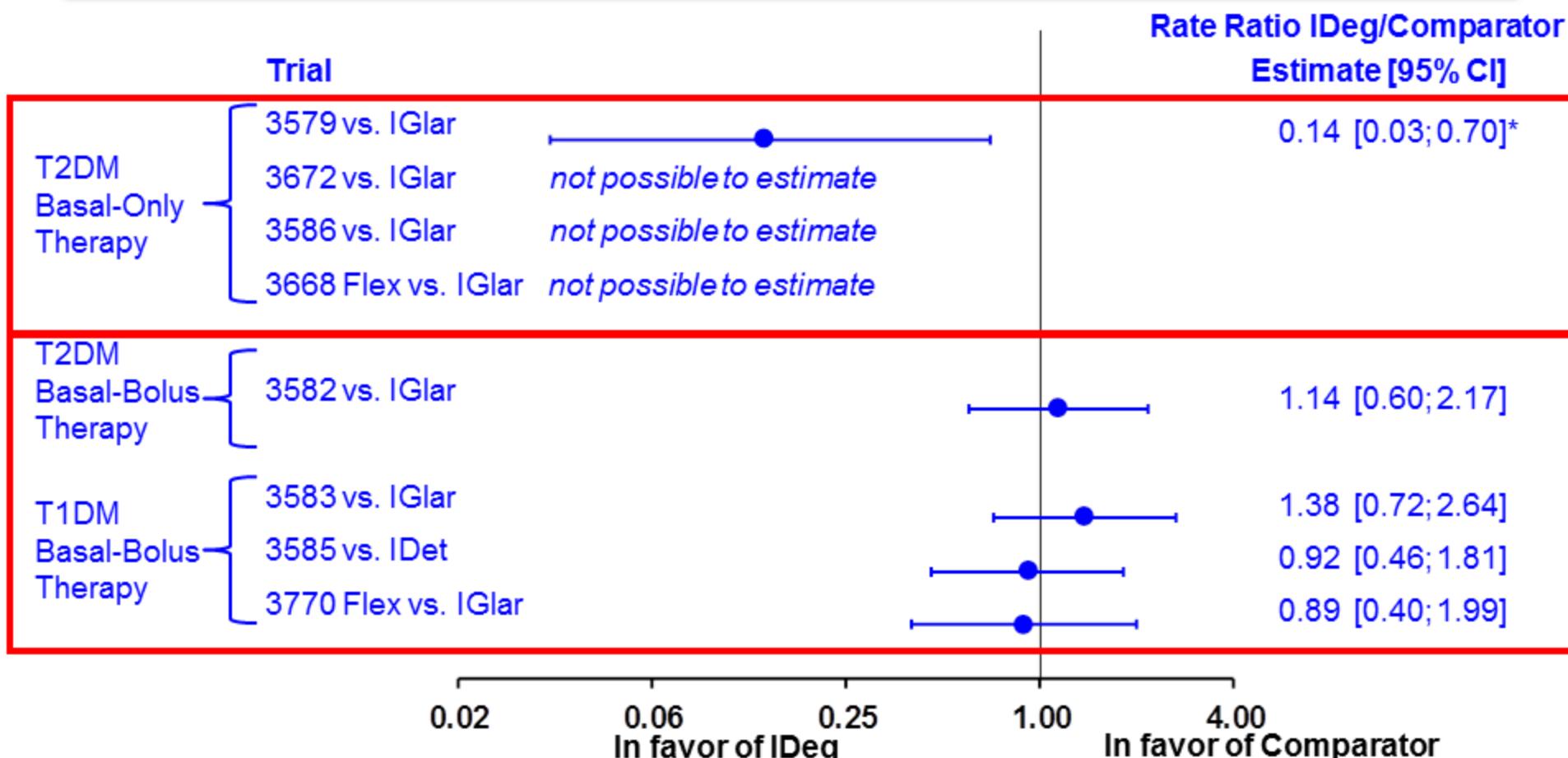
Overview of Hypoglycemia



Overview of Hypoglycemia

	T1DM	T2DM
Severe Hypoglycemia		
Overall Confirmed Hypoglycemia		
Nocturnal Confirmed Hypoglycemia		

Severe Hypoglycemia – IDeg vs. Comparator Insulins



Observed rates of severe hypoglycemia:

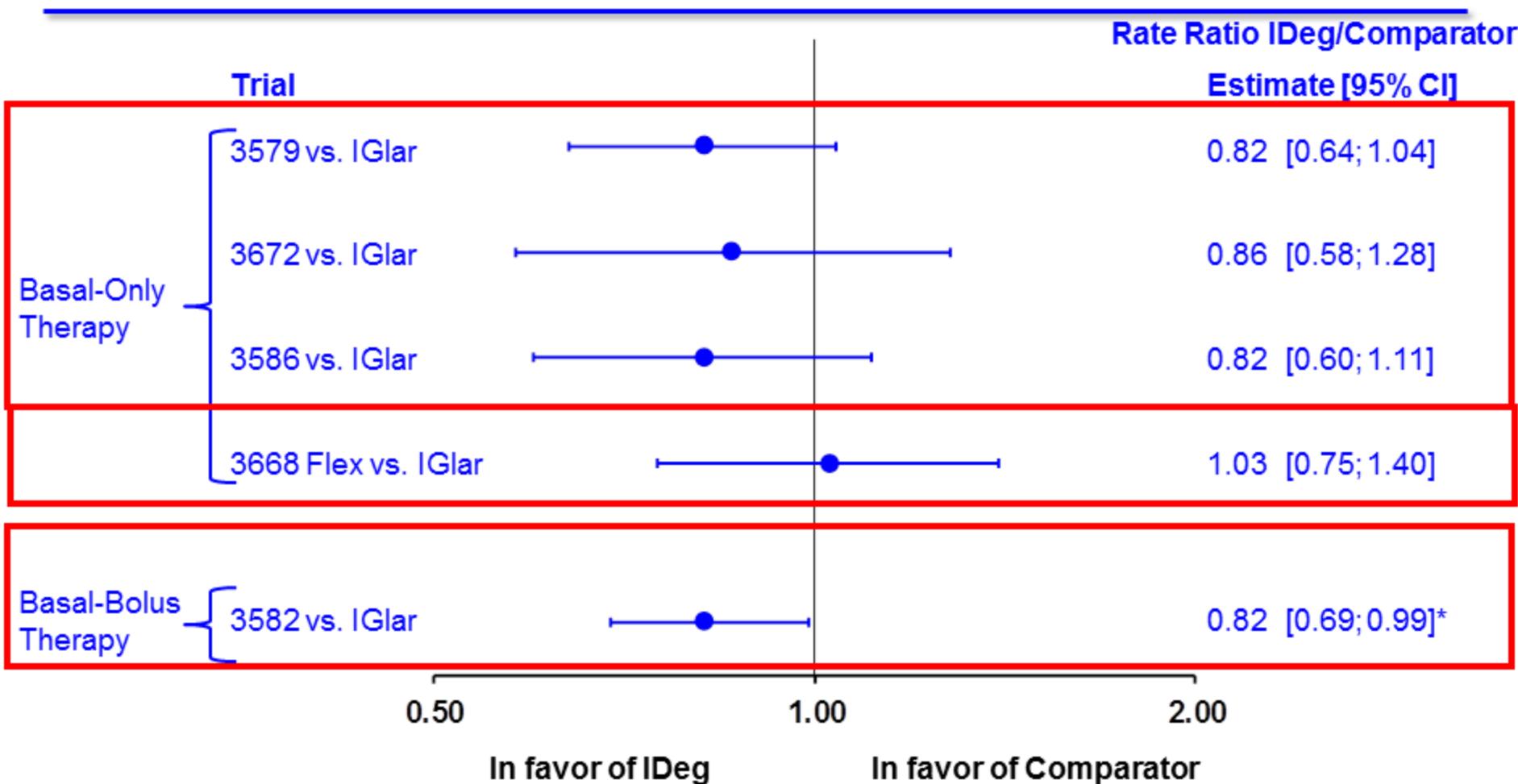
T2DM BOT 0-2.3/100 PYE; **T2DM BB** 5.2-6.1/100 PYE; **T1DM** 16-47/100 PYE

* $p < 0.05$, FAS. Not possible to estimate: ≤ 2 episodes in each treatment arm

Overview of Hypoglycemia

	T1DM	T2DM
Severe Hypoglycemia		
Overall Confirmed Hypoglycemia		
Nocturnal Confirmed Hypoglycemia		

Overall Confirmed Hypoglycemia in T2DM – IDeg vs. Glargine



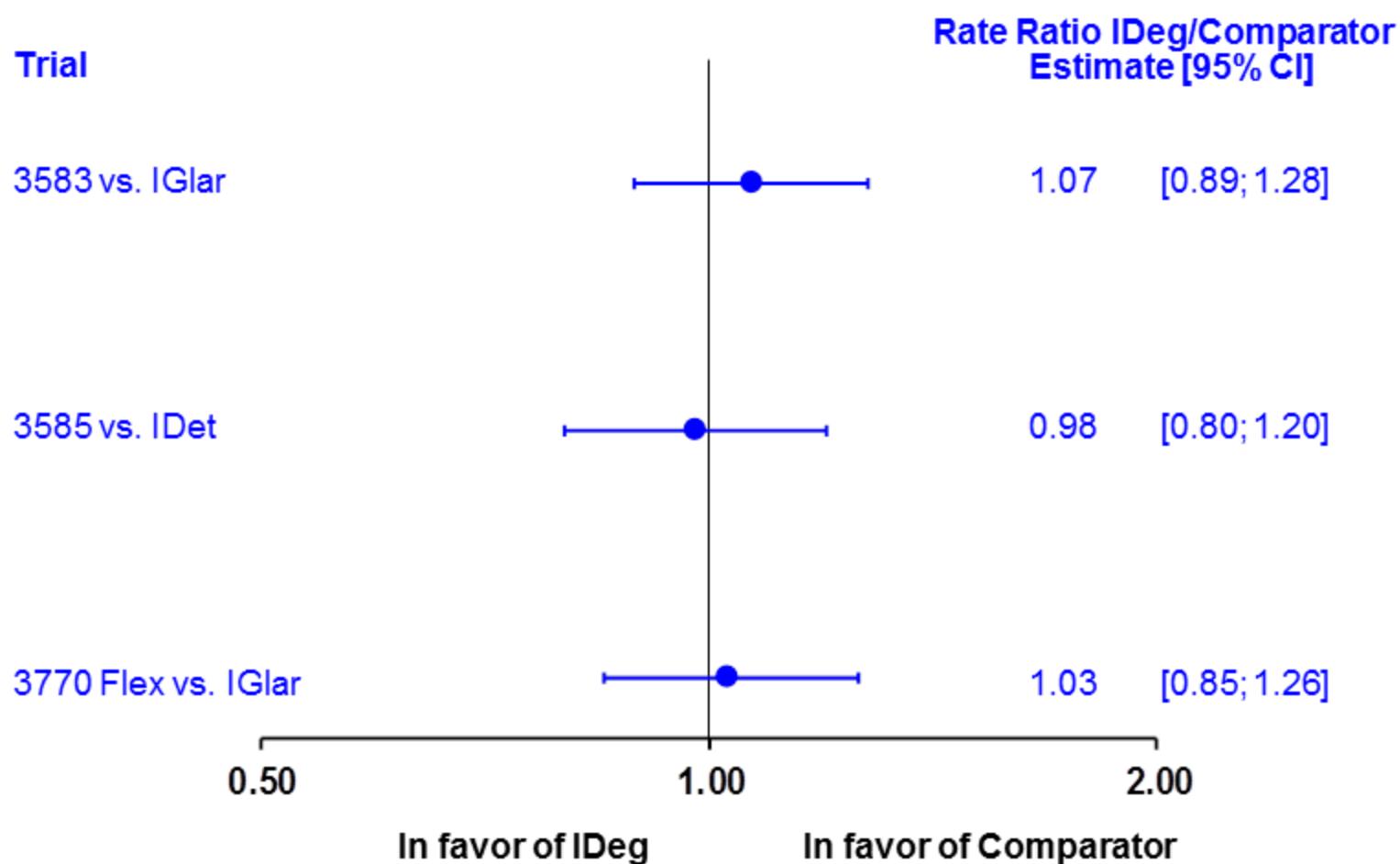
Observed rates of overall confirmed hypoglycemia:

T2DM BOT 122-370/100 PYE; T2DM BB 1109-1363/100 PYE

Overview of Hypoglycemia

	T1DM	T2DM
Severe Hypoglycemia		
Overall Confirmed Hypoglycemia		
Nocturnal Confirmed Hypoglycemia		

