Insulin Degludec (TRESIBA)

National Drug Monograph

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Indication(s) Under Review	Long-acting human insulin analog to improve glycemic control in adults with type 2 diabetes.
Dosage Form(s) Under Review	100 units/mL AND 200 units/mL insulin degludec in 3mL FlexTouch disposable prefilled pen
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C

Executive Summary	
Efficacy	• Clinical trials show noninferiority of once daily insulin degludec (administered at the same time of day or flexible dosing) to once daily glargine (administered at the same time of day) in patients with type 1 or type 2 diabetes. • Insulin degludec was noninferior to detemir (33% required twice daily administration of detemir) in patients with type 1 diabetes. • Noninferiority criteria were not met for 3times weekly administration of insulin degludec compared to once daily glargine.
Safety	• Concern for errors in product selection, dosing, dispensing among the various insulins and the availability of different concentrations. • Based on an analysis of the safety data base for insulin degludec, an increased risk of major adverse cardiovascular events (defined as the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) was identified with insulin degludec relative to the comparators (HR 1.67; 95%CI 1.01, 2.75). The DEVOTE trial is a large cardiovascular safety trial and will evaluate the first occurrence of a MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Based on an interim analysis of the results of this trial, the FDA granted marketing approval for insulin degludec. • In general, the difference in overall confirmed or severe hypoglycemia was similar between insulin degludec and glargine; however, the risk of confirmed nocturnal hypoglycemia was lower with insulin degludec. • There was no clinically meaningful difference in mean weight gain between insulin degludec and glargine.
Other Considerations	• The maximum dose per single injection of the 100 units/mL pen is 80 units. Doses are adjusted in 1 unit increments.

	• The maximum dose per single injection of the 200 units/mL pen is 160 units. Doses are adjusted in 2 unit increments • Euglycemic clamp studies have shown, the glucose-lowering effect of insulin degludec lasted 42 hours after the last dose in type 1 diabetes and beyond 26 hours in type 2 diabetes (longest duration of each clamp study).

Background

Purpose for Review

The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating insulin degludec (IDeg) for possible addition to the VA National Formulary

Other Therapeutic Options

Formulary Alternatives	Other Considerations
NPH insulin Insulin glargine 100 units/mL* Insulin detemir* *VISNs can choose either as a preferred agent	Significantly lower cost
Non-formulary Alternatives	**Other Considerations**
Insulin glargine 300 units/mL	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to Mar 15, 2016) using the search term insulin degludec. The search was limited to studies performed in humans and published in the English language. The premixed combination degludec/aspart (Ryzodeg) and the investigational fixed-dose combination of degludec/liraglutide are not included in this review.

Review of Efficacy

The FDA approval of IDeg was based on the phase 3BEGIN program which includes eight randomized, open-label trials in patients with T2DM and three trials in those with T1DM (**Appendix 1**). Trials were 26-52 weeks in duration. Extension trial data are available for four trials. Of the T2DM trials, seven were add-on to oral agents and one was add-on to mealtime insulin ± metformin and or pioglitazone. In all but two trials, the active comparator was insulin glargine; the active comparators in the remaining trials were sitagliptin and insulin detemir. Two trials also compared flexible administration of IDeg to same time administration and two trials evaluated three-times-weekly (3TW) administration of IDeg to daily glargine (not FDA-approved). The concentrated formulation IDeg 200units/mL was evaluated in three trials; two of which were the 3TW administration trials.

The primary outcome was change in A1C from baseline. The trials were designed to show non-inferiority versus the comparator insulin. The IDeg vs. sitagliptin trial was designed as a superiority trial.

Inclusion/Exclusion Criteria

General **inclusion criteria for T2DM trials:** all trials T2DM for ≥ 6 months, age ≥18 years, BMI≤40kg/m^2, A1C 7-10% (exceptions: Philis-Tsmikas 7.5-11%; Meneghini insulin-naïve subgroup 7-11%), and stable dosing of the following drugs for ≥ 3 months.

