Drug Use Research & Management Program
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New Drug Evaluation: Insulin degludec, subcutaneous injection

Date of Review: March 2016
Generic Name: Insulin degludec
PDL Class: Insulins

End Date of Literature Search: November 11, 2015
Brand Name (Manufacturer): Tresiba®
Dossier Received: yes

Research Questions:

- What is the difference in efficacy between insulin degludec and other long-acting insulins in patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM) when microvascular outcomes (i.e., retinopathy, nephropathy, neuropathy), macrovascular outcomes (i.e., stroke, myocardial infarction) and mortality outcomes are assessed? Alternatively are there differences between degludec and other long-acting insulins in achievement of goal glycated hemoglobin (A1c) in T1DM or T2DM?
- Is there evidence of comparative safety between degludec and other insulins for important safety outcomes such hypoglycemia, weight gain, or cardiovascular events in patients with T1DM or T2DM?
- Are there subpopulations of patients with T1DM or T2DM for which degludec may be more effective or associated with less harm than other long-acting insulins?

Conclusions:

- Insulin degludec was studied in 8 open-label, randomized controlled trials (RCTs).[1-8] Active comparisons included insulin glargine, insulin detemir, and sitagliptin. Most trials were 26-52 weeks in duration and designed to test non-inferiority of degludec to an active control, with both arms openly titrating doses to achieve a fasting blood glucose level of approximately 70-90 mg/dL.[1-4,6-8] The primary endpoint for each study was change in A1c from baseline. Secondary efficacy endpoints were frequently the reduction in fasting blood glucose (FBG) from baseline and achievement of an A1c of less than 7%.
- There is insufficient evidence to determine if insulin degludec has any effect on mortality, macrovascular outcomes or microvascular outcomes.
- There is low strength evidence that degludec is non-inferior to insulin glargine or detemir at A1c reduction in patients with T1DM or T2DM with mildly elevated A1c at baseline.[1-8]
- Adverse effects such as hypoglycemia, specifically nocturnal hypoglycemia, were assessed in each trial. However, the open-label study design prohibits a fair comparison of degludec to insulin glargine or detemir. Hypoglycemia was the most common adverse effect associated with all insulin products studied. There is low strength evidence that use of degludec had similar overall hypoglycemia rates as insulin comparators.[1-4,6-8] Nocturnal hypoglycemia, defined as confirmed blood glucose readings less than 56 mg/dL during the hours of 1:00-5:59 am, was 2-10% lower with degludec compared to glargine (NNT 14-50.[1,3,4,7] The clinical impact of these differences are unclear considering the open-label study design.
- All insulin comparator trials used a treat-to-target insulin titration scheme, preventing superiority comparisons. The use of an open-label study design may introduce bias that produces results in favor of the study drug. Additionally, many studies had high or unclear risk of detection bias. Differences in reduction

of A1c between degludec and its comparators were small and do not suggest clinical significance. Double-blinded trials that evaluate outcomes such as goal A1c, and long-term studies that evaluate microvascular and macrovascular outcomes would be helpful to clarify the role of degludec in relation to other long-acting insulins for the management of patients with T1DM and T2DM

Recommendations:
- Make insulin degludec non-preferred and subject to current PA criteria for insulin pens (appendix 2).