Overall Confirmed Hypoglycemia in T1DM – IDeg vs. Comparator Insulins

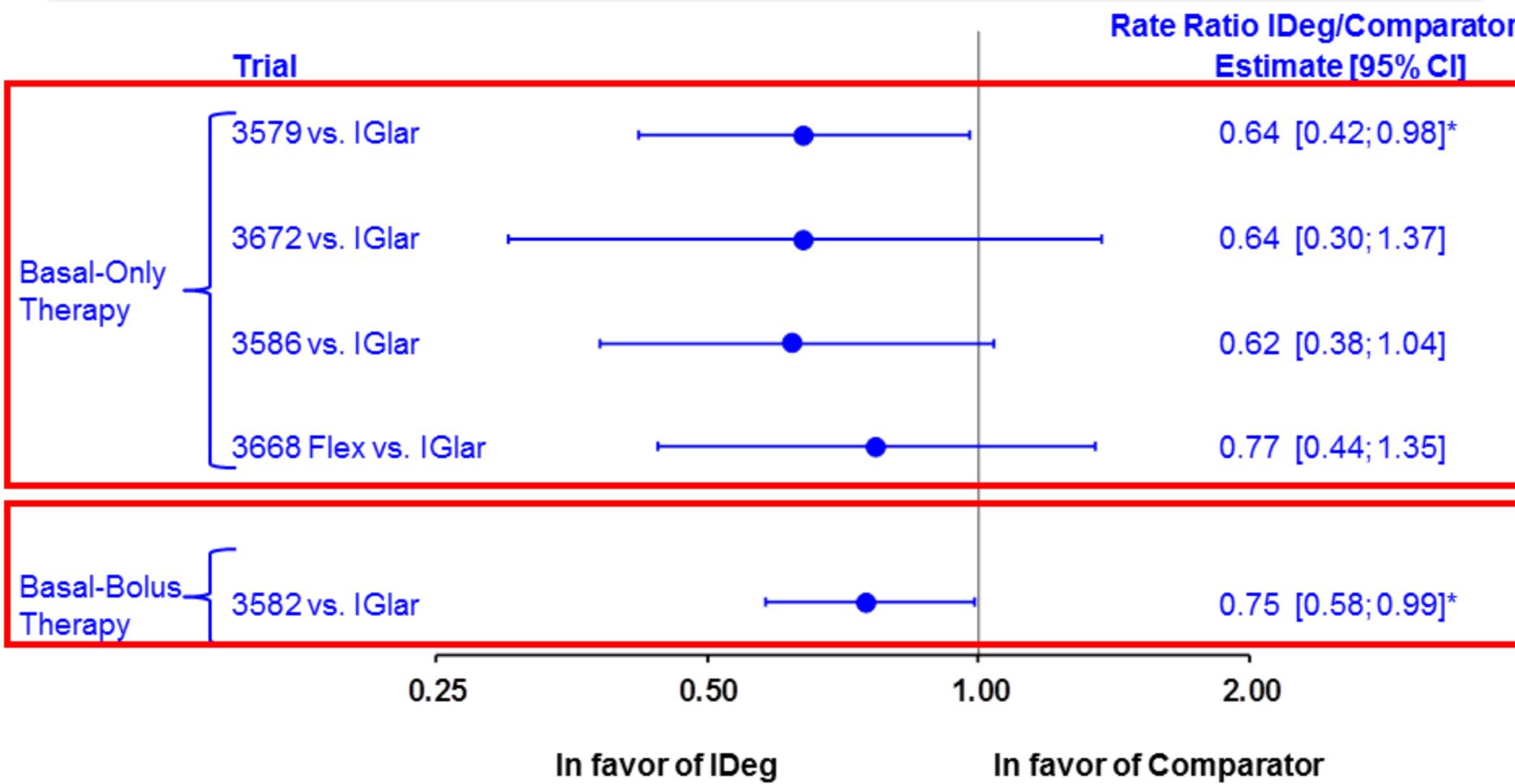


Observed rates of overall confirmed hypoglycemia:
T1DM: 4018-8238/100 PYE

Overview of Hypoglycemia

	T1DM	T2DM
Severe Hypoglycemia		
Overall Confirmed Hypoglycemia		
Nocturnal Confirmed Hypoglycemia		

Nocturnal Confirmed Hypoglycemia in T2DM – IDeg vs. Glargine



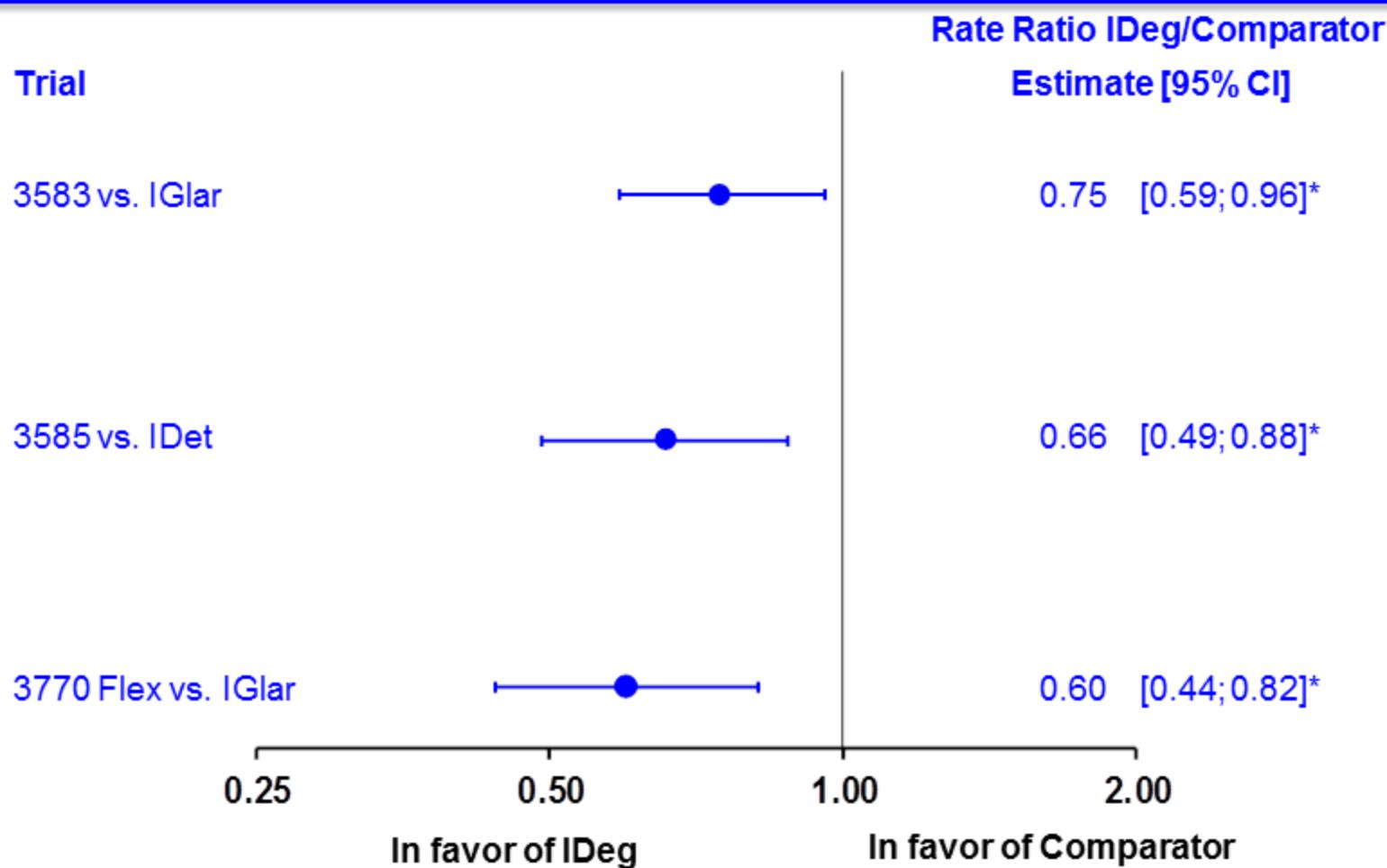
Observed rates of nocturnal hypoglycemia:

T2DM BOT 18-124/100 PYE; T2DM BB 139-184/100 PYE;

Overview of Hypoglycemia

	T1DM	T2DM
Severe Hypoglycemia		
Overall Confirmed Hypoglycemia		
Nocturnal Confirmed Hypoglycemia		

Nocturnal Confirmed Hypoglycemia in T1DM – IDeg vs. Comparator Insulins



Observed rates of nocturnal hypoglycemia T1DM:
414-996/100 PYE (4-10/pye)

Prespecified Hypoglycemia Meta-Analysis All IDeg vs. Glargine Trials

- Prospectively planned, reviewed by FDA before analyzing data from any Phase 3 trials
- Primary endpoint was overall confirmed hypoglycemia (T2DM+T1DM)
- Key predefined secondary analyses
 - Nocturnal confirmed hypoglycemia
 - T2DM and T1DM separately
 - T2DM basal-only therapy separately

FDA Recommendations for Hypoglycemia Analyses

- Assess hypoglycemia in maintenance period
- Differentiate incident cases of hypoglycemia vs. event rates
- Assess hypoglycemia event rate for patients at glycemic target ($\text{HbA}_{1\text{c}} < 7\%$)
- Conduct sensitivity analysis of nocturnal hypoglycemia using different time windows

Meta-Analysis – Overall Confirmed and Nocturnal Confirmed Hypoglycemia

	Rate Ratio IDeg/Glargine Estimate [95% CI]
Overall Confirmed Hypoglycemia	
Primary Meta-Analysis (T2DM + T1DM)	0.91 [0.83; 0.99]*
Nocturnal Confirmed Hypoglycemia	
Meta-Analysis (T2DM + T1DM)	0.74 [0.65; 0.85]*

* p<0.05, FAS, All trials are versus glargine

Meta-Analysis of Overall Confirmed Hypoglycemia by Treatment Type

	Rate Ratio IDeg/Glargine Estimate [95% CI]	
Overall Confirmed Hypoglycemia		
Basal-Only Therapy	0.83 [0.70; 0.98]*	 17%
T2DM	0.83 [0.74; 0.94]*	 17%
T1DM	1.10 [0.96; 1.26]	 10%
T2DM+T1DM Pooled	0.91 [0.83; 0.99]*	 9%

Meta-Analysis of Nocturnal Confirmed Hypoglycemia by Treatment Type

	Rate Ratio IDeg/Glargine Estimate [95% CI]	
Nocturnal Confirmed Hypoglycemia		
Basal-Only Therapy	0.64 [0.48; 0.86]*	 36%
T2DM	0.68 [0.57; 0.82]*	 32%
T1DM	0.83 [0.69; 1.00]	 17%
T2DM+T1DM Pooled	0.74 [0.65; 0.85]*	 26%

Overall Confirmed Hypoglycemia: Robust Results with Symptomatic Episodes

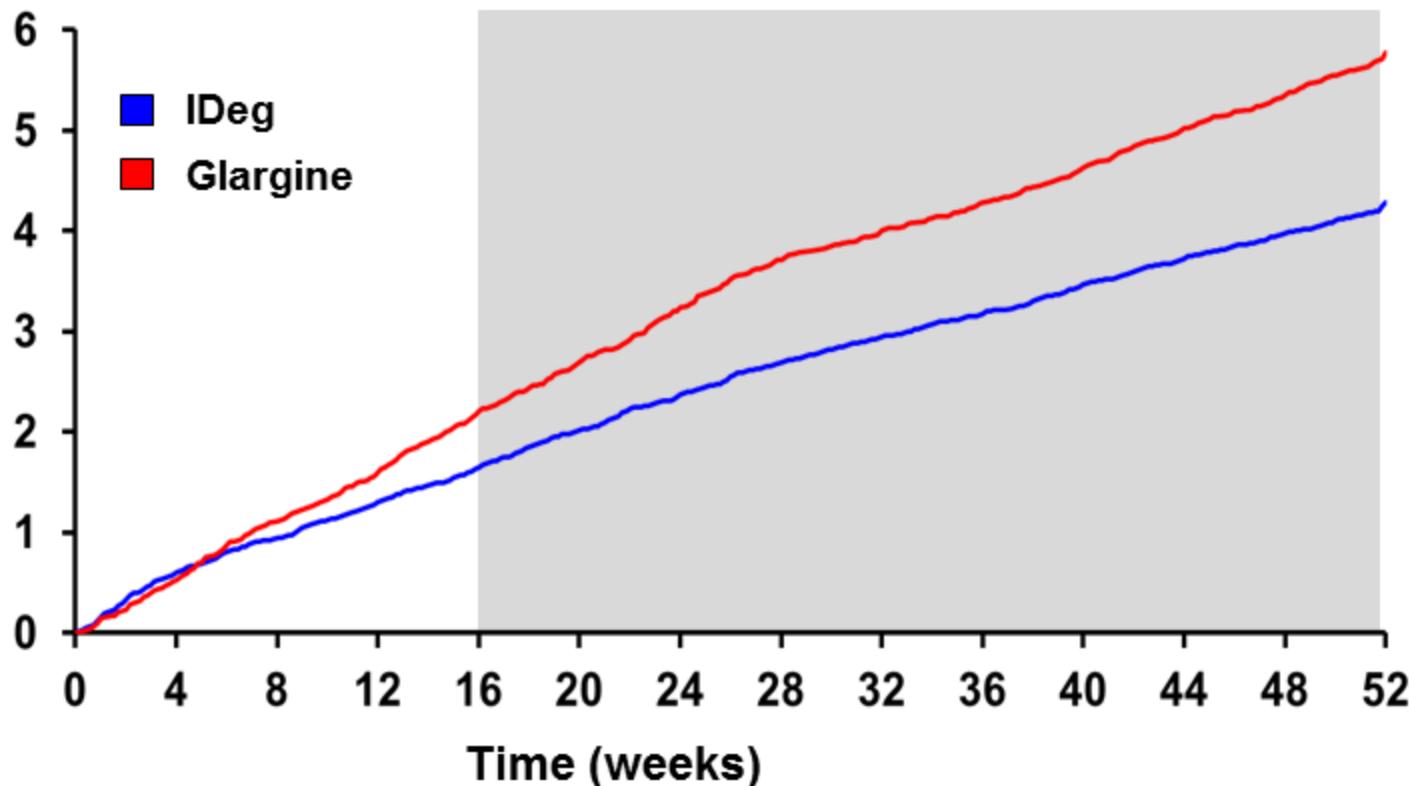
IDeg/Glargine T2DM+T1DM Pooled Analysis Rate Ratio [95%CI]		
	Overall Confirmed Episodes	Nocturnal Confirmed Episodes
All Confirmed Episodes (Primary Analysis)	0.91 [0.83; 0.99]*	0.74 [0.65; 0.85]*
Only Symptomatic Confirmed Episodes (<i>post hoc</i>)	0.87 [0.78; 0.96]*	0.72 [0.62; 0.84]*