- Zinman (all 3 trials): insulin-naïve; metformin ± OAD (insulin secretagogue, DPP-4 inhibitor, or alpha-glucosidase inhibitor)
- Gough: metformin ± OAD
- Meneghini: OADs or basal insulin ± OADS (metformin, insulin secretagogues, pioglitazone)
- Garber: Any insulin regimen ± OADs
- Philis-Tsimakas: 1-2 OADs (metformin, insulin secretagogues, pioglitazone

General **exclusion criteria for T2DM trials:** use of GLP-1 agonists within past 3 months, cardiovascular disease (stroke; decompensated heart failure New York Heart Association class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty) in past 6 months, uncontrolled hypertension, impaired hepatic or renal function, recurrent severe hypoglycemia, proliferative retinopathy or maculopathy, and use of any thiazolidinediones (Zinman, Gough) and rosiglitazone (Meneghini, Garber, Philis-Tsimakas) in the past 3 months.

General **inclusion criteria for T1DM trials:** T1DM ≥1 year, age ≥ 18 years, basal-bolus insulin therapy ≥1 year, A1C ≤10%, BMI ≤35kg/m^2

General **exclusion criteria for T1DM trials:** same as T2DM trials (excluding those relating to medications used in T2DM)

Baseline Characteristics (excludes 3TW trials)
Baseline characteristics of patients in T2DM trials were mean A1C 8.3%, age 58 years, 58% male, 71% White, BMI 30kg/m^2, duration of diabetes 11 years, eGFR 83mL/min/1.73m^2 (9% had eGFR <60), history of neuropathy (14%), ophthalmopathy(10%), nephropathy (6%), and cardiovascular disease (0.6%)

Baseline characteristics of patients in T1DM trials were mean A1C 7.8%, age 43 years, 57% male, 81% White, BMI 26 kg/m^2, duration of diabetes 18 years, eGFR 87mL/min/1.73m^2 (7% had eGFR <60), history of neuropathy (11%), ophthalmopathy(16%), nephropathy (7%), and cardiovascular disease (0.5%)

Dosing of study drug
Trials adjusted insulin doses using treat-to-target approach according to a pre-specified algorithm. Insulin degludec was administered once daily with the evening meal and glargine was administered any time of day at the same time. Two trials included a flexible dosing arm of IDeg. For flexible dosing, IDeg was given in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday which resulted in a minimum of 8 and a maximum of 40 hours between doses. Morning dose could be taken upon waking until the first meal of the day. The evening dose could be taken from the start of the evening meal until bedtime. The trial by Mathieu allowed dosing of IDeg at any time of day as long as there was a minimum of 8 and a maximum of 40 hours between doses (time dose was taken recorded in patient diary). In the 3TW trials, IDeg was administered on Monday, Wednesday, and Friday (one trial administered the dose in the AM and the other in the PM). Please note that the 3TW dosing regimen is not FDA approved.

Insulin degludec or glargine was started at 10 units daily in patients who were insulin naïve. For the 3TW trials, the starting dose of IDeg was 20 units and glargine 10 units.

Those previously receiving once daily basal insulin were switched unit-for-unit to the study drug. Those receiving prior twice daily basal insulin had the glargine dose reduced by approximately 20-30%; the starting dose of IDeg or insulin detemir was individually determined. The trial using detemir as the comparator also allowed a second dose to be added if there was inadequate glycemic control after 8 weeks of treatment.
Patients in the T1DM trials were switched unit-for-unit from their pre-trial mealtime dose to insulin aspart. Doses were administered immediately before the meal. Patients in the T2DM basal-bolus trial were started on insulin aspart before meals. Bolus doses were titrated after the basal insulin had been titrated.

Oral antiglycemic medication use was as follows: In Zinman (all 3 trials) and Gough, metformin and DPP-4 inhibitors were continued at prestudy dose. In Garber, metformin, pioglitazone were continued at prestudy dose. Other OADs in these three trials were discontinued. In Meneghini and Philis-Tsimakas, prior OADs were continued.