Background:
There are five long-acting insulin products to treat hyperglycemia associated with T1DM and T2DM: insulin glargine (Lantus U100 and Toujeo U300); insulin detemir (Levemir; U100); insulin degludec (Tresiba U100 and U200); and a long-acting/short-acting combination of insulin degludec/aspart (Ryzodeg 70/30).[11-15] Comparative evidence on long-term, clinically relevant health outcomes (i.e., macrovascular outcomes, microvascular outcomes, mortality or cancer) between the long-acting insulins has not been studied.[15] Absolute A1c reduction is similar for glargine, detemir and insulin NPH.[16,17] Insulin NPH has been associated with a higher incidence of hypoglycemia, defined as confirmed blood glucose measurement of < 56 mg/dL, and nocturnal hypoglycemia, defined as blood glucose levels < 56 mg/dL from the hours of 1:00 to 5:59 am, compared to glargine and detemir. However, no difference in the incidence of severe hypoglycemia, defined as hypoglycemia requiring assistance, has been found between these agents.[14] Evidence on the efficacy and safety of degludec is presented below.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Insulin degludec is only available via an insulin pen device called the FlexTouch®. Approval of degludec was based on 9 phase 3, open-label trials.[14] Open-label trials may be associated with a high degree of reporting bias favoring the results of the intervention. The delivery devices for degludec were different than comparators preventing masking of treatments and placebo-filled pens were not available. Three trials were in patients with T1DM and 6 trials in T2DM patients. One trial involving T2DM patients was excluded due to limited applicability to OHP patients, since only Asian patients were studied.[9] Subjects in the trials self-titrated their own insulin to achieve a goal fasting blood glucose (FBG). All studies in patients with T2DM allowed use oral anti-diabetic medications. Initial approval of degludec was denied by the FDA due to associated cardiovascular (CV) risk based on a meta-analysis of CV events from 17 efficacy trials. An interim analysis of a separate study designed to specifically investigate the CV implications demonstrated that degludec was not associated with any CV risk beyond glargine or detemir. The study is ongoing, with results expected at the end of 2016. Final analysis of results will provide more robust evidence on the effect of degludec on CV risk.[10,18]

Type 1 Diabetes Mellitus
Once Daily Insulin Degludec vs. Once Daily Insulin Glargine
Once daily insulin degludec was compared to once daily glargine in an open-label, non-inferiority, phase 3 study with the concomitant use of mealtime (bolus) insulin aspart.[1] Patients (n=629) had a mean age of 44 years, A1C of 7.7%, 58% were male, and subjects had been previously on a basal-bolus insulin regimen. Patients with cardiovascular, renal and liver disorders. The primary outcome was change from baseline A1C at 52 weeks. Key secondary outcomes included change from baseline in FBG and number of patients who obtained a goal A1C <7% at 52 weeks. Degludec was found to be non-inferior to glargine for A1c lowering at 52 weeks: it was -0.40% for degludec and -0.39% for glargine (estimated treatment difference (ETD) -0.01%; 95% CI, -0.14 to 0.11%; P<0.0001 for

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non-inferiority). FPG values were also not significantly different. The percent of patients who achieved an A1C <7% were also similar at 40% for degludec and 43% for glargine (p-value not provided).[1] At the end of the study basal insulin doses were 14% less for degludec compared to glargine.

<u>Flexible Insulin Degludec vs. Once Daily Insulin Degludec vs. Once Daily insulin Glargine</u>
In this phase 3, open-label RCT, 490 patients with T1DM using mealtime insulin aspart were given degludec (forced-flex) (provided in a fixed interval schedule with a minimum of 8 and maximum of 40 hours between doses) compared to degludec or glargine given at the same time each day.[2] Seventy percent of patients were transferred from a basal-bolus regimen with 63% having used glargine prior to the study. Patients were reasonably well controlled with a mean A1C of 7.7% and age of 44 years. Forty-two percent were female. The primary and secondary outcomes were the same as the previous trial except the percent of patients who obtained a goal A1C <7% was not studied. A 26-week extension trial was offered at the conclusion of the original trial (results reported below).[19] Degludec forced flex was non-inferior to glargine and A1c lowering from baseline, -0.40% for degludec forced flex vs. -0.58% for glargine (ETD 0.17%; 95% CI, -0.04 to 0.30%; p= NS). Reduction in FPG were 23 mg/dL for flexible degludec, 24 mg/dL for once daily glargine, and 46 mg/dL for once daily degludec (no p-value given).[2] Small differences in A1c are common in trials that use treat-to-target design but prevent efficacy comparisons of superiority, especially when trials are conducted in an open-label setting. Basal insulin doses were 4% less for degludec compared to glargine upon study completion.