* $p < 0.05$, FAS

IDeg Reduces Risk of Hypoglycemia Throughout Maintenance Period

Basal-Bolus, T1DM, (Trial 3583)
Nocturnal Confirmed Hypoglycemia

Cumulative Events
Per Patient



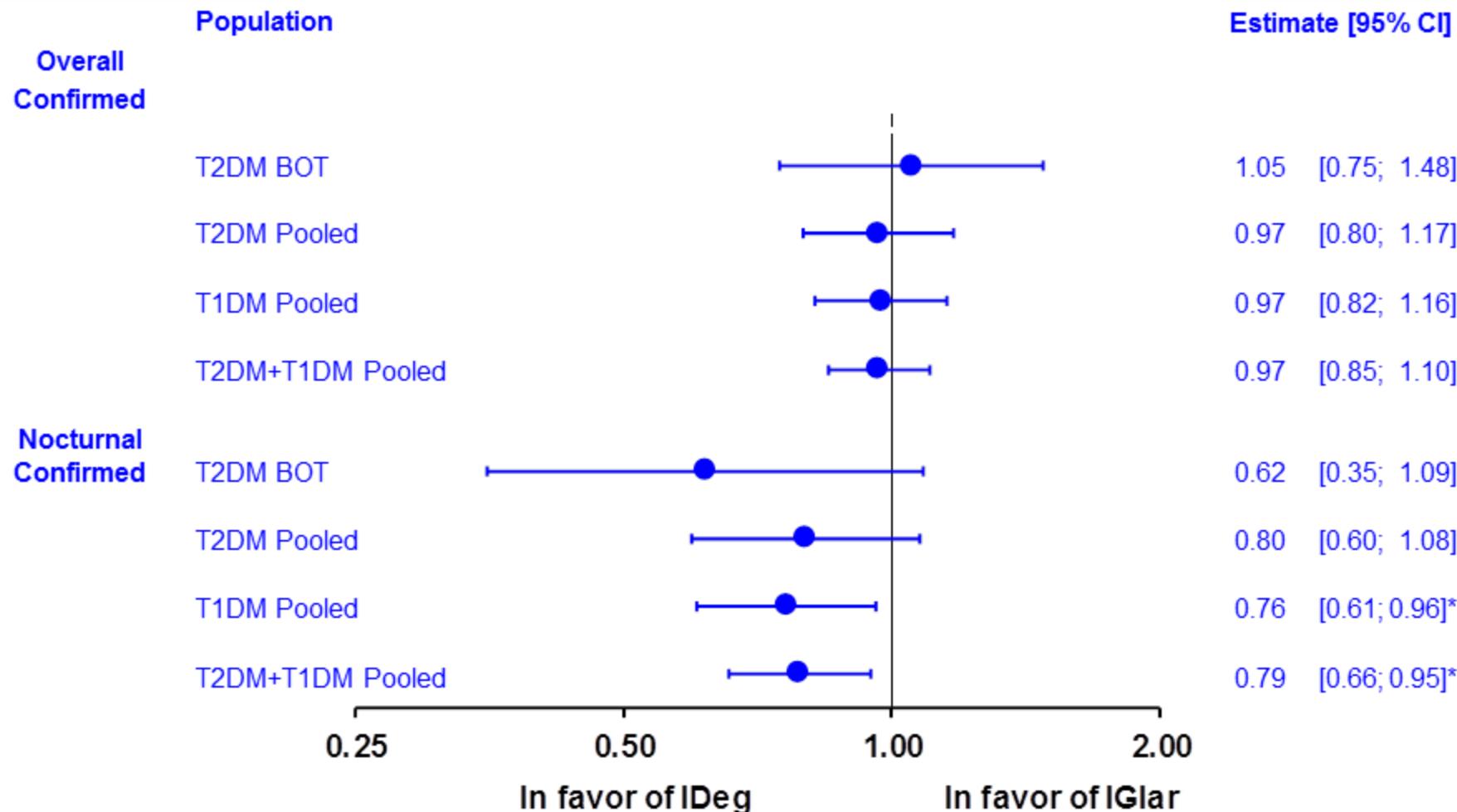
Lower Rates of Overall Confirmed Hypoglycemia in Maintenance Period

<u>Maintenance Period</u>		
	Rate Ratio IDeg/Glargine Estimate [95% CI]	
Overall Confirmed Hypoglycemia		
Basal-Only Therapy	0.72 [0.58; 0.88]*	 28%
T2DM	0.75 [0.66; 0.87]*	 25%
T1DM	1.02 [0.88; 1.19]	 2%
T2DM+T1DM Pooled	0.84 [0.75; 0.93]*	 16%

Lower Rates of Nocturnal Confirmed Hypoglycemia in Maintenance Period

<u>Maintenance Period</u>		
	Rate Ratio	IDeg/Glargine Estimate [95% CI]
Nocturnal Confirmed Hypoglycemia		
Basal-Only Therapy	0.51 [0.36; 0.72]*	 49%
T2DM	0.62 [0.49; 0.78]*	 38%
T1DM	0.75 [0.60; 0.94]*	 25%
T2DM+T1DM Pooled	0.68 [0.58; 0.80]*	 32%

Hypoglycemia Meta-Analysis, US Patients, IDeg vs. Glargine



* p<0.05, FAS

US: T1DM: 3583, 3770 (excluding IDeg Flex); T2DM BOT: 3579, 3672; T2DM: 3582, 3579, 3672; FAS

Lower Rates of Hypoglycemia in Patients with HbA_{1c} < 7%, IDeg vs. Glargine

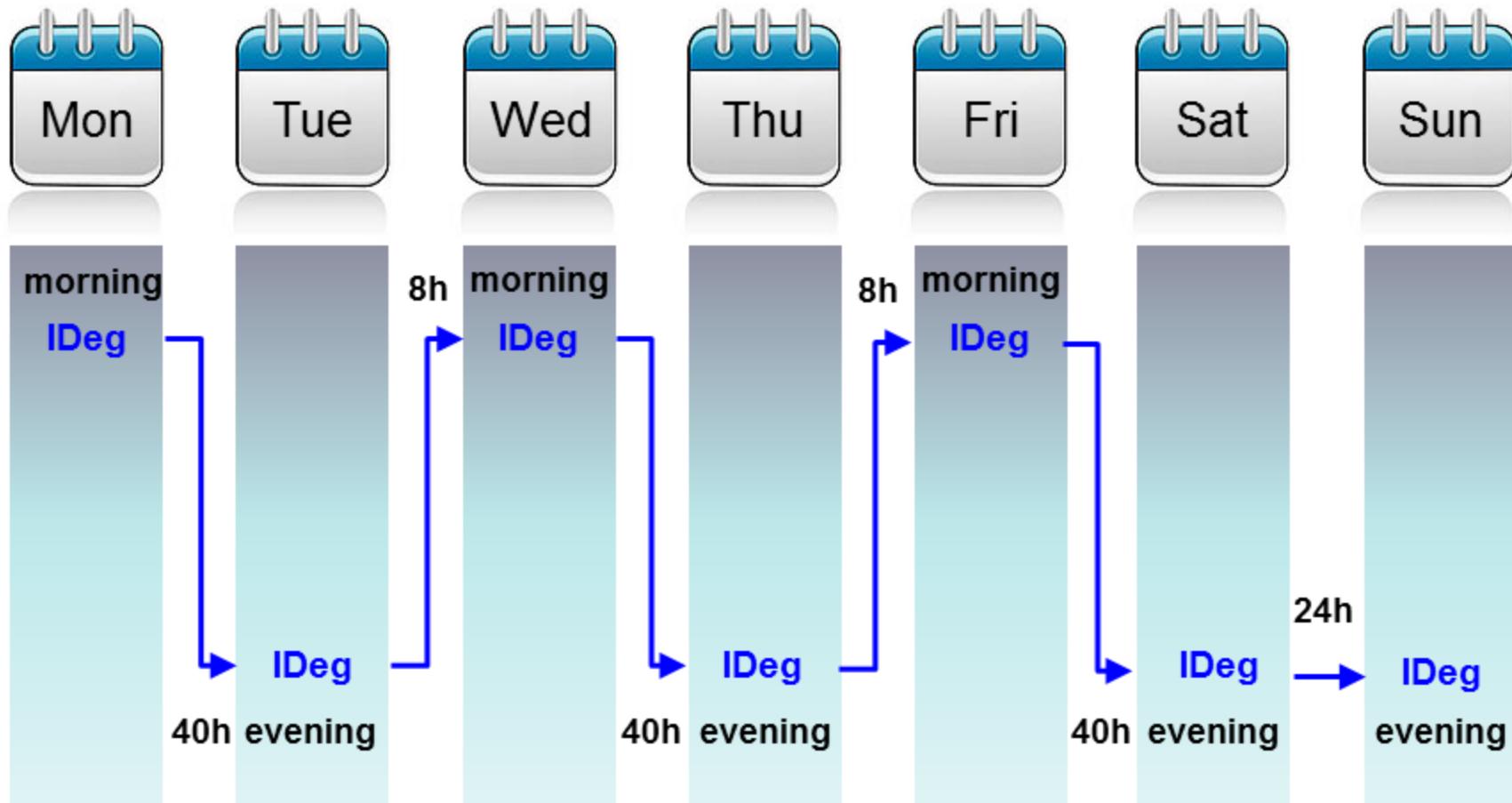
	<u>Maintenance Period</u>	Rate Ratio	IDeg/Glargine	Estimate [95% CI]
Overall Confirmed Hypoglycemia				
Basal-Only Therapy		0.77 [0.58; 1.02]		↓ 23%
T2DM		0.74 [0.61; 0.89]*		↓ 26%
T1DM		1.00 [0.78; 1.30]		↔
T2DM+T1DM Pooled		0.79 [0.68; 0.92]*		↓ 21%
Nocturnal Confirmed Hypoglycemia				
Basal-Only Therapy		0.49 [0.30; 0.81]*		↓ 51%
T2DM		0.53 [0.39; 0.72]*		↓ 47%
T1DM		0.67 [0.47; 0.95]*		↓ 33%
T2DM+T1DM Pooled		0.57 [0.45; 0.72]*		↓ 43%

* p<0.05, FAS

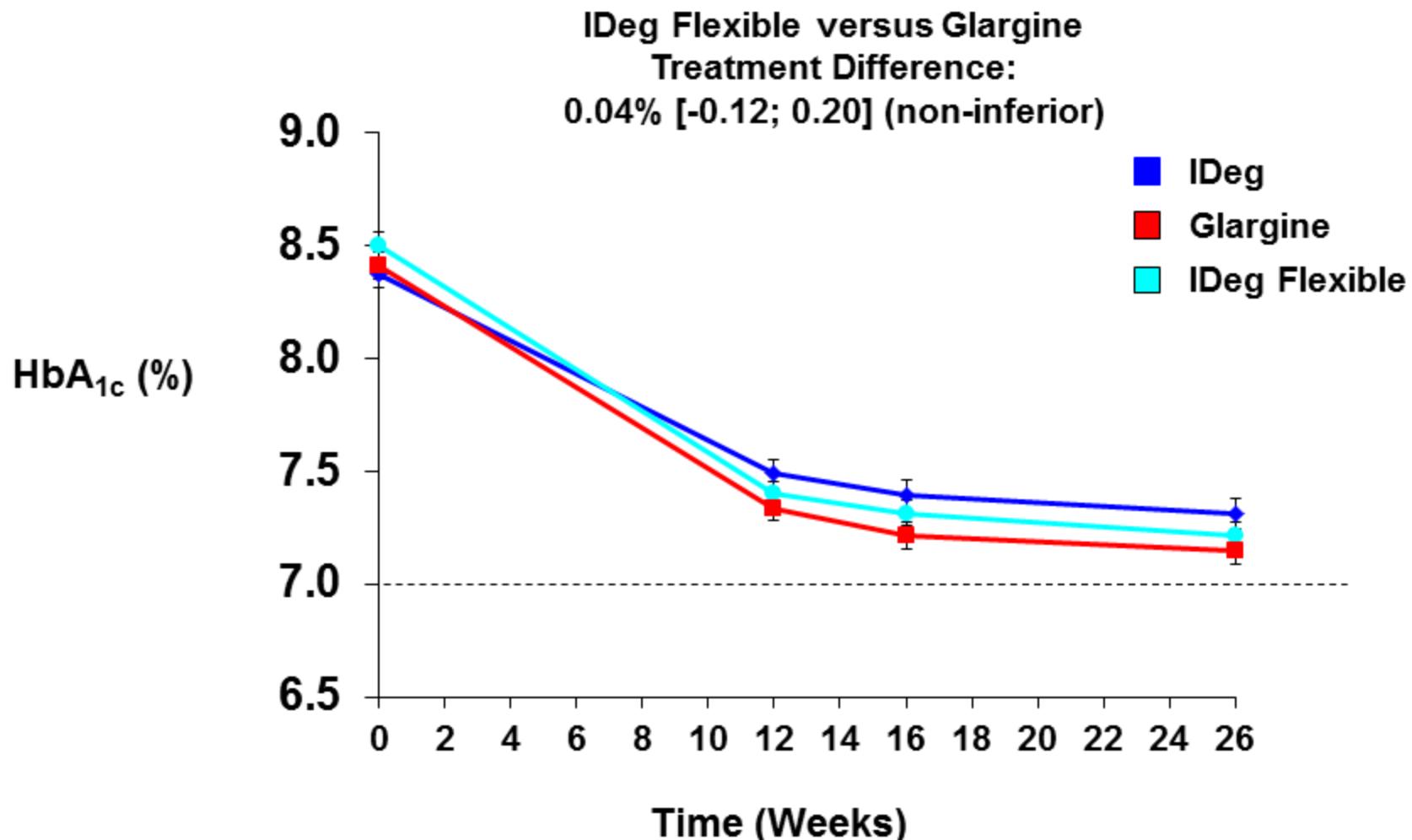
Summary of Prespecified Hypoglycemia Meta-Analysis

- T2DM+T1DM lower rate
 - Overall confirmed hypoglycemia
 - Nocturnal confirmed hypoglycemia
- T2DM lower rate
 - Overall confirmed hypoglycemia
 - Nocturnal confirmed hypoglycemia
- T1DM lower rate
 - Nocturnal confirmed hypoglycemia
- Greater effect during maintenance period
- Effects seen in important subgroups

Dosing Schedule Used in Trial 3668



Comparable HbA_{1c} for Alternative Dosing Schedule for IDeg



IDeg U200 – Allows Single Injection of Up to 160 Units

- IDeg U200 vs. Glargine U100 trial design
 - 26 weeks, parallel design
 - 460 patients with T2DM
 - Allowed BMI up to 45 kg/m^2
- Non-inferior $\text{HbA}_{1\text{c}}$ reductions
- Up to 40% of patients in US required >80 U in individual trials