Glycemic Efficacy
Insulin degludec was found to be non-inferior to glargine and detemir and was superior to sitagliptin. Studies that also compared flexible and same time dosing had a similar reduction in A1C. Noninferiority criteria were not met for 3TW IDeg compared to glargine. Reduction in FPG tended to be greater with IDeg than the comparators. The final mean daily dose of IDeg was similar to or less than glargine/detemir. (**Appendix 1**)

Quality of Life/Treatment Satisfaction
Seven trials evaluated health-related quality of life using the Short Form 36 (SF-36v.2) questionnaire. The physical component assesses physical functioning, role-physical, bodily pain, and general health. The mental component assesses vitality, social functioning, role-emotional, and mental health.

In general there was no significant difference in scores between IDeg and glargine. In three trials, some of the individual component scores did show significant improvement with IDeg compared to glargine. The overall physical and physical functioning scores were significantly improved in Zinman 2012. In Gough, the bodily pain and vitality scores were significantly improved, and in Garber, the bodily pain score improved.

The trial comparing IDeg to sitagliptin, showed the improvement in perceived treatment burden and overall treatment satisfaction was smaller with IDeg compared to sitagliptin.

Extension Trials
At the time of this writing, published data for the extension trials were available for the T2DM trials by Zinman and Garber and the T1DM trials by Mathieu and Heller (**Table 1**).

There was no significant difference in A1C between IDeg and glargine. Two trials showed a significantly greater reduction in FPG with IDeg than glargine. The final insulin dose was similar with both insulins in the type 2 diabetes trials; however, the final insulin dose in the type 1 diabetes trials was slightly lower with IDeg than glargine.

Table 1: Glycemic Efficacy in Extension Trials

	Type DM	Study duration	Treatment arms	n	A1C (%)	FPG (mg/mL)	Basal dose (U/kg)	Bolus dose (U/kg)
Rodbard 2013	2	52 week parent trial + 52 week extension	IDeg + MET±DPP-4 GLA + MET±DPP-4	551 174	-1.1 -1.3	-75.1* -64.1	0.63 0.63	NA NA
Hollander 2015	2	52 week parent trial + 26 week extension	IDeg + Asp ±MET/PIO GLA+Asp ±MET/PIO	566 191	-1.0 -1.2	-43 -40	0.76 0.71	0.75 0.79
Bode 2013	1	52 week parent trial + 52 week extension	IDeg +Asp GLA+Asp	351 118	-0.31 -0.24	Similar	Dose ratio (IDeg:IGla) 0.88	Dose ratio (IDeg:IGla) 0.94
Mathieu 2013	1	26 week parent trial + 26 week extension	IDeg +Asp GLA+Asp	239 133	-0.13 -0.21	-31.1* -11	0.40 0.42	0.35 0.42

*Significant vs. glargine

Potential Off-Label Use
None

Safety
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	None
Contraindications	• During episodes of hypoglycemia • Hypersensitivity to insulin degludec or its excipients
Warnings/ Precautions	• Never share insulin degludec FlexTouch pen between patients even if the needle is changed • Risk for hypoglycemia

- Medication Errors: Potential for mix-up between different types of insulin. Instruct patients to always check the insulin label before each injection
- As with other insulin products, there is a risk for hypersensitivity and allergic reactions, hypokalemia, and fluid retention/heart failure with concomitant use of thiazolidinediones.

Safety Considerations

Hypoglycemia

The following definitions of hypoglycemia were used in the clinical trials.

- Confirmed hypoglycemia: episode of SMBG <56mg/dL (with or without symptoms) or severe episodes requiring assistance (no SMBG confirmation required)
- Nocturnal: episode occurring between 0001-0559h

In general, the difference in overall confirmed or severe hypoglycemia between IDeg and glargine was similar. However, a meta-analysis indicates a lower risk of nocturnal hypoglycemia. Included in the meta-analysis were those trials using insulin glargine as the active-comparator (n=5 T2DM trials and n=2 T1DM trials). Only the same time daily dosing arms of the IDeg were included.