<u>Once Daily Insulin Degludec vs. Once Daily Insulin Detemir</u>
Patients with T1DM were randomized 2:1 to degludec or detemir in another open label, non-inferiority phase 3 RCT.[3] All patients remained on mealtime insulin aspart. Patients were a mean age of 41 years with a baseline A1C of 8% and diabetes history of 14 years.[3] Forty percent of patients were from Japan and 13% were from India. No US sites were included in the study. The primary outcome was change from baseline A1c at 26 weeks for which degludec was found to be non-inferior to detemir, -0.73% for degludec vs. -0.65% detemir (ETD -0.09%; 95% CI, -0.23 to 0.05; p=0.21). Change in baseline FPG was studied as a secondary endpoint. Degludec lowered FBG from baseline by 46.8 mg/dL and detemir lowered FBG by 11.16 mg/dL (ETD -29.88 mg/dL; 95% CI, -42.66 to -17.1 mg/dL; P<0.0001). The number of patients who obtained a goal A1C <7% was similar in both groups.[3] At the end of the study, degludec insulin doses were 0.54 U/kg compared to 0.63 U/kg for detemir.

Type 2 Diabetes Mellitus
<u>Once Daily Insulin Degludec vs. Once Daily Insulin Glargine</u>
Insulin degludec was compared to glargine in an open label, non-inferiority, phase 3 RCT of 1,030 patients with T2DM who were insufficiently controlled on oral diabetes medications.[4] Participants were predominately male (62%), white (89%), with a mean age of 59 years and an A1C of 8.2%. Most patients were on metformin and a sulfonylurea (SU) at the time of screening. All patients were insulin naïve. The primary outcome was change from baseline A1C at 52 weeks. Key secondary outcomes included change in FBG from baseline and proportion of patients who obtained an A1c < 7%.[4] Degludec decreased A1C by -1.06% after 52 weeks which was similar to the -1.19% decrease seen with glargine (ETD 0.09%; 95% CI -0.04 to 0.22; p-value not given). Mean insulin doses used at the end of the study were similar (0.59 units/kg for degludec and 0.60 units/kg for glargine). Mean change in FBG was greater with degludec compared to glargine (-67.68 mg/dL for degludec vs. -59.4 mg/dL for glargine; p= 0.005) but the number of patients who obtained an A1C < 7% was similar between groups (51.7% for degludec vs. 54.1% for glargine; p=0.40).[4]

<u>Insulin Degludec vs. Sitagliptin</u>
In another 26 week, open label, phase 3 study degludec (titrated to a FBG level of 90 mg/dL) was compared to sitagliptin 100 mg daily in insulin-naïve patients already on 1-2 oral diabetes medications (most commonly metformin and SU).[5] Patients were 56 years with a baseline A1c of 8.9% and 8-year history of T2DM. The primary outcome was similar to the studies already noted. Degludec lowered A1c by -1.52% compared to sitagliptin -1.09% (ETD 0.43%; 95% CI, -0.61 to -

0.24; p<0.0001). Mean change in FPG for degludec was (61.4 mg/dL) compared to sitagliptin (22.3 mg/dL) (p<0.0001). More patients achieved a goal A1c < 7% with degludec (41%) compared to sitagliptin (28%) (odds ratio [OR] 1.60; 95% CI, 1.04 to 2.47; p=0.034).[5]

Insulin Degludec vs. Insulin Glargine

In another 26 week, open label, non-inferiority, phase 3 RCT, degludec U200 was compared to glargine U100. Insulin doses were titrated weekly based on self-reported blood glucose levels levels.[6] Adult patients with T2DM taking metformin with or without a DPP-4 inhibitor were enrolled. There were 457 participants with a mean A1C of 8.3%, BMI of 32.4 kg/m^2 and a mean age of 57 years. Sixty percent were taking 2 oral diabetes medications: all patients were on metformin, 65% were on a SU and 16% were on DPP-4 inhibitor. The primary endpoint was change in A1C from baseline after 26 weeks. Degludec was non-inferior to glargine with similar A1c reductions (-1.3%) in both groups (ETD 0.04%; 95% CI, -0.11 to 0.19; p-value not given).[6] Fifty-six percent of patients achieved an A1c of < 7% with degludec compared to 52% with glargine (no p-value given). Reduction in FPG was also greater with degludec (-66.7 mg/dL) compared to glargine (-60.9 mg/dL) (ETD -7.56 mg/dL; 95% CI, -14.04 to -1.08 mg/dL; p-value not given).[6]