IDegAsp Provides Clinical Advantages

- IDegAsp non-inferior to comparators
- Lower rates of overall confirmed hypoglycemia vs. mixed analog insulins
- Lower rates of nocturnal confirmed hypoglycemia vs. all comparators

Safety of IDeg and IDegAsp

Safety Profile Established in > 7500 Patients

- Most common adverse events
- Serious adverse events
- Deaths
- Neoplasms
- Weight
- Injection-site reactions
- Immunogenicity
- Cardiovascular safety

Similar Safety Profile – IDeg+IDegAsp vs. Comparator

- Similar rate of AEs, SAEs, and death
- Similar rate of malignant neoplasms
- No difference in weight gain
- Low rate of injection-site reactions
- No evidence of increased immunogenicity

Cardiovascular Safety of IDeg and IDegAsp

Anne Phillips, MD

Corporate Vice President

Clinical Development, Medical and
Regulatory Affairs

Novo Nordisk

Considerations in Assessing Cardiovascular Safety

- IDeg biology same as human insulin
- Comprehensive collection/adjudication
- Prespecified definitions and analysis plan

Baseline Characteristics for Cardiovascular Risk in NDA Dataset

Baseline Characteristics	IDeg+IDegAsp N = 5647	Comparator N = 3312
	%	%
Prior Cardiovascular History	16.0	15.0
Age >65 and Diabetes >10 years	13.4	13.4
Male	56.0	54.6
Hypertension	59.6	62.5
Mild or Moderate Renal Impairment	15.8	15.2
BMI >30 kg/m ²	40.9	44.9
Concomitant Medications		
Lipid-Lowering Drugs	52.3	55.0
Aspirin	30.9	33.2
Beta Blocker	17.8	17.5
RAS Inhibitors	53.7	55.7

N = Number of patients, % = Proportion of patients in analysis set, FAS

Comprehensive Cardiovascular Safety Assessment in Phase 3 Trials

- Blood pressure and pulse rate
- ECG
- Lipids
- Prespecified cardiovascular adverse events
 - Captured up to 7-day post-treatment
 - Patients then returned to primary care physician

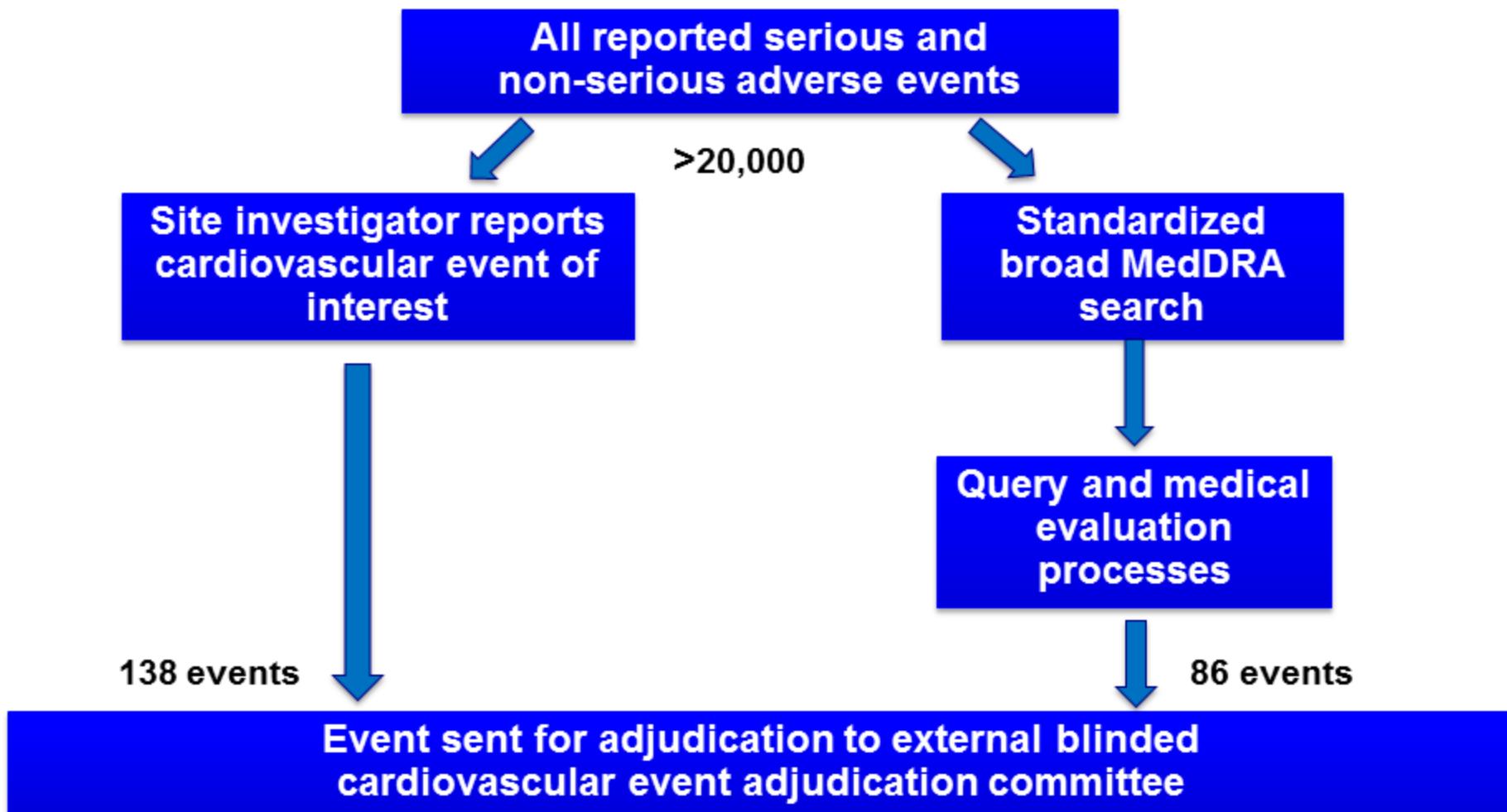
Independent Adjudication of MACE Conducted Under Prespecified Charter

- Charter developed between Novo Nordisk and independent adjudication committee
 - Chaired by C. Michael Gibson
- Events defined based on established criteria for diagnosis
- Established process for consensus

MACE Definition was Prespecified in All Phase 3 Trials

- *A priori* MACE definition
 - Cardiovascular death
 - Stroke
 - Acute Coronary Syndrome (ACS)
 - Myocardial Infarction (MI)
 - Unstable Angina Pectoris (UAP)

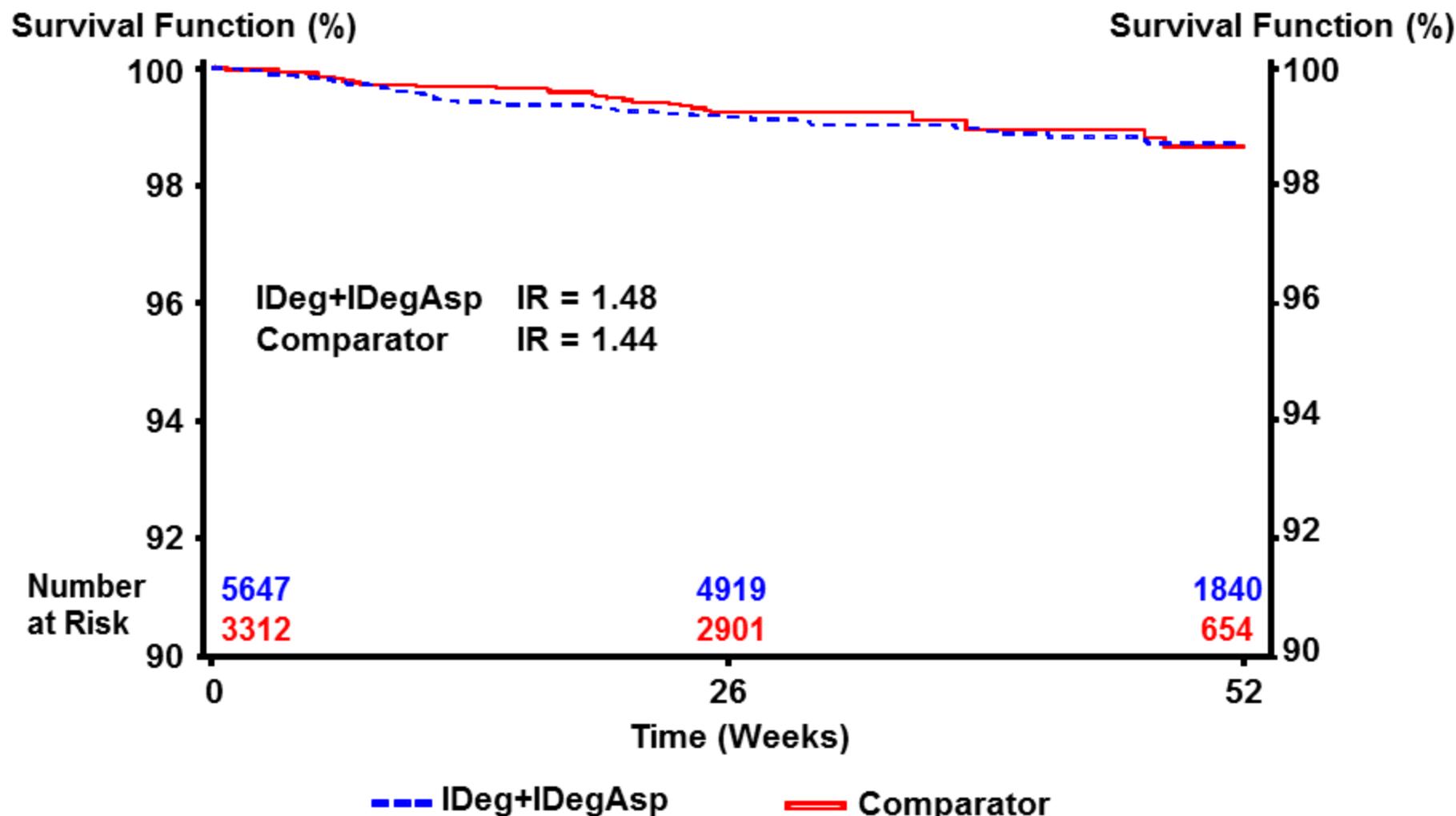
Dual Pathways to Trigger Adverse Events for MACE Adjudication



Prespecified Statistical Approach for MACE Meta-Analysis

- Prespecified Analysis
 - Time until 1st MACE
 - Analyzed using Cox Proportional Hazards
 - Stratified by trial
- IDeg+IDegAsp (T2DM+T1DM) = Full Analysis Set from NDA

Similar Incidence Rates in Prespecified MACE - NDA Dataset

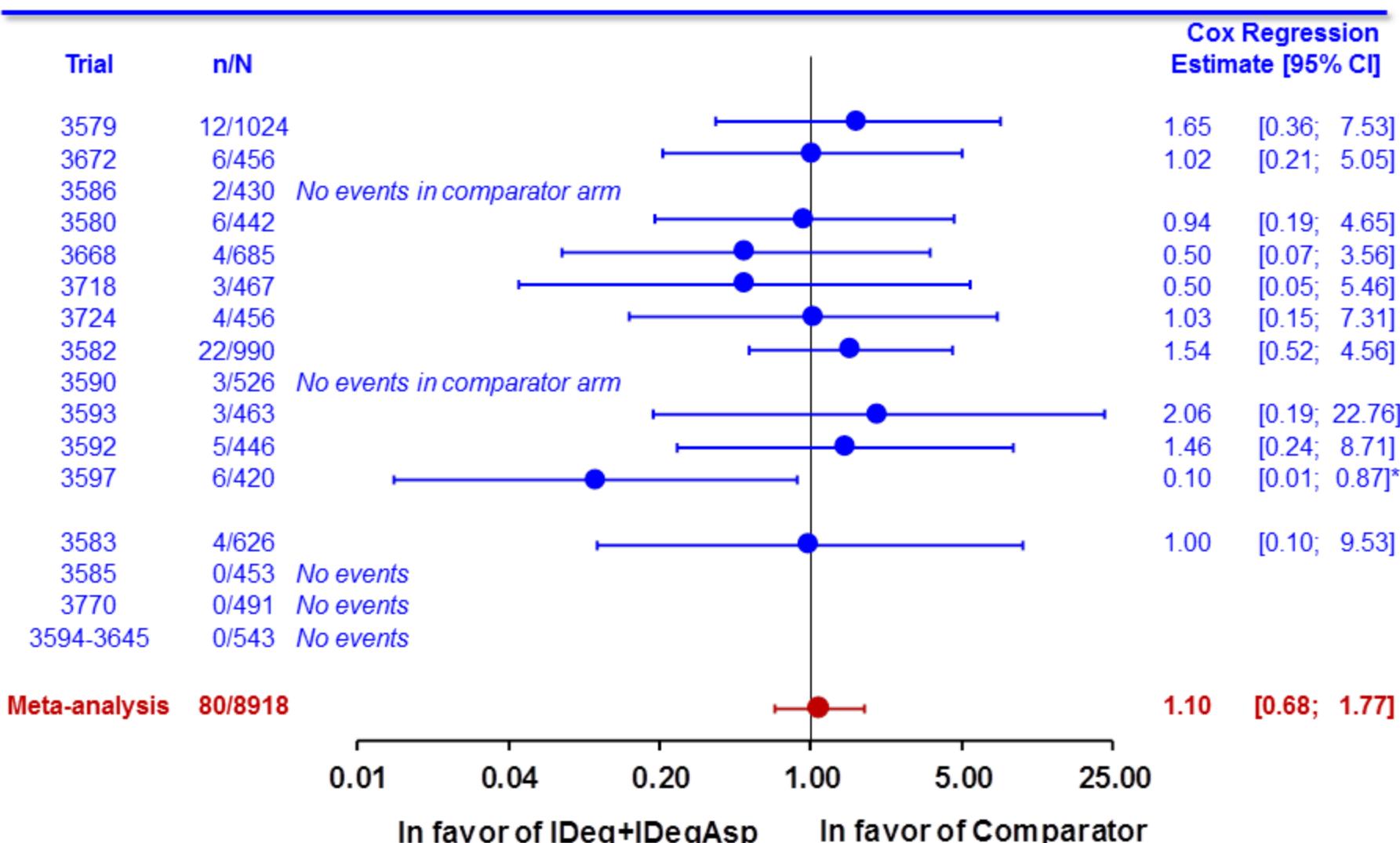


Prespecified MACE - NDA Dataset

	IDeg+IDegAsp N = 5647		Comparator N = 3312	
	N	IR	N	IR
Total MACE	53	1.48	27	1.44
Acute Coronary Syndrome	34	0.95	19	1.01
Unstable Angina Pectoris	14	0.39	12	0.64
Myocardial Infarction	20	0.56	7	0.37
Stroke	11	0.31	4	0.21
Cardiovascular Death	8	0.22	4	0.21

N = Number of Patients; IR = Incidence Rate
FAS

Prespecified MACE - NDA Dataset



n/N: number of patients with a MACE/number of patients contributing to the analysis, FAS.