Table 2: Confirmed Nocturnal Hypoglycemia (Meta-analysis)

	Rate ratio IDeg vs. GLA [95%CI]		
	End of trial	**Dose Titration Period**	**Maintenance Period**
T2D pooled studies	0.68 [0.57, 0.82]*	0.81 [0.64, 1.02]	0.62 [0.49, 0.78]*
T1D pooled studies	0.83 [0.69, 1.00]	0.88 [0.72, 1.08]	0.75 [0.60, 0.94]*
T2D and T1D pooled studies	0.75 [0.65, 0.85]*	0.86 [0.74, 1.00]	0.68 [0.58, 0.80]*

*Significant vs. insulin glargine

Russell-Jones, et al. Nutrition Metab Cardiovasc Dis; 2015

Of the four extension trials, three showed significantly lower rates of nocturnal and severe hypoglycemia (**Appendix 2**).

See **Appendix 2** for results by individual trial included in this PBM review.

Cardiovascular Safety

In a prior FDA submission of phase 3 trials, a safety signal was identified with IDeg relative to the comparators suggesting an increased risk of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal MI, nonfatal stroke. MACE+ included the MACE composite plus unstable angina.

- MACE: HR 1.67 [95%CI 1.01, 2.75]
- MACE+: HR1.30 [95%CI 0.88, 1.93]

The FDA required that the sponsor conduct a safety trial comparing IDeg to glargine (n~7500). The DEVOTE trial will evaluate the first occurrence of a MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke).

The population included in the DEVOTE trial are those with T2DM, previous CV disease, CV risk factors, or renal disease, and on basal insulin ≥20 units + ≥ 1 other antidiabetic drug. Patients with an acute coronary or cerebrovascular event in the previous 60days and those with heart failure NYHA Class IV were excluded. The study is expected to be completed in September 2016.

Based on an interim analysis of the results of this trial, the FDA granted marketing approval for IDeg.

Injection site reactions

In those with T1DM and T2DM, the rate of reported injection site reactions from the phase 3 clinical development program (FDA review) was 6.2 and 5.9 events per 100PYE for IDeg and

comparators respectively. Injection site bruising was the most commonly reported event.

See **Appendix 2** for reported events for individual studies included in this PBM review.

Weight
There was no clinically significant difference in mean weight gain between IDeg and glargine. In the IDeg vs. detemir trial, mean weight gain was 1.5kg and 0.4kg respectively. See **Appendix 2** for results by trial. Change in weight in the extension trials was similar to their respective parent trials.

Malignancy
In the FDA review, the IDeg and premixed IDeg/IDegAsp trials were combined in order to have a larger patient pool to better detect rare events. The number of patients and exposure years for the combined IDeg studies and comparators were 9015 (6695.1 years) and 4098 (2969.6 years) respectively.

Malignant neoplasms were reported in 0.7% (1.0 event per 100PYE) and 0.6% (0.9 events per 100PYE) for the combined IDeg studies and comparators respectively.

Adverse Reactions

Common adverse reactions

Common AEs, defined as reactions occurring in ≥5% of the population that received IDeg were nasopharyngitis and upper respiratory tract infection.

Table 3 : Adverse Events with IDeg Occurring in ≥5% of the Population

	T2DM (n=2713)	T1DM (n=1102)
Nasopharyngitis	12.9	23.9
Upper Respiratory Tract Infection	8.4	11.9
Headache	8.8	11.8
Sinusitis	-	5.1
Gastroenteritis	-	5.1
Diarrhea	6.3	-

Information from product package insert

Death/Serious adverse reactions (SAE)

Phase 3 clinical development program (FDA review)
Deaths among those with T1DM were reported in 0.5% and 0.6% of patients receiving IDeg and comparator respectively. Reported deaths in those with T2DM were 0.4% and 0.4% for IDeg and comparator respectively.

The rate of SAEs for those with T1DM with IDeg and comparators were 11.9 and12.2 events per 100 PYE, respectively. For those with T2DM, the rates were 14.8 and 13.7 events per 100 PYE for IDeg and the comparators respectively.

See **Appendix 2** for reported events for individual studies included in this PBM review.