Insulin Degludec vs. Insulin Glargine

Degludec was compared to glargine, both with mealtime insulin aspart, in another open label, phase 3 RCT in patients with T2DM previously on insulin, with or without metformin and/or pioglitazone.[7] Patients were a mean age of 59 years, with a 13-year history of diabetes and A1C of 8.3%. Fifty percent of patients were on a basal-bolus insulin regimen with at least one oral diabetes medication. Insulin doses were titrated to effect. Metformin was used in 60% of patients and pioglitazone was used in 6%. The primary endpoint was change in A1C after 52 weeks. Degludec was non-inferior to glargine with similar A1C reduction (-1.10% vs. -1.18%, respectively; ETD 0.08%; 95% CI, -0.05 to 0.21; p-value not given). The percent of patients who obtained an A1C <7% was also similar between degludec (50%) and glargine (49%). Differences in FPG were not significantly different between degludec (41.4 mg/dL) and glargine (36 mg/dL) (p= 0.1075).[7]

Insulin Degludec vs. Insulin Glargine

In another open label, phase 3 RCT, degludec on a forced flex schedule (FF) and once daily degludec given the same time daily was compared to once daily glargine in both insulin-naïve insulin-experienced patients.[8] Patients randomized to degludec FF administered their dose in a morning and evening rotating regimen with 8-40 hours between doses. The once daily degludec and glargine groups were dosed at the same time each day. Patients had a 10-year history of T2DM, mean A1C of 8.4%, and mean age of 56 years, with 58% of patients with prior use of oral diabetes medications (primarily metformin and SU) and 39% with prior basal insulin use.[8] The primary outcome was the change in A1c from baseline at 26 weeks. Degludec FF was non-inferior to glargine with similar A1C changes (-1.28% vs. -1.26%, respectively; ETD 0.04%; 95% CI, -0.12 to 0.20%). Changes in A1C between degludec FF and once daily dosing were not significantly different (-1.28% vs. -1.07%, respectively; ETD -0.13%; 95% CI, -0.29 to 0.03%). The percent of patients who achieved an A1C <7% was highest with glargine (43.9%), followed by once daily degludec (40.8%) and degludec FF (38.9%); however, none of the differences were statistically significant. Insulin doses were similar across treatment groups, including both insulin-experience and insulin-naïve patients.[8]

Study Limitations

All of the results in the trials presented must be interpreted with caution as all of them used an open-label study design which introduces high risk of performance bias. Masking of treatments was not an option due to delivery device limitations, however, making the product available in vials would have limited this issue and allowed for blinded trials yielding more conclusive results. Trials only lasted 26-52 weeks which sufficient only to assess surrogate endpoints like A1c and FBG but cannot assess clinically relevant morbidity and mortality outcomes. In addition, the applicability of study results to the OHP population is limited by the exclusion of patients with comorbid conditions and enrollment of a high number of Japanese and Indian patients in some trials. Adherence to intensive self-monitoring of blood glucose required in studies may not be replicable in the general population.

Clinical Safety:

Hypoglycemia is the most common adverse event associated with insulin. Hypoglycemia, blood glucose measurements below 56 mg/dL, were not significantly different in 7 out of 8 of the trials evaluated. One study showed degludec to be superior to glargine with an ARR of 1% and a NNT of 100.[7] In clinical trials, hypoglycemia, confirmed blood glucose measurement below 55.8 mg/dL between the hours or 1:00 and 5:59 am, were the most common adverse even observed with degludec (29-99%) and was similar to glargine (31-96%) with an ARR of 2-10%.[1,2,4,6-8] Nocturnal hypoglycemia occurred at a similar rate with degludec compared to detemir, 58% for both groups.[3]

Other important safety outcomes are: adverse reactions causing discontinuation of treatment, changes in weight and injection site reactions. Mean adverse event rates causing early discontinuation of therapy were similar between degludec (2.4%) and glargine (2.2%).[1,2,4,6-8] The incidence of injection site reactions was 3.7% for degludec compared to 3.9% for glargine. The difference in injection site reaction was 2% favoring detemir compared to degludec, 2% vs. 4%, based on one study.[3] Weight gain was similar with degludec, 2.1 kg, compared to glargine, 2.1 kg, and higher than detemir, 0.7 kg. [1,2,4,6-8]