No Differences in Cardiovascular Parameters

- Blood pressure
- Pulse rate
- ECG
- Lipids

Summary of Prespecified MACE Analysis from NDA

- Not designed as CV outcome program
- *A priori* MACE definition
- CV safety assessed using both
 - MedDRA query search
 - Blinded adjudication of all potential MACE
- Similar incidence rate in primary analysis

IDeg+IDegAsp IR = 1.48
Comparator IR = 1.44

} HR: 1.10 [0.68;1.77]

Trials Contributing Additional Data in *post hoc* MACE Analyses

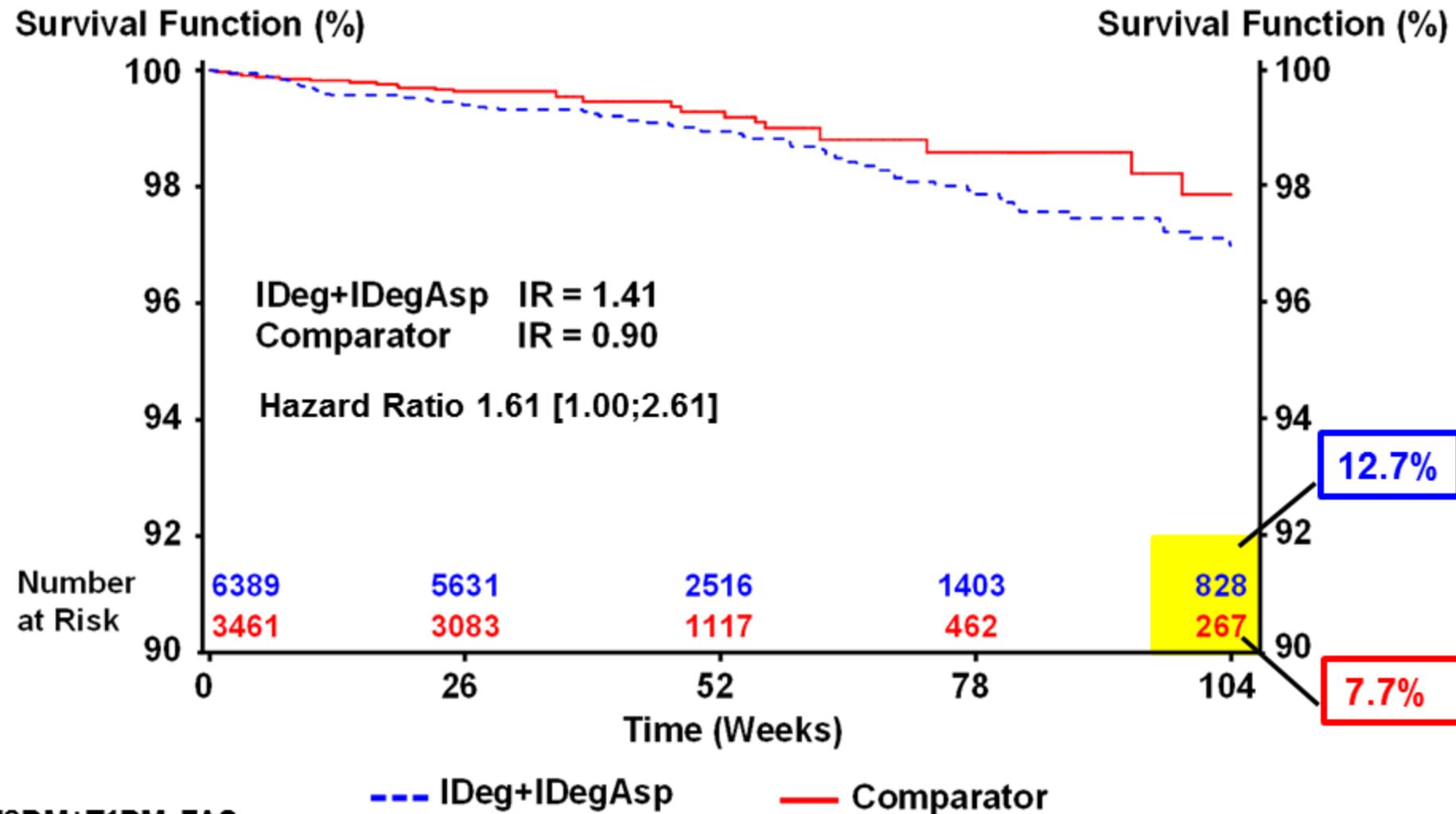
- Three Phase 3 trials
 - 1 Phase 3a trial Japanese patients
 - 2 Phase 3b trials T2DM (IDeg vs. IDeg)
- Six extensions requiring re-consent
 - Potentially compromising randomization
 - Different durations of follow-up

Post hoc MACE Analyses

	Adverse Event Capture	MACE Definition	Dataset
Prespecified	7 days	Death, Stroke, ACS (MI and UAP)	NDA
<i>Post hoc #1</i>	30 days	Exclude UAP “Restricted MACE”	May 1
<i>Post hoc #2</i>	7 days	Death, Stroke, ACS (MI and UAP)	May 1 Randomized Trials Only

Restricted MACE, 30 Day

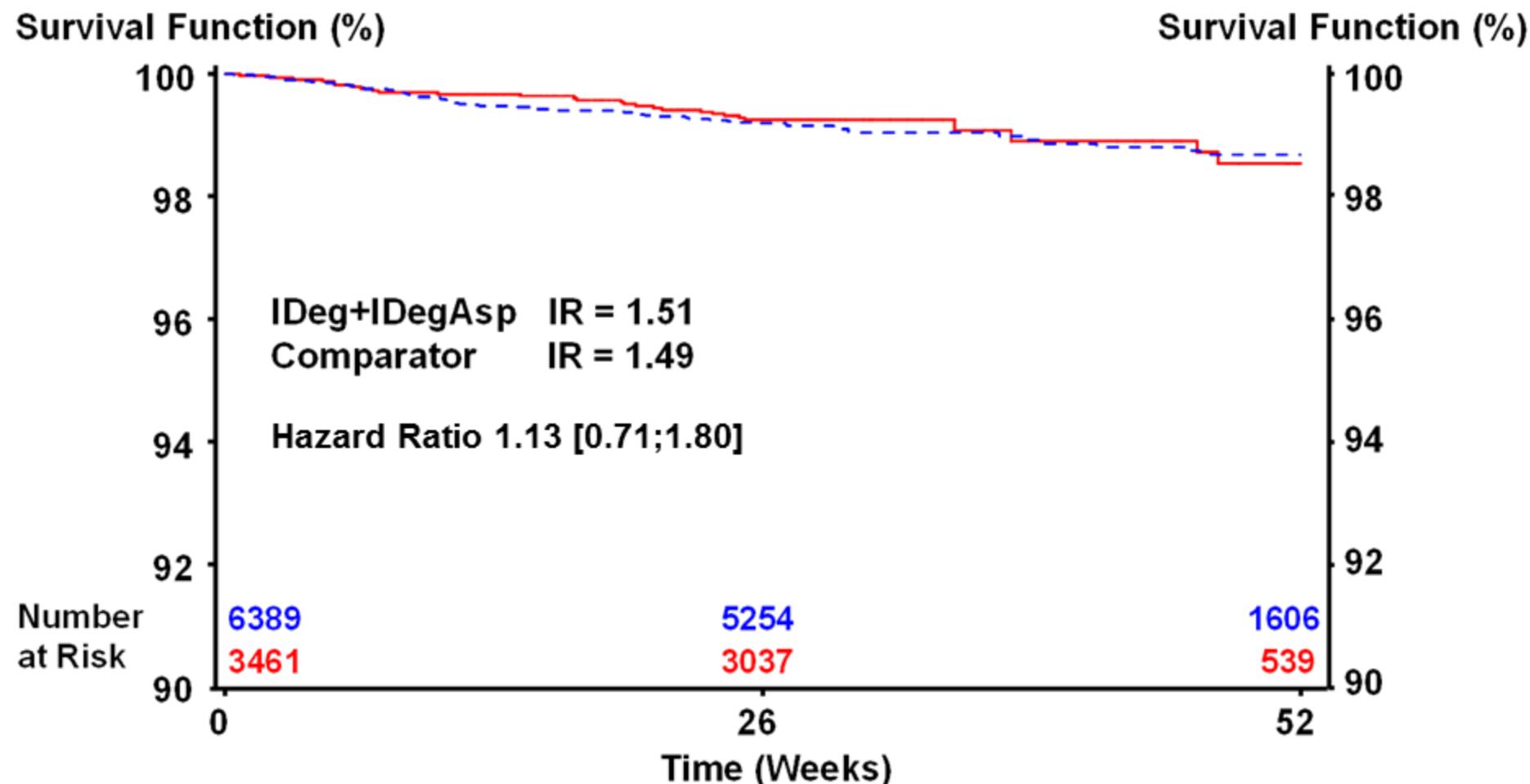
May 1 Dataset



T2DM+T1DM; FAS

Number at Risk: IDeg+IDegAsp (1st row) and Comparator (2nd row)

Prespecified MACE, 7 Day, Randomized Trials, May 1 Dataset

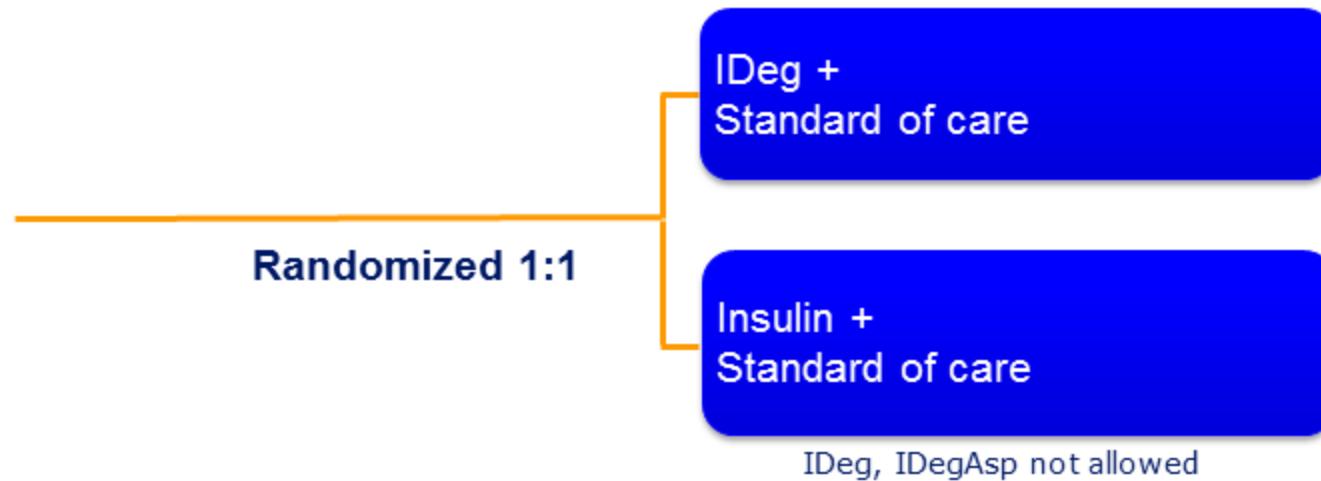


Number at Risk: IDeg+IDegAsp (1st row) and Comparator (2nd row)

Summary of MACE Analysis

- Phase 3 trials assessed effects on glycemic control, not CV outcome program
- No evidence of unacceptable CV risk in prespecified MACE analysis
- CV signal in *post hoc* analyses driven by
 - Extension data characterized by decreasing number of patients and unequal exposure
 - Revised definition of MACE

Proposed Design – CV Outcome Trial



- **Primary endpoint:** Time until 1st MACE (CV death, non-fatal MI, non-fatal stroke)
- **Primary outcome event rate:** ~2.0% per year
- **Estimated trial population:** 7,500 patients with T2DM
- **Expected duration:** 5 years

Insulin Degludec - Assessing Cardiovascular Risk

Steven P. Marso, MD, FACC, FAHA, FSCAI

Saint Luke's Mid America Heart Institute

Kansas City, Missouri

Professor of Medicine

University of Missouri, Kansas City



Presentation Overview

- Comparison of degludec program and Cardiovascular Outcome Trials (CVOT)
- Rationale for a Four-Component MACE

Cardiovascular Risk Assessment

CV Outcome Trial vs. Degludec Program

	CV Outcome Trial	Degludec Program
Prespecified endpoint	✓	✓
Blinded adjudication	✓	✓
Adequate event accrual	✓	✗
Duration of follow-up	✓	✗