Discontinuations due to adverse reactions

Phase 3 clinical development program (FDA review)
The rate of discontinuations due to AE for patients with T1DM was 3.3 and 1.5 events per 100 PYE for IDeg and comparators respectively. For those with T2DM, the rates were 3.6 and 2.8 events per 100 PYE.

See **Appendix 2** for reported events for individual studies included in this PBM review.

Drug Interactions

Drug-drug interactions	Same as those reported for the insulin class
Drug-food interactions	None
Drug-lab interactions	None

Risk Evaluation

As of May 2015

Sentinel event advisories	! The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used. Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Insulin degludec	None	None	None	Insulin detemir Insulin degludec/Insulin apart
Tresiba	None	None	None	Trivora Truvada

Other Considerations

Storage

- Unopened pens should be stored in a refrigerator (36-46°F). Discard after expiration date.
- Open (in-use) pens should be kept at **room temperature** (below 86°F) away from direct heat and light. The pen may be used for up to 56 days (8 weeks) after being opened if kept at room temperature.
- Unopened not in-use pens can be stored in room temperature for 56 days or 8 weeks

Pharmacokinetics/Pharmacodynamics

The pharmacokinetics and pharmacodynamics of IDeg after 8-days of daily dosing were assessed in patients with T1DM (n=21) in a euglycemic clamp study. The glucose-lowering effect of IDeg lasted 42 hours after the last dose.

Duration of action of beyond 26 hours has been shown in patients with T2DM (n=49) receiving IDeg 0.4, 0.6, or 0.8 units/kg.

A study of patients with T1DM (n=54) demonstrated four times less within-patient variability in glucose lowering effect over a 24-hour period with IDeg compared to glargine.

Dosing and Administration

- Insulin degludec can be administered once daily at any time of the day.
- Instruct patients who miss a dose of degludec to inject their daily dose during waking hours upon discovering the missed dose (ensure that at least 8 hours have elapsed between consecutive injections).
- Insulin naïve T1DM: approximately 1/3-1/2 of the total daily insulin dose given as degludec. As a general rule, 0.2 to 0.4units/kg can be used to calculate initial daily dose.
- Insulin naïve T2DM: recommended starting dose is 10 units once daily.
- T1DM or T2DM already on insulin therapy: The starting dose of degludec is the same unit dose as the daily long-acting or intermediate-acting insulin unit dose.
- The maximum dose per single injection of the 100 units/mL pen is 80 units. Doses are adjusted in 1 unit increments.
- The maximum dose per single injection of the 200 units/mL pen is 160 units. Doses are adjusted in 2 unit increments
- The dose of degludec should be titrated no more frequently than every 3-4 days

Special Populations (Adults)

	Comments
Elderly	7% and 25% of the studied population with T1DM and T2DM respectively were ≥65 years old (1% and 3% respectively were ≥75 years old). There were no overall differences in efficacy and safety between the older and younger age groups.
Pregnancy	There are no clinical studies of the use of degludec in pregnant women. Because animal reproduction studies are not always predictive of human response, degludec should be used in pregnancy during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Endogenous insulin is found in human milk. It is unknown whether degludec is excreted in human milk; therefore, use with caution. Women who are lactating may require adjustment of their insulin dose.
Renal Impairment	7% and 9% of the studied population with T1DM and T2DM respectively had an eGFR <60mL/min/1.73m^2 (0.1% and 0 respectively had an eGFR <30). A single-dose study (n=32) comparing healthy subjects and those with renal impairment, including end-stage renal disease, found no clinically relevant differences in the pharmacokinetics of degludec between groups. However, glucose monitoring should be intensified in patients with renal impairment.
Hepatic Impairment	A single-dose study (n=24) comparing healthy subjects and those with hepatic impairment (mild, moderate, and severe)found no difference in the pharmacokinetics of degludec between healthy subjects and those with hepatic impairment. However, glucose monitoring should be intensified in patients with hepatic impairment.
Pharmacogenetics/genomics	None

Projected Place in Therapy

There is no clear projected place in therapy with IDeg over insulin glargine. Pharmacokinetic/pharmacodynamic trials show a longer duration of action of IDeg than glargine U100; however, clinical trials show noniferiority of once daily IDeg to once daily glargine and 3TW administration of IDeg to be inferior to once daily glargine.