Adverse events (excluding hypoglycemia) occurring in ≥5% or more of T1DM patients studied in patients with T1DM with a mean exposure duration to degludec of 34 weeks were the following: nasopharyngitis (24%), upper respiratory tract infection (12%), headache (12%), sinusitis (5%) and gastroenteritis (5%).[13] similar adverse reactions were seen in patients with T2DM exposed to degludec.[13]

Pharmacology and Pharmacokinetic Properties:

Table 2. Degludec Pharmacology and Pharmacokinetics[13]

Parameter	
Mechanism of Action	Regulation of glucose metabolism by stimulating peripheral glucose uptake and inhibiting hepatic glucose production
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Plasma protein binding >99%
Elimination	Similar to human insulin – dependent on rate of absorption from subcutaneous tissue
Half-Life	25 hours
Metabolism	Similar to human insulin

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Mortality
2) Macrovascular outcomes
3) Microvascular outcomes
4) Severe or Symptomatic Hypoglycemia
5) Premature Discontinuation due to Adverse Event
6) Goal A1c <7%

Primary Study Endpoint:

1) Change in A1C from baseline

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Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Heller, et al.[1] PG, OL, NI, RCT Phase 3	1. Insulin degludec Qday (D)* 2. Insulin glargine Qday (G)* * Given with meal-time insulin aspart * Doses titrated to achieve a FBG target of 70.2-90.0 mg/dL Duration 52 weeks	Demographics: Mean age: 44 years Male: 58% Baseline A1c: 7.7% White: 94% Black: 2% Asian: 2% Key Inclusion Criteria: - **T1DM** - Age ≥18 years - A1c ≤10% - BMI ≤35 kg/m² - Basal-bolus insulin therapy ≥1 year before screening Key Exclusion Criteria: - Use of non-insulin antidiabetic drug - Impaired liver or renal function - CVD - Cancer	ITT: 1. 472 2. 157 PP: 1. 448 2. 147 Attrition: 1. 14% 2. 13%	Primary Outcome: <u>Change in A1c from baseline:</u> D -0.40% vs. G -0.39%; ETD 0.01% (95% CI, -0.14 to 0.11%; p<0.0001 for non-inferiority) Secondary Outcome: <u>A1c <7.0%:</u> D 40% vs. G 43% p-value not given	NA NA	<u>Nocturnal hypoglycemia*:</u> D 72% G 74% p=0.021 <u>Severe hypoglycemia**:</u> D 12% G 10% p=0.34 <u>Weight gain at 26 weeks:</u> D +1.8 kg G +1.6 kg p=0.62 <u>Early D/C due to AE:</u> D 2.5% G 1.3% p-value not given * Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am. ** Severe hypoglycemia – hypoglycemia requiring assistance	2/50 NS NA NA	**Risk of Bias (low/high/unclear):** <u>Selection Bias:</u> (low) randomized 3:1 by computer generated blocked allocation sequence via central interactive response system. <u>Performance Bias:</u> (high) open-label. <u>Detection Bias:</u> (high) Titration surveillance committee and members responsible involved in defining analysis sets until data were locked for statistical analysis were blinded to treatment group assignment. <u>Attrition Bias:</u>(low) Overall attrition was similar between groups with a value of 13-14%. Analysis was done on the ITT population with LOCF for missing data. <u>Reporting Bias:</u> (low) Study protocol followed and outcomes reported as specified. **Applicability:** <u>Patient:</u> T1DM, well controlled without significant comorbidities. <u>Intervention:</u> Dosing titration appropriate. <u>Comparator:</u> Glargine appropriate comparator. <u>Outcomes:</u> Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. <u>Setting:</u> Six countries and 79 sites.