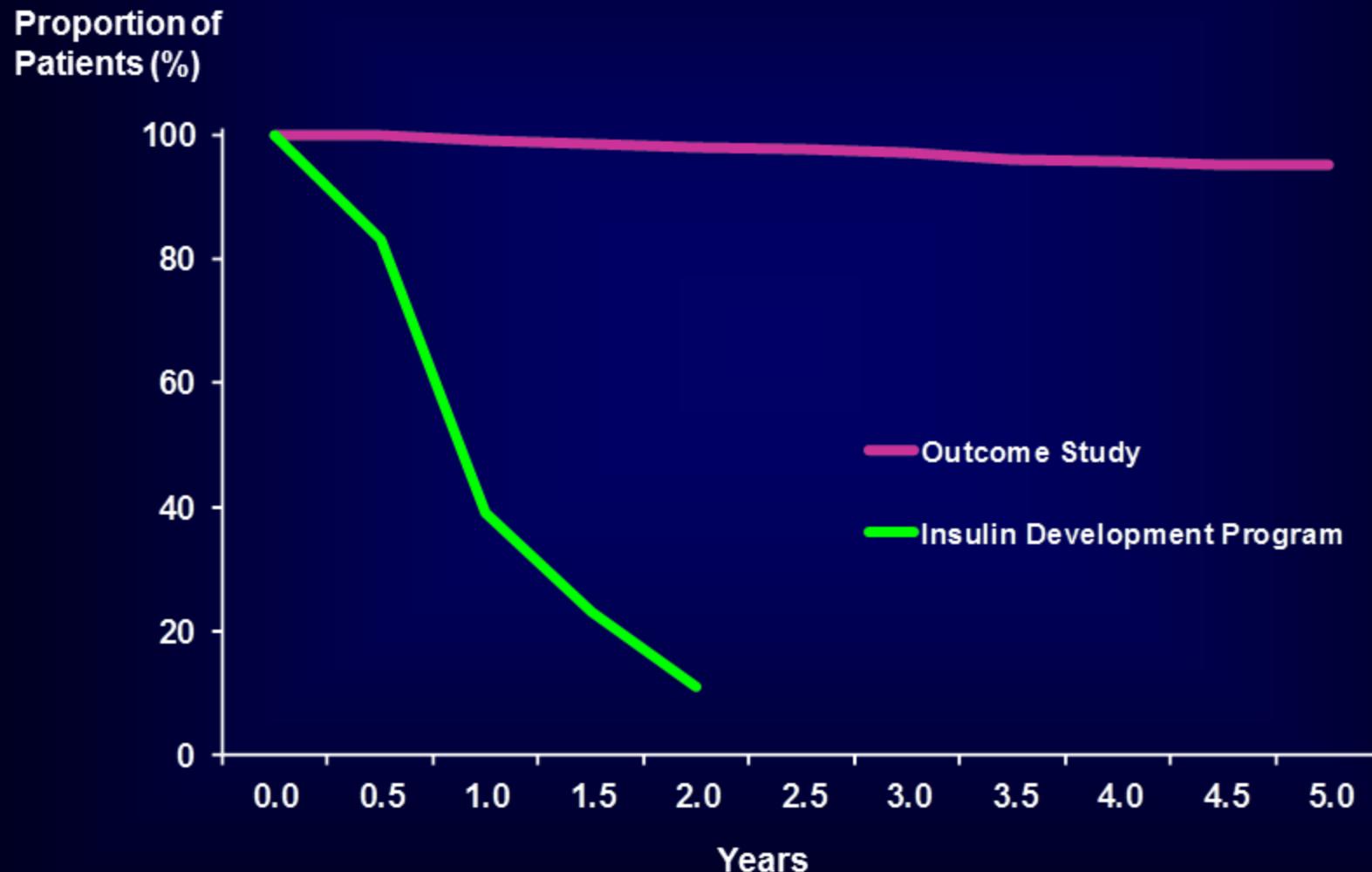
Degludec Program Included CV Trial Design Elements

- Randomized, controlled, active comparators
- Pre-specified MACE appropriate for this type of program
- Robust efforts to collect/adjudicate CV risk

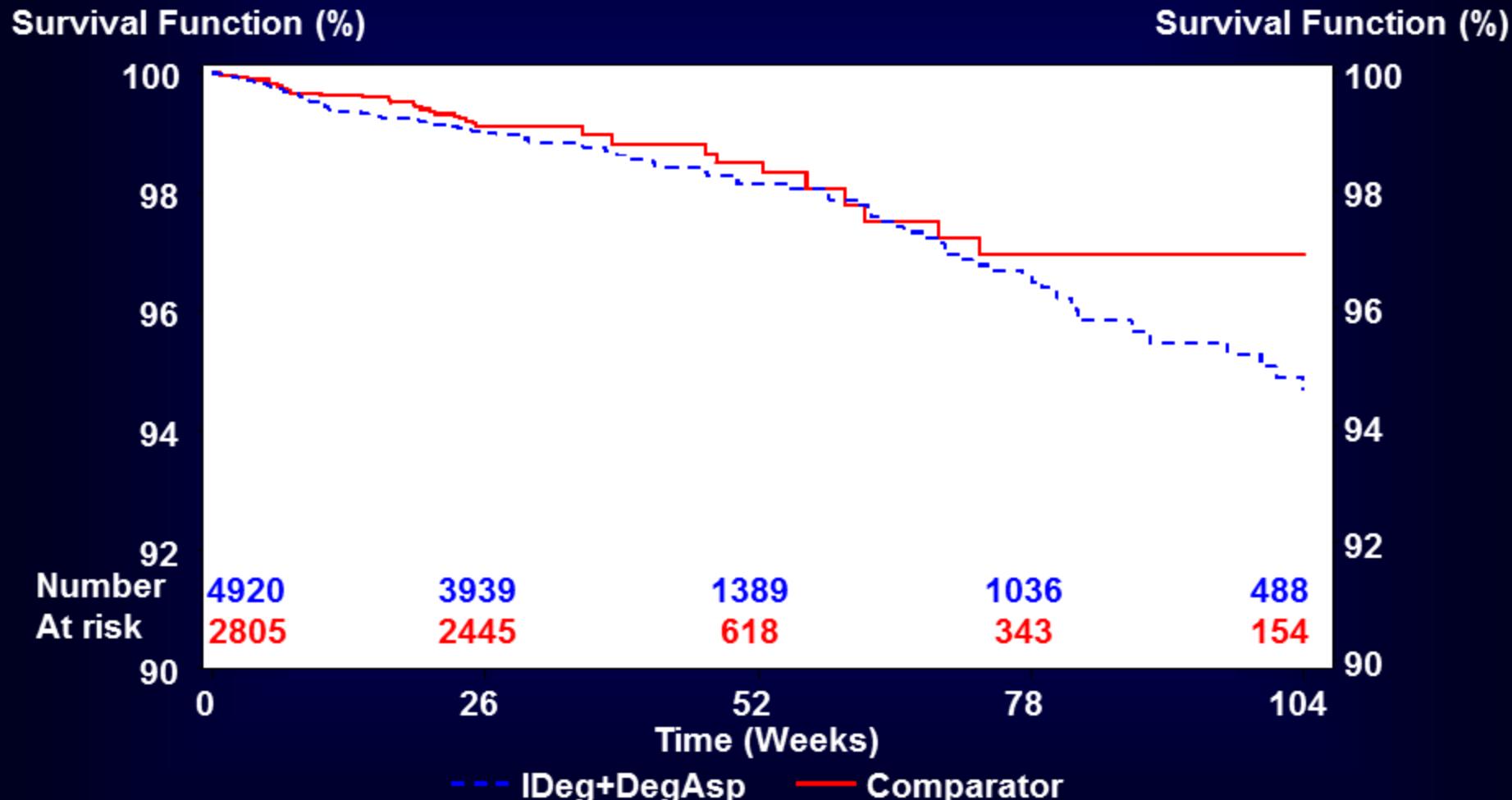
Lower Risk Population in Degludec vs. CV Outcome Trials

- 2.5% event rate in LEADER®
- 1.0% event rate in degludec program

Duration of Follow-Up



MACE Events Degludec vs. Comparator in T2DM



Numbers are subjects at risk for IDeg+IDegAsp (1st row) and Comparator (2nd row)
MACE: Major adverse cardiovascular event

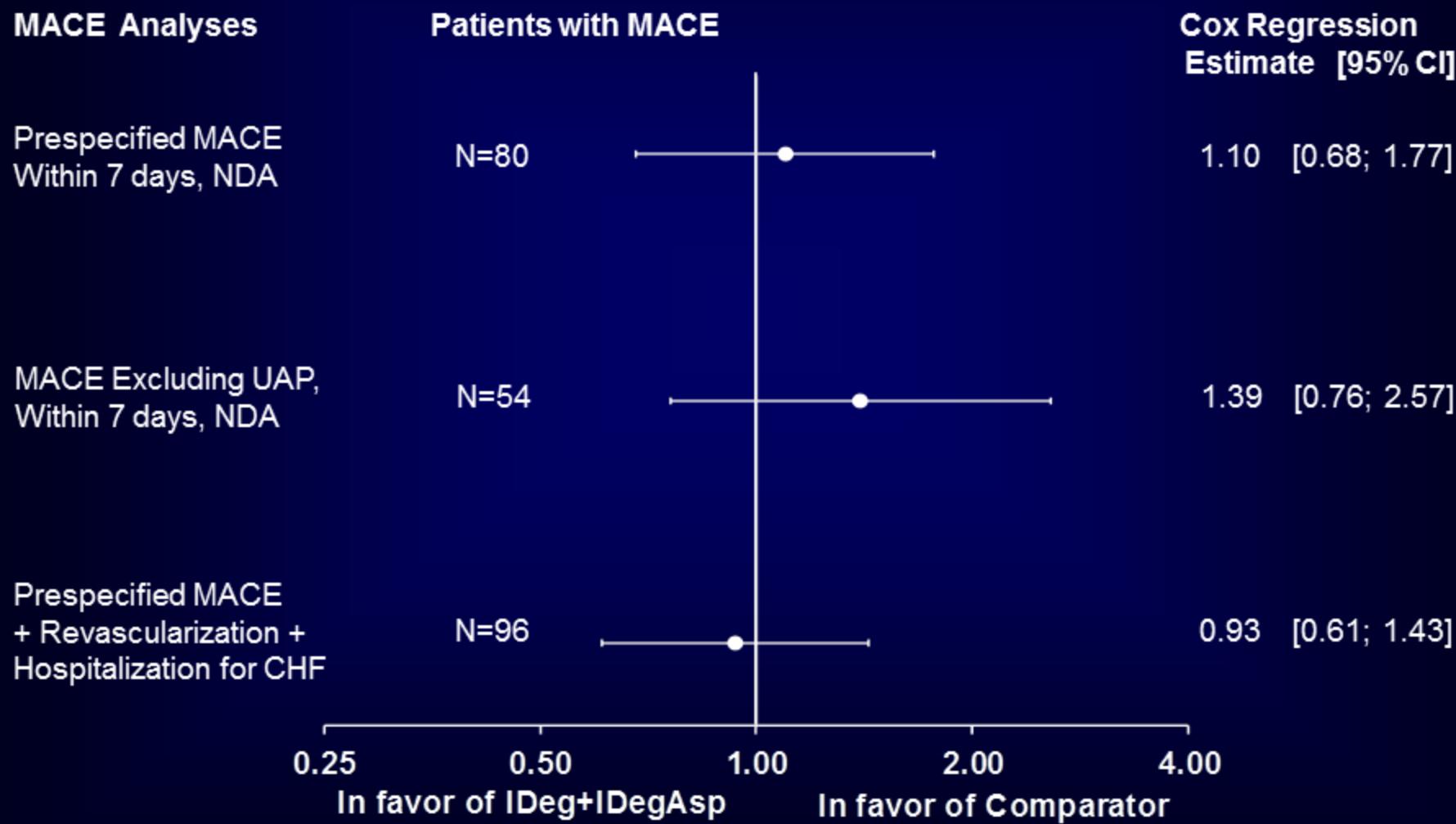
Four-Component MACE

- Unstable angina
- Myocardial infarction
- Stroke
- CV death

Rationale for a Four-Component MACE

- Pre-specified endpoint
- Rigorously defined
- Adjudicated by expert panel
- Each endpoint in causal pathway
- 3 large, ongoing CV outcome trials use 4-Component MACE

Varied Definitions Change Sensitivity and Specificity for Detecting Events



N: number of patients with a MACE, FAS.

Summary: Degludec Program Not Designed for CV Risk Assessment

- Not designed as CV Outcome Trials
- Robust efforts to collect, adjudicate events
- Four-Component MACE appropriate given population

IDeg and IDegAsp Benefit/Risk Discussion

Anne Phillips, MD
Corporate Vice President
Clinical Development, Medical and
Regulatory Affairs
Novo Nordisk

IDeg Efficacy Established in Extensive Clinical Program

- Included trials across spectrum of insulin-requiring diabetes in both T2DM and T1DM
- IDeg, comparator both successfully titrated to target HbA_{1c}
- IDeg produced consistent reductions in FPG

IDeg Provides Additional Benefits to Patients and Physicians

- Low variability in PK/PD profile results in lower risk of hypoglycemia
- Flexibility if patient inadvertently misses, or needs to delay a dose
- U200 allows up to 160 units in single injection
- Soluble co-formulation with insulin aspart in single injection (IDegAsp)

Reducing Hypoglycemia is Important for Patients

- T1DM patients
 - 25% lower rate of nocturnal confirmed hypoglycemia*
 - Similar rates of overall confirmed hypoglycemia (confounded by bolus)
- T2DM patients
 - 38% lower rate of nocturnal confirmed hypoglycemia*
 - 25% lower rate of overall confirmed hypoglycemia*

* $p < 0.05$, maintenance phase

IDeg – Safety Considerations

- AE safety profile consistent with insulin
- Similar incidence rates in prespecified NDA MACE analysis
- Point estimates change based on *post hoc* analyses
 - Removal of UAP from MACE definition
 - Data cut off extended to include additional exposure
- Post-approval CV outcome trial