Potential place in therapy may include:

- <24 hour coverage with glargine U100, after consideration is given for split dosing or other interventions
- Recurrent nocturnal hypoglycemia, only after other interventions have been made to address the hypoglycemia (e.g., dosage adjustment of insulin/DM medications, timing of meals/snacks, exercise, etc.)
- Patient who works varying shifts (or a dialysis patient) and cannot take their basal insulin at the same time every day

Use of IDeg should be restricted to endocrinologists, diabetologists, or other locally designated expert.

References:

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Product package insert for Tresiba (insulin degludec injection) 09/2015.

FDA Medical Review for insulin degludec
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000MedR.pdf

Prepared by Deb Khachikian, PharmD

Appendix 1: Selected Outcomes from Clinical Trials (Glycemic Improvement, Insulin Dose)

Study	Duration (weeks)	Patients	Treatment arms	Background Medications	n	BL A1C (%)	ΔA1C (%)	A1C < 7% (%pts)	BL FPG (mg/dL)	ΔFPG (mg/dL)	Basal dose (Units/d)	Bolus dose (Units/d)
Zinman^ 2012	52	T2DM Insulin naive	IDeg + MET±DPP-4 GLA + MET±DPP-4	MET (82.5%) MET+DPP-4 (17.5%)	773 257	8.2 8.2	-1.06 -1.15	51.7 54.1	174 174	-68 -60.2	56 58	NA
Gough 2013	26	T2DM Insulin naive	**IDeg-200** + MET±DPP-4 GLA + MET±DPP-4	MET (84%) MET+DPP-4 (16%)	228 229	8.3 8.2	-1.18 -1.22	52.2 55.9	172 174	-71.1 -63.5	59 62	NA
Package insert	26	T2DM (Asian) Insulin naïve	IDeg + OADs GLA + OADs		289 146	8.4 8.5	-1.42 -1.52	40.8 48.6	152 156	-54.6 -53.0	19 24	NA
Meneghini^ 2013	26	T2DM On OADs or basal insulin ±OADs	IDeg same time + OADs IDeg flex + OADs GLA + OADs	OAD only (57.9) Basal+OAD (38.7) MET (91), SU (66), TZD (6.8), GLN (4.7)	228 229 230	8.4 8.5 8.4	-1.03 -1.17 -1.21	40.8 38.9 43.9	158 162 163	-54.2 -55.0 -47.5	45 46 44	NA
Garber^ 2012	52	T2DM Inadeq control on insulin and/or OADs	IDeg + Asp ±MET/PIO GLA+Asp ±MET/PIO	MET or PIO alone or in combination (65%)	744 248	8.3 8.4	-1.10 -1.18	49.5 50.0	166 166	-40.6 -35.3	74 67	70 73
Philis-Tsimikas 2013	26	T2DM	IDeg + OADs SIT + O ADs	MET (25%) MET+SU (69.6) PIO±MET/SU (5.6)	225 222	8.8 9.0	-1.52ǂ -1.09	40.9ǂ 27.9	170 179	-61.4ǂ -22.3	43 NA	NA
Zinman 2013	26	T2DM Insulin naïve **3TW trial (AM)**	**IDeg -200**+ MET±DPP-4 GLA+ MET±DPP-4	MET (30%) MET+DPP-4 (23%)	229 230	8.2 8.3	-0.93* -1.28	48§ 58	168 173	IDeg-GLA 13	50 62	NA
Zinman 2013	26	T2DM Insulin naïve **3TW trial (PM)**	**IDeg-200**+ MET±DPP-4 GLA+ MET±DPP-4	MET (23%) MET+DPP-4 (16%)	233 234	8.3 8.3	-1.09* -1.35	46§ 54	178 178	IDeg-GLA 9	51 56	NA
Heller^ 2012	52	T1DM	IDeg +Asp GLA+Asp		472 157	7.7 7.7	-0.36 -0.34	39.8 42.7	165 174	-27.6 -21.6	29 31	32 35
Davies^ 2014	26	T1DM	IDeg +Asp DET+ ASP	32.9% used detemir BID	302 153	8.0 8.0	-0.71 -0.61	41.1 37.3	178 171	-43.3 -13.5	25 29	36 41
Mathieu^ 2013	26	T1DM	IDeg same time + Asp IDeg flex+ Asp GLA + Asp		165 164 164	7.7 7.7 7.7	-0.41 -0.40 -0.57	37.0 37.2 40.9	179 173 175	-41.8 -24.7 -23.9	32 36 35	27 30 35