2. Mathieu, et al.[2]	1. Insulin degludec Qday Forced-Flex (DFF)*	Demographics: Mean age: 44 years Female: 42.4% Baseline A1C: 7.7% White: 97% Black: 3.6% Asian: 0.4%	ITT: 1. 164 2. 165 3. 164	Primary Outcome: Change in A1c from baseline: DFF: -0.40% D: -0.41% G: -0.58%		Nocturnal hypoglycemia*: DFF 67.7% D 73.3% G 72.7% p=NS for all		Risk of Bias (low/high/unclear): Selection Bias: (low) randomized 1:1:1 via a central interactive response system. Performance Bias: (high) open-label. Detection Bias: (high) Titration surveillance committee and members responsible involved in defining analysis sets until data were locked for statistical analysis were blinded to treatment group assignment.
PG, OL, NI, RCT	2. Insulin degludec Qday (D)*		PP: 1. 138	DFF vs. G: ETD 0.17% (95% CI, -0.04 to 0.30%; p-value not given)	NA	Severe hypoglycemia**: DFF 17.4% D 12.7%	NS	Attrition Bias: (low) Attrition with degludec was higher (16%) than for glargine (7%). Analysis was done on the ITT population with
Phase 3	3. Insulin glargine Qday (G)*	Key Inclusion Criteria:	2. 139 3. 152			G 9.9% p=NS for all		LOCF for missing data. Reporting Bias: (low) Study protocol was
		- **T1DM**	Attrition:	DFF vs. D: ETD 0.01% (95%			NS	followed and outcomes were reported as
	*Given with meal-time insulin aspart	- Age ≥18 years - A1c ≤10%	1. 16% 2. 16%	CI, -0.13 to 0.14%; p-value not given)	NA	Weight gain at 26 weeks:		specified.
	*Doses titrated to achieve a FBG target of 70.2-90.0 mg/dL	- BMI ≤35 kg/m^2 - Basal-bolus insulin therapy before screening	3. 7%			DFF +1.2 kg D +0.8 kg G +1.6 kg p=NS for all	NS	**Applicability**: Patient: T1DM without significant comorbidities; 70.6% on 1 basal injection and 3 or more bolus injections prior to trial. Intervention: Dosing titration appropriate.
	Duration 26 weeks	Key Exclusion Criteria: - Use of non-insulin antidiabetic drug				Early D/C due to AE: DFF 3.0% D 2.4%		Comparator: Glargine an appropriate comparator. Outcomes: Change in A1C from baseline is not
		- Impaired liver or renal function - CVD - Cancer				G 0.6% p-value not given	NA	an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like
						* Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am		hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: Six countries and 71 sites.
						** Severe hypoglycemia – hypoglycemia requiring assistance		

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| 3. Davies, et al.[3]

PG, OL, NI, RCT

Phase 3 | 1. Insulin degludec Qday (Deg)*

2. Insulin detemir Qday (Det)*

*Given with meal-time insulin aspart

*Doses titrated to achieve a FBG target of 70.2-90.0 mg/dL

Duration 26 weeks | Demographics:
Mean age: 41 years
Male: 52%
Baseline A1c: 8.0%
White: 45%
Black: 0.4%
Asian: 54%

Key Inclusion Criteria:
- **T1DM**
- Age ≥18 years
- A1c ≤10%
- BMI ≤35 kg/m^2
- Basal-bolus insulin therapy for ≥1 year before screening

Key Exclusion Criteria:
- Recurrent major hypoglycemia
- Impaired hepatic or renal function
- CVD | ITT:
1. 302
2. 153

PP:
1. 283
2. 138

Attrition:
1. 7%
2. 10% | Primary Outcome:
Change in A1c from baseline:
Deg: -0.73%
Det: -0.65%

ETD -0.09% (95% CI, -0.23 to 0.05%; p=0.21)

Secondary Outcome:
A1c <7.0%:
Deg: 41.1%
Det: 37.3%

OR 1.27 (95% CI, 0.77 to 2.09; p=0.34) | NS

NS | Nocturnal hypoglycemia*:
Deg: 58.5%
Det: 58.6%
p<0.0001

Severe hypoglycemia**:
Deg: 10.6%
Det: 10.5%;
p=0.80

Weight gain:
Deg: +1.5 kg
Det: +0.4 kg
p<0.0001

Early D/C due to AE:
Deg: 1.0%
Det: 0.7%
p-value not given

Injection site reactions:
Deg: 4%
Det: 2%
p-value not given

* Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am.