Novo Nordisk Experience with Post-Marketing CV Outcome Trial

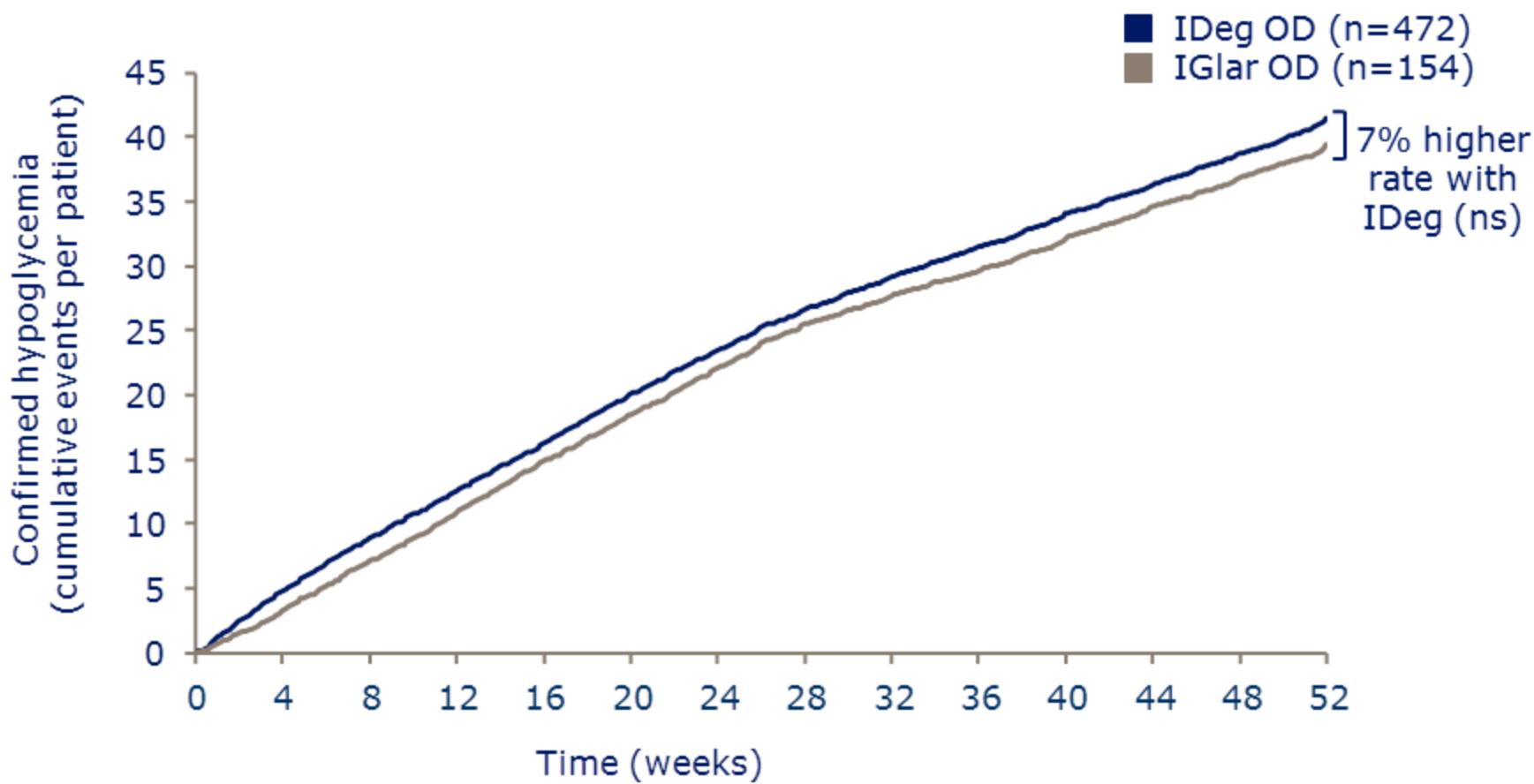
- Current post-approval CV outcome trial for Victoza® (LEADER®)
- Fully enrolled with 9,000+ patients
- >99% patient retention rate

IDeg and IDegAsp Positive Benefit/Risk

- Provide effective glycemic control
- Safety profile consistent with insulin
- Less confirmed and nocturnal hypoglycemia
- Administration benefits for missed injections, delivery of large insulin doses (U200)
- Committed to work with FDA on post-approval CV outcome trial
- IDeg/IDegAsp represent important advance

Backup Slides Shown

3583 – Confirmed hypoglycemia



ns = not significant

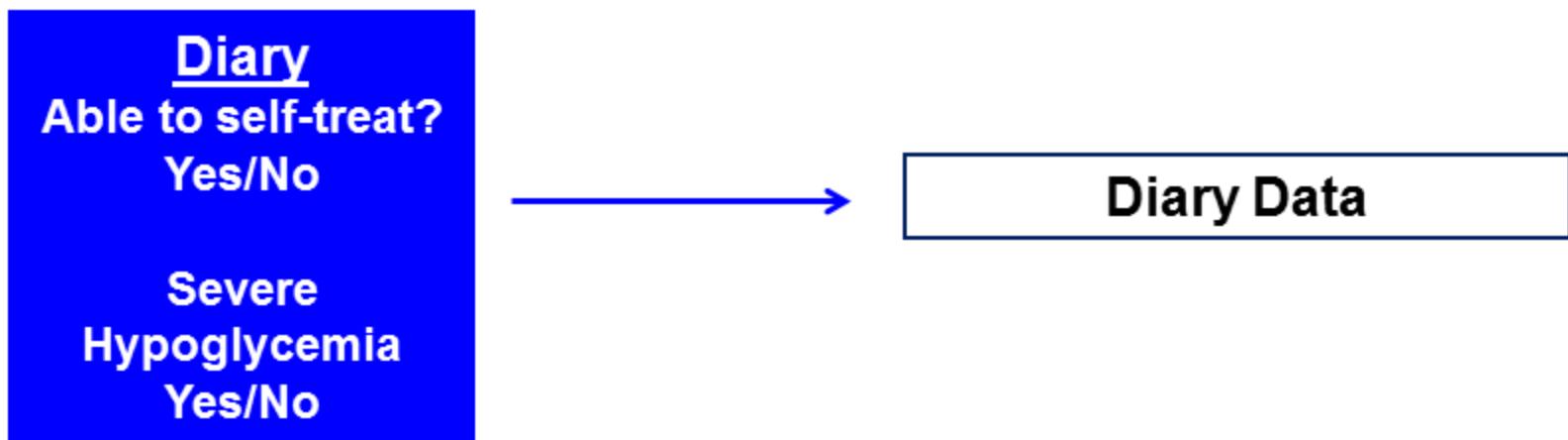
n = number of patients in SAS

Comparisons: Estimates adjusted for multiple covariates; FAS

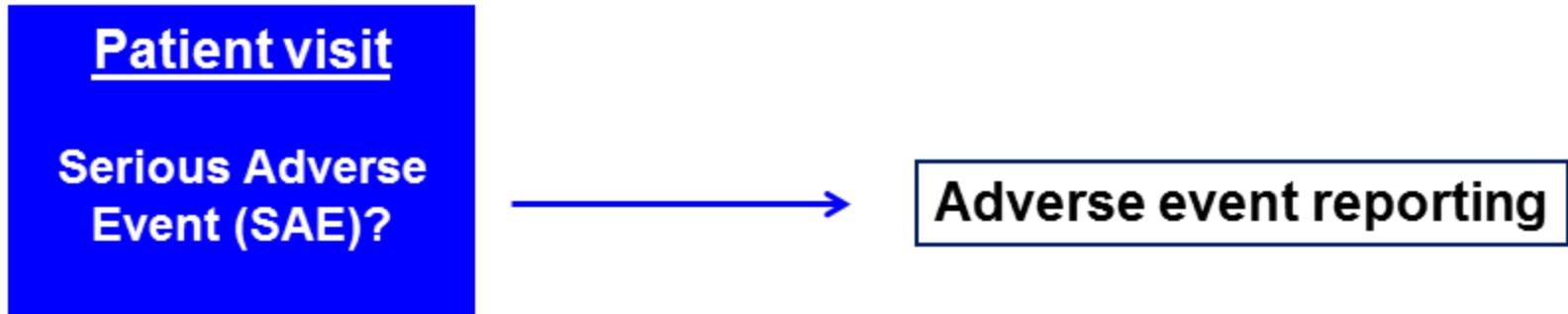
NN1250-3583; IDeg basal-bolus in T1DM

Hypoglycemia Episode Reporting

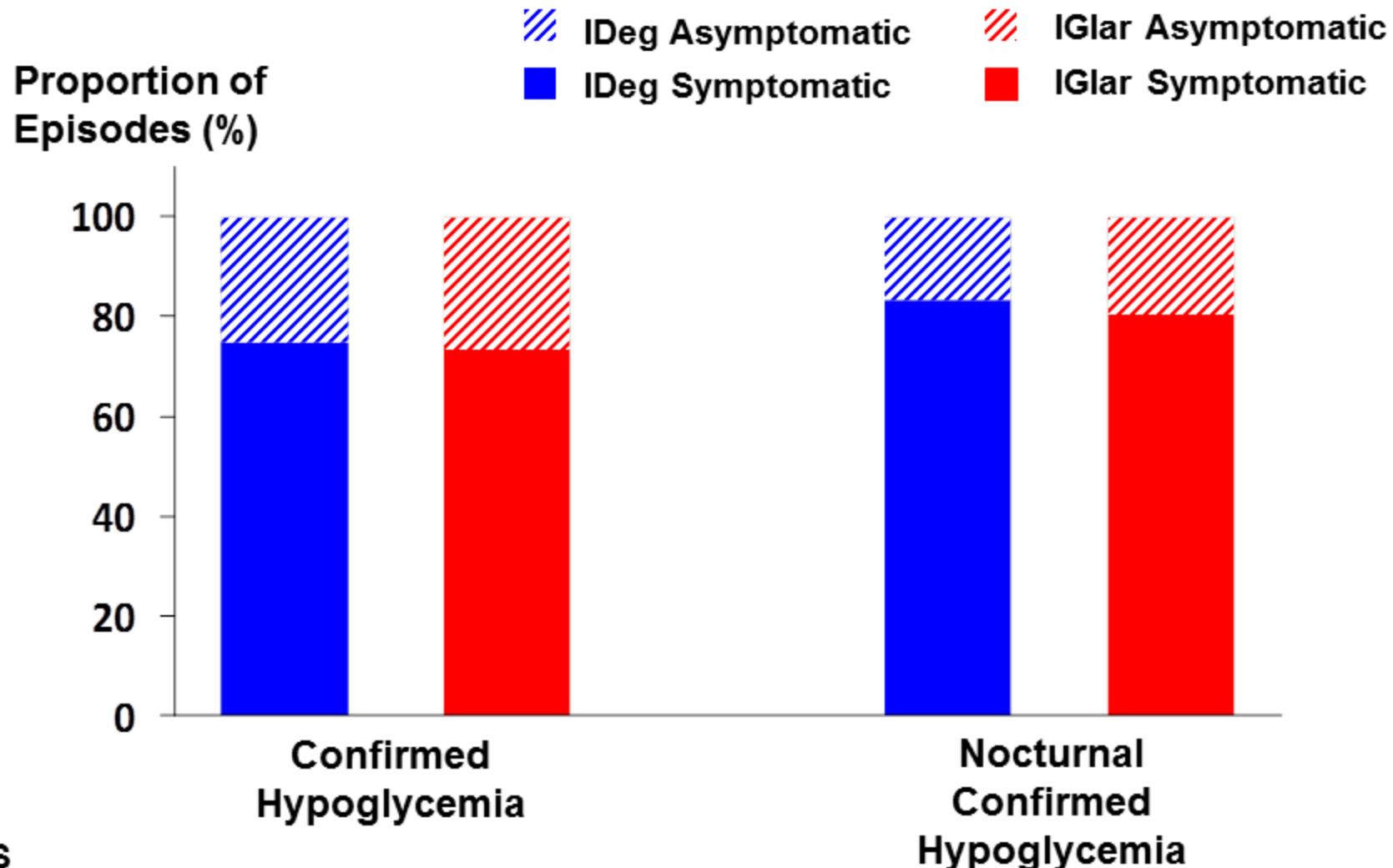
Patient Reports Hypoglycemia
in Diary Proximal to Episode



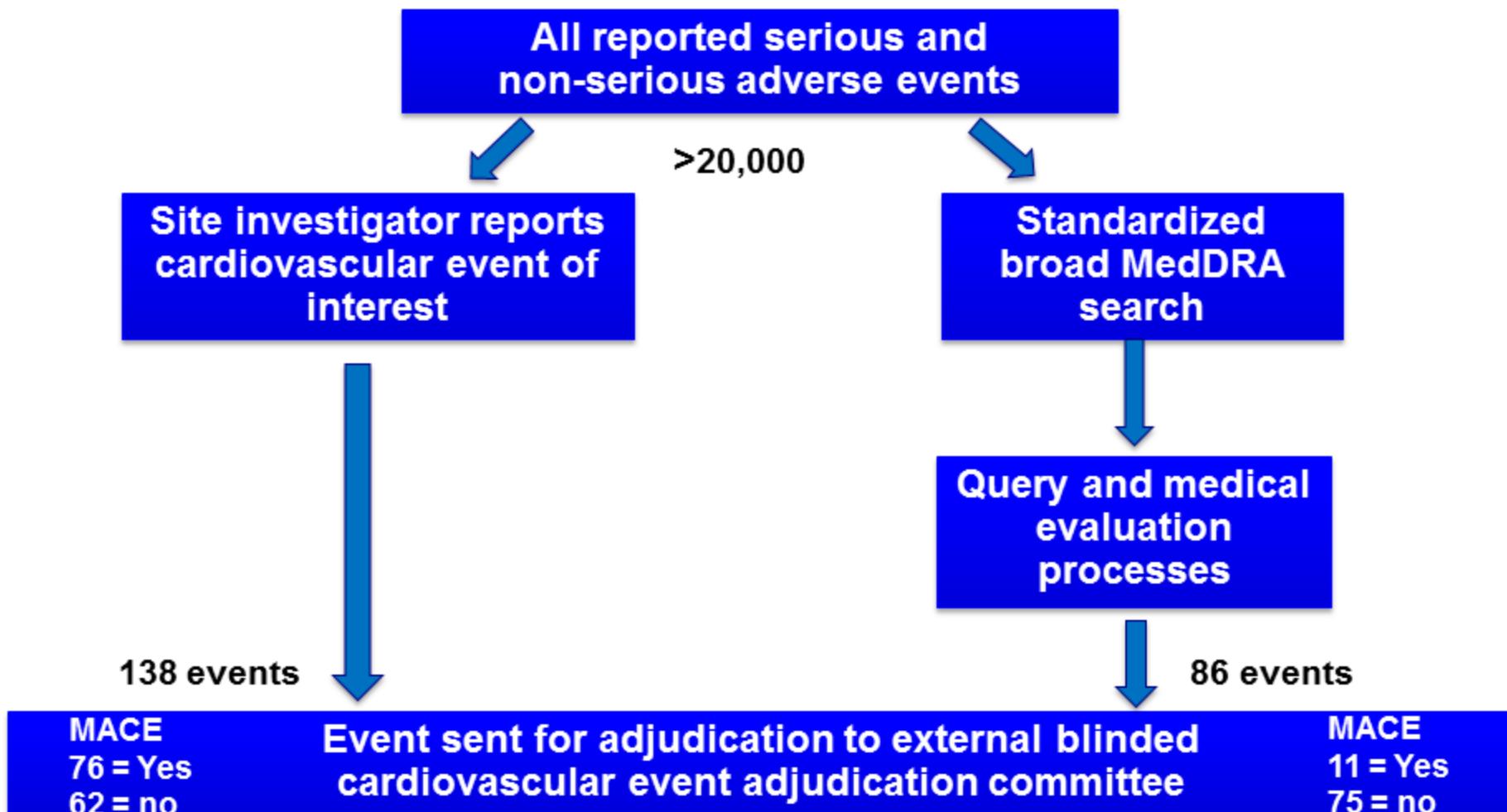
Investigator Assessment at Clinic Visits