Abbreviations: Asp=aspart; BID=twice daily; BL=baseline; DET=detemir; DPP-4=dipeptidylpeptidase-4; Flex=flexible dosing; FPG=fasting plasma glucose; GLA=glargine; GLN=glinides; IDeg=insulin degludec; MET=metformin; NA=not applicable; OAD=oral antiglycemic PIO=pioglitazone; agent; SU=sulfonylurea; TW=times weekly; TZD=thiazolidinedione

^indicates studies that have a completed or ongoing extension trial

*noninferiority of IDeg 3TW vs. GLA daily not reached

§ Significant difference favoring GLA

ǂIDeg superior to sitagliptin

Appendix 2: Selected Safety Outcomes from Clinical Trials

Study	Duration (weeks)	Type DM	Treatment arms	n	Deaths (n)	SAE % (rate[ǂ])	D/C due to AE (%)	Overall hypo % (rate PYE)	Severe hypo % (rate PYE)	Nocturnal hypo % (rate PYE)	Injection site reactions (%)	BL weight (kg)	Δ weight (kg)
Zinman 2012	52	2	IDeg + MET±DPP-4	773	1	8.1 (12)	2.6	46.5 (1.52)	0.3 (0.003)*	13.8 (0.25)*	5.9	89.4	2.4
			GLA + MET±DPP-4	257	1	10.1 (15)	1.9	46.3(1.85)	1.9 (0.023)	15.2 (0.39)	7.0	91.8	2.1
Gough 2013	26	**2**	**IDeg-200** + MET±DPP-4	228	0	6.6 (22)	2.2	28.5 (1.22)	0/0	6.1 (0.18)	6.1	92.2	1.9
			GLA + MET±DPP-4	229	2	4.4 (13)	1.7	30.7 (1.42)	0/0	8.8 (0.28)	6.1	92.7	1.5
Meneghini 2013	26	2	IDeg same time + OADs	228	1	4 (0.11)	0.4	44 (3.6)	n=2	11 (0.6)	3.5	81.8	1.5
			IDeg alt + OADs	229		3 (0.08)	0.9	51 (3.6)	n=2	13 (0.6)	1.3	81.3	1.5
			GLA + OADs	230	1	2 (0.04)	0.9	49 (3.5)	n=2	21 (0.8)	1.7	82.1	1.3
Garber 2012	52	2	IDeg + Asp ±MET/PIO	744	8	14.9 (21)	4.0	81 (11.09)*	5 (0.06)	40 (1.39)*	4.0	92.6	3.6
			GLA+Asp ±MET/PIO	248	2	15.9 (20)	4.0	82 (13.63)	4 (0.05)	47 (1.84)	3.0	92.2	4.0
Philis-Tsimikas 2013	26	2	IDeg + OADs	225	1	6.2 (17)	3.9	42.5 (3.07)*	0.4 (0.01)	12.8 (0.52)	NR	83.9	2.28
			SIT + OADs	222	0	4.4 (10)	0.9	12.7 (1.26)	0 (0)	5.7 (0.30)		86.1	-0.35
Zinman 2013	26 **3TW-AM**	2	**IDeg -200**+ MET±DPP-4	229	0	4.8 (0.1)	0	27.3 (1.3)	n=1	11.5 (0.4)*	11.9	90.8	0.8
			GLA+ MET±DPP-4	230	0	5.0 (0.1)	0	28.4 (1.2)	n=1	7.4 (0.2)	13.1	95.7	1.2
Zinman 2013	26 **3TW-PM**	2	**IDeg-200**+ MET±DPP-4	233	0	5.6 (0.1)	1.7	32.2 (1.6)*	n=1	4.3 (0.2)	6.4	92.3	0.8