** Severe hypoglycemia – hypoglycemia requiring assistance | 0.1/1000

NS

NA

NA

NA | **Risk of Bias (low/high/unclear):**
Selection Bias: (low) randomized 2:1 by interactive voice/web response system with centralized block randomization.
Performance Bias: (high) open-label.
Detection Bias: (low) All personnel working with assessment, handling and evaluation of trial data were blinded.
Attrition Bias:(low) Overall attrition was low and similar between groups with a value of 7-10%. Analysis was done on the ITT population with LOCF for missing data.
Reporting Bias: (low) Study protocol followed and outcomes reported as specified.

Applicability:
Patient: moderately well controlled T1DM patients without significant comorbidities.
Intervention: Dosing titration appropriate.
Comparator: Glargine is an appropriate comparator.
Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful.
Setting: Seven countries. No U.S. sites. |

4. Zinman, et al.[4] PG, OL, NI, RCT Phase 3	1. Insulin degludec Qday (D)* 2. Insulin glargine Qday (G)* *Doses titrated to achieve a FBG of 70.2-88.2 mg/dL *Both groups on concomitant metformin Duration 52 weeks	Demographics: Mean age: 59 years Male: 62% Baseline A1c: 8.2% BMI: 31.5 kg/m^2 White: 89% Black: 6.8% Asian: 2% Key Inclusion Criteria: - **T2DM** - Age ≥18 years - A1c 7-10% - BMI ≤40 kg/m^2 - Stable doses of OADs 3 months prior to study - Insulin-naïve Key Exclusion Criteria: - TZD, exenatide, or liraglutide within 3 months of screening - Significant CVD, - Impaired hepatic or renal function - Cancer - Severe, recurrent hypoglycemia - Hypoglycemia unawareness - Proliferative retinopathy	ITT: 1. 773 2. 257 PP: 1. 655 2. 221 Attrition: 1. 14% 2. 14%	Primary Outcome: Change in A1c from baseline: D -1.06% G -1.19% ETD 0.09% (95% CI, -0.04 to 0.22%; p-value not given) Secondary Outcome: A1c <7.0%: D 51.7% G 54.1% OR 0.88 (95% CI, 0.65 to 1.19; p= 0.40)	NA NS	Nocturnal hypoglycemia*: D 13.8% G 15.2% RR 0.64 (95% CI, 0.42 to 0.98; p=0.038) Severe hypoglycemia**: D 0.3% G 1.9% RR 0.14 (95% CI, 0.03 to 0.70; p=0.017) SAE: D 8.1% G 10.1% p-value not given Injection site reactions: D 5.9% G 7.0% p-value not given Weight gain from baseline: D +2.4 kg G +2.1 kg p=0.28 * Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am ** Severe hypoglycemia – hypoglycemia requiring assistance	1.4/71 1.6/63 NA NA NS	**Risk of Bias (low/high/unclear):** Selection Bias: (low) randomized 3:1 by centralized, computer-generated, interactive voice and web response system. Performance Bias: (high) open-label. Detection Bias: (high) All personnel working with assessment, handling and evaluation of trial data were blinded. Attrition Bias: (low) Overall attrition was similar between groups at 14%. Analysis was done on the ITT with LOCF for missing data. Reporting Bias:(low) Study protocol was followed and outcomes reported as specified. **Applicability:** Patient: Predominately male, white patients who were insulin-naïve on background OADs. Intervention: Patients started on 10 units and titrated to target. Mean insulin doses were similar at the end of treatment for both therapies. Comparator: Glargine is an appropriate comparator. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: Twelve countries and 166 sites.

| 5. Philis-Tsimikas, et al.[5] PG, OL, RCT Phase 3 | 1. Insulin degludec Qday (D)* 2. Sitagliptin 100 mg Qday (S) *Dose titrated to achieve a FBG target of <90 mg/dL Duration 26 weeks | Demographics: Mean age: 56 years Male: 59% Baseline A1c: 8.9% BMI: 30 kg/m^2 White: 62% Black: 8% Asian: 25% Key Inclusion Criteria: - **T2DM** - Age ≥18 years - A1c 7-11% - BMI ≤40 kg/m^2 - Stable doses of 1-2 OADs 3 months prior to study - Insulin-naïve Key Exclusion Criteria: - GLP-1 receptor agonist, DPP-4 inhibitor, or rosiglitazone within 3 months of screening | ITT: 1. 225 2. 222 PP: 1. 174 2. 174 Attrition: 1. 24% 2. 24% | Primary Outcome: Change in A1c from baseline: D: -1.52% S: -1.09% ETD -0.43% (95% CI, -0.61 to 0.24%; p<0.0001 for superiority) Secondary Outcome: A1c <7.0%: D: 41% S: 28% OR 1.60 (95% CI, 1.04 to 2.47; p=0.034) | NA | Nocturnal hypoglycemia*: D 12.8% S 5.7% p-value not given Severe hypoglycemia**: D 0.4% S 0% p-value not given Weight gain from baseline: D +2.28 kg S -0.35 kg ETD 2.75 kg (95% CI, 1.97 to 3.54 kg; p-value not given) Early D/C due to AE: D 3.9% S 0.9% p-value not given * Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am ** Severe hypoglycemia – hypoglycemia requiring assistance | NA 13/8 NA NA | **Risk of Bias (low/high/unclear):** Selection Bias: (low) randomized 1:1 by centralized, interactive voice and web response system. Performance Bias: (high) open-label. Detection Bias: (low) All personnel working with assessment, handling and evaluation of trial data were blinded. Attrition Bias:(low) Overall attrition was high for both groups at 24%. Analysis was done on the ITT with LOCF for missing data. Reporting Bias: (low) Study protocol was followed and outcomes reported as specified. **Applicability:** Patient: Patients were on 1-2 OADs (most commonly metformin and SU) and overweight or obese, which is representative of T2DM population. Intervention: Degludec titrated to 90.0 mg/dL FBG, which is appropriate. Comparator: Sitagliptin is an inappropriate comparison for a long-acting insulin. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: Twelve countries and 166 sites. |

Author: K. Sentena, Pharm.D.

| 6. Gough, et al.[6]

PG, OL, NI, RCT

Phase 3 | 1. Insulin degludec Qday (U200) (D)*

2. Insulin glargine Qday (U100) (G)*

*Doses titrated to achieve a FBG of < 90.0 mg/dL once weekly

*Concomitant metformin $\pm$ DPP-4 inhibitor

Duration 26 weeks | Demographics:
Mean age: 57 years
Male: 53%
Baseline A1c: 8.3%
BMI: 32.4 kg/m^2
White: 79%
Black: 14%
Asian: 11%

Key Inclusion Criteria:
- **T2DM**
- Age ≥18 years
- A1c 7-10%
- BMI ≤45 kg/m^2
- OADs 3 months prior to study
- Insulin-naïve

Key Exclusion Criteria:
- TZD, exenatide, or liraglutide within 3 months of screening
- Significant CVD
- Uncontrolled HTN
- Impaired hepatic or renal function
- Severe, recurrent hypoglycemia
- Hypoglycemia unawareness
- Proliferative retinopathy or maculopathy | FAS:
1. 228
2. 229

PP:
1. 201
2. 212

Attrition:
1. 13%
2. 8% | Primary Outcome:
Change in A1c from baseline:
D: -1.3%
G: -1.3%

ETD 0.04% (95% CI, -0.11 to 0.19; p-value not given)

Secondary Outcome:
A1c <7.0%:
D: 52%
G: 56%
OR 0.85 (95% CI, 0.56 to 1.30; p-value not given) | NA

NA | Nocturnal hypoglycemia*:
D 6.1%
G 8.8%
p=NS

Severe hypoglycemia**:
D 0%
G 0%
SAEs:
D 6.6%
G 4.4%
p-value not given

Injection site reactions:
D 6.1%
G 6.1%
p=NS

Weight gain from baseline:
D +1.9 kg
G +1.5 kg
p= NS

Early D/C due to AE:
D 2.0%
G 2.0%
p-value not given

* Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am

** Severe hypoglycemia – hypoglycemia requiring