Majority of Hypoglycemic Episodes are Symptomatic, Meta-analysis, IDeg vs IGlar, T2DM+T1DM, Phase 3, NDA



Dual Pathways to Trigger Adverse Events for MACE Adjudication



MACE Excluding UAP, 7 vs. 30 Day Censoring, NDA and May 1

	NDA		May 1	
	IDeg+IDegAsp N=5647	Comparator N=3312	IDeg+IDegAsp N=5794	Comparator N=3461
7 Day Censoring				
MACE excl. UAP, N	39	15	71	21
HR, Estimate (CI)		1.39 [0.76; 2.56]		1.67 [1.01; 2.75]
30 Day Censoring				
MACE excl. UAP, N	42	15	76	23
HR, Estimate (CI)		1.50 [0.82; 2.75]		1.61 [1.00; 2.61]

Time to First MACE excluding UAP, All Randomized Trials, 7 Day Censoring, May 1

	IDeg+IDegAsp (N=6389, PYE=3767)	Comparator (N=3461, PYE=1883)		
	N	IR	N	IR
MACE	42	1.12	16	0.85
MI	21	0.56	7	0.37
Stroke	13	0.35	5	0.27
Cardiovascular Death	8	0.21	4	0.21

Cox regression [95% CI]: 1.43 [0.79;2.58]

Definition of Unstable Angina Pectoris

- Ischemic discomfort or equivalent ≥ 10 minutes at rest, or repeated episodes at rest ≥ 5 minutes, or an accelerating pattern of ischemic discomfort considered to be **myocardial ischemia** upon final diagnosis
AND at least one of below criteria for coronary artery disease and/or ischemia:
 - New and/or dynamic ST-depression >0.05 mV, ST-elevation >0.1 mV, or symmetric T wave inversion >0.2 mV on resting ECG
 - Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy, or ECG-only stress test
 - Angiographic evidence of epicardial coronary artery stenosis of $>70\%$ diameter reduction and/or evidence for intraluminal arterial thrombus

FlexPen® pen-injector used in basal bolus phase 3 clinical trials - comparator

T2DM trial 3582

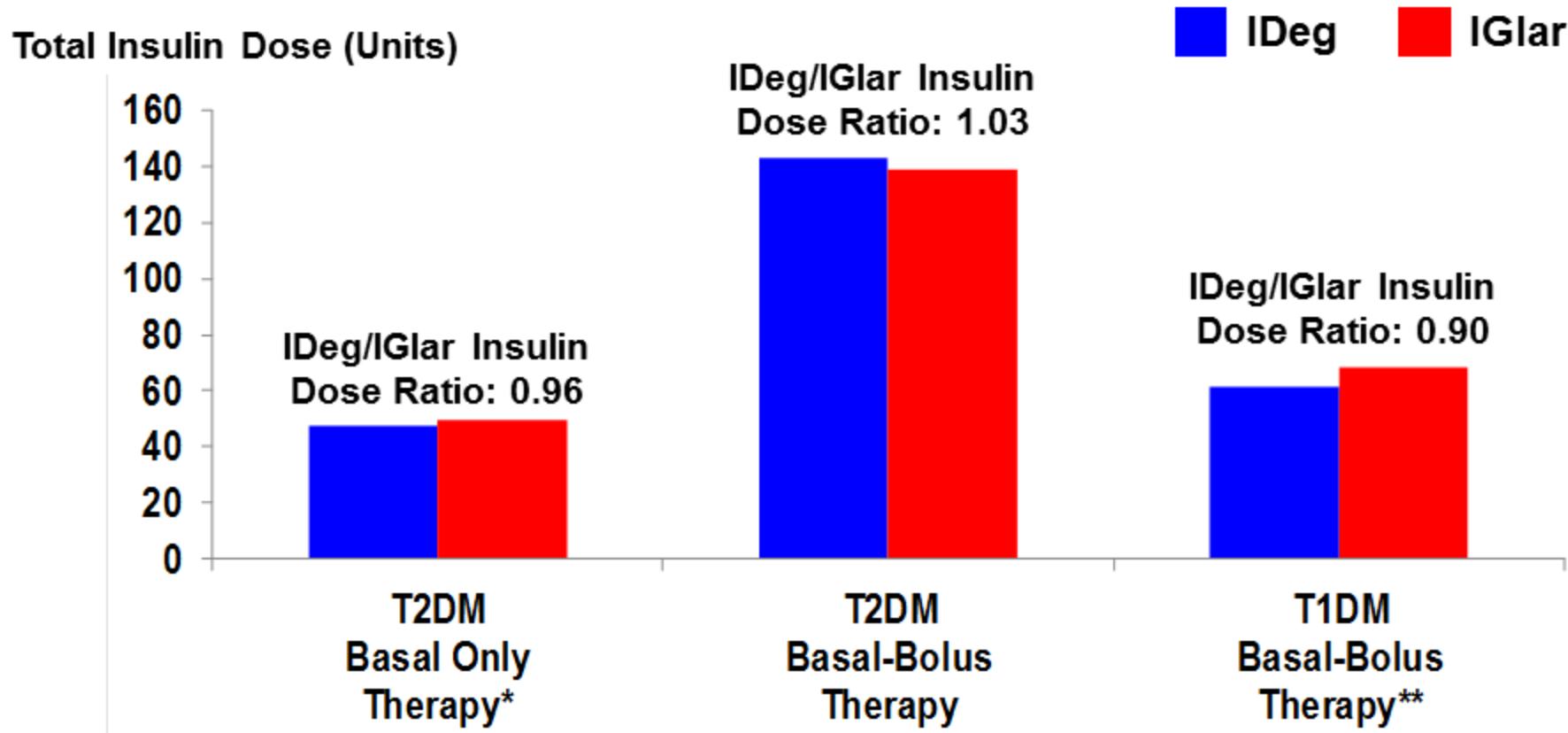
Insulin Glargine
(comparator basal insulin)



Insulin Aspart
(bolus insulin)



Total Insulin Doses, IDeg vs. IGlar, Phase 3 IDeg Trials, T1DM and T2DM, NDA



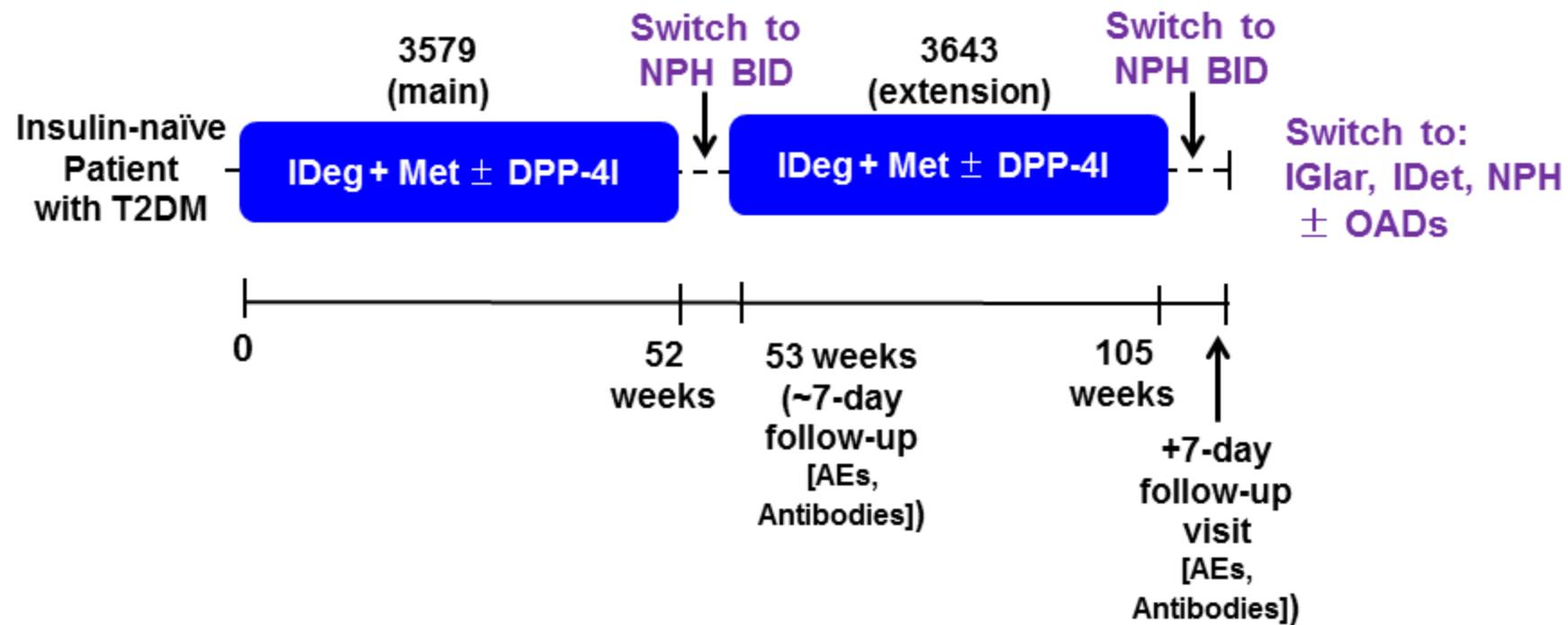
*Not including Trial 3580 with sitagliptin as comparator; **Not including Trial 3585 with IDet as comparator
SAS

Daily Basal and Bolus Doses at End of Trial, Trial 3583, T1DM

	IDeg Mean (U)	IGlar Mean (U)	Insulin Dose Ratio IDeg/IGlar
	(%/%)	(%/%)	
Basal Insulin Dose	29.2	31.4	0.93
Bolus Insulin Dose	32.4	34.9	0.93
Total Insulin Dose	61.4	66.2	0.93
Basal:Bolus Split	47:53	47:53	

Dose Split (%:%) = Basal and bolus dose given as proportion of the total daily insulin dose
SAS, LOCF

Treatment Flow in Trial 3579-3643, Main Trial and Extension



Meta-Analysis, All vs. Symptomatic Nocturnal Confirmed Hypoglycemia with Use of Different Definitions, T2DM+T1DM Pooled, Phase 3, NDA

Nocturnal Hypoglycemia Defined as:	All Episodes	Symptomatic Episodes
	Rate Ratio (IDeg/IGlar)	Rate Ratio (IDeg/IGlar)
Midnight to 6 AM	0.74*	0.72*
10 PM to 6 AM	0.74*	0.73*
Midnight to 8 AM	0.91	0.86*

*p <0.05, FAS

Confirmed Hypoglycemia in Maintenance Period: Robust Results When Adjusting for Average HbA_{1c} and Dose, NDA

IDeg/I Glar
T2DM + T1DM Pooled¹ Analysis
Rate Ratio [95%CI]

	Overall Confirmed Episodes	Nocturnal Confirmed Episodes
Not Adjusted for HbA _{1c} Nor Dose ²	0.84 [0.75 ; 0.93]*	0.68 [0.58 ; 0.80]*
Adjusted for HbA _{1c} and Dose ³	0.84 [0.76 ; 0.93]*	0.65 [0.55 ; 0.76]*

1) Trials included: 3579, 3582, 3583, 3586, 3668 (not FF arm), 3672 and 3770 (not FF arm)

2) Negative Binomial Regression model with a log link, the logarithm of the exposure time as offset , and trial, anti-diabetic therapy at screening, region, sex and age as explanatory variables.

3) Negative Binomial Regression model with a log link, the logarithm of the exposure time as offset , and trial, anti-diabetic therapy at screening, region, sex, age at baseline and average HbA1c and dose during the maintenance period as explanatory variables

Maintenance Period: week 16 and onwards.; FAS

*p <0.05

FPG and Nocturnal Confirmed Hypoglycemia at End of Trial, Phase 3 IDeg Trials, NDA

Trial	Mean FPG at end-of-trial (mg/dL)		Nocturnal Confirmed Hypoglycemia Rate Ratio IDeg/Comparator
	IDeg	Comparator	
T2DM, Basal Only Therapy			
3579: BOT 12m	106	115	0.64 [0.42 ; 0.98]*
3672: BOT 6m	106	113	0.64 [0.30 ; 1.37]
3586: BOT 6m Asia	100	102	0.62 [0.38 ; 1.04]
3668: BOT 6m, IDeg Flex	105	112	0.77 [0.44 ; 1.35]
T2DM, Basal-Bolus Therapy			
3582: BB 12m	122	127	0.75 [0.58 ; 0.99]*
T1DM, Basal-Bolus Therapy			
3583: BB 12m	141	149	0.75 [0.59 ; 0.96]*
3585: BB 6m	131	161	0.66 [0.49 ; 0.88]*
3770: BB 6m, IDeg Flex	149	151	0.60 [0.44 ; 0.82]*

*Statistically significant; CI: Confidence interval; Trial 3580 with sitagliptin as comparator is not presented
 Mean FPG (FAS) and hypoglycemia (SAS), LOCF