			GLA+ MET±DPP-4	234	0	5.1 (0.2)	0.4	21.4 (1.0)	0	6.8 (0.2)	3.0	91.4	0.5
Heller 2012	52	1	IDeg +Asp	472	2	10 (14)	3.0	96 (42.54)	12 (0.21)	72 (4.41)*	3.0	78.9	1.8
			GLA+Asp	157	1	11 (16)	1.0	95 (40.18)	10 (0.16)	74 (5.86)	5.0	78.3	1.6
Davies 2014	26	1	IDeg +Asp	302	0	7 (0.23)	1.0	93 (45.83)	10.6 (0.31)	58.3 (4.14)*	4.0	66.5	1.5
			DET+ ASP	153	0	5 (0.18)	0.7	91.4 (45.69)	10.5 (0.39)	58.6 (5.93)	2.0	66.7	0.4
Mathieu 2013	26	1	IDeg same time + Asp	165	1	4.2 (12)	2.4	99.4 (88.3)	12.7 (0.4)	73.3 (9.6)	1.8	79.5	0.8
			IDeg alt+ Asp	164		5.5 (17)	3.0	93.9 (82.4)	10.4 (0.3)	67.7 (6.2)*^	4.9	81.7	1.2
			GLA + Asp	164	0	5.0 (10)	0.6	96.9 (79.7)	9.9 (0.5)	72.7 (10.0)	2.5	80.4	1.6
Rodbard 2013	Extension 104 total	2	IDeg + MET±DPP-4	551	4	15.1 (0.15)	1.6	68.2 (1.74)	1.1 (0.006)*	24.9 (0.27)*	0.07E/pt-yr		2.7
			GLA + MET±DPP-4	174	3	16.0 (0.17)	1.9	69 (2.06)	3.4 (0.021)	30.5 (0.42)	0.08E/pt-yr		2.4
Hollander 2015	Extension 78 total	2	IDeg + Asp ±MET/PIO	566	3	18.5 (0.20)	0.5	86 (9.84)*	5.3 (0.05)	45.1 (1.27)*	4.2		4.0
			GLA+Asp ±MET/PIO	191	0	21.1 (0.20)	0	86.4 (12.76)	7.3 (0.06)	58.1 (1.77)	3.2		4.4
Bode 2013	Extension 104 total	1	IDeg +Asp	351	2	15.1 (12)	<1	NS (graph)	0.17E/pt-yr	3.9 E/pt-yr*	3.0		2.1
			GLA+Asp	118	2	20.3 (17)	2.0		0.15E/pt-yr	5.3 E/pt-yr	5.8		2.0
Mathieu 2013	Extension 52 total	1	IDeg same time + Asp	239	0	7.6 (13)	0	98.7 (65.5)	13.4 (0.2)*	83.7 (6.3)*	3.6		1.3
			GLA + Asp	133	0	7.5 (10)	0.6	97.7 (61.4)	15.0 (0.4)	81.2 (8.4)	2.5		1.9

Abbreviations: Asp=aspart; BL=baseline; D/C=discontinued; DET=detemir; DPP-4=dipeptidylpeptidase-4; Flex=flexible dosing; GLA=glargine; GLN=glinides; hypo=hypoglycemia; IDeg=insulin degludec; MET=metformin; NR=not reported; OAD=oral antiglycemic PIO=pioglitazone; PYE=events per patient-year; SAE=serious adverse event; SU=sulfonylurea; TW=times weekly; TZD=thiazolidinedione

* Significant difference

[ǂ]Rates are shown as per 100 patient-years for Zinman 2012, Gough, Garber, Philis-Tsimakas, Mathieu, and Bode. For all others, rates are shown as per patient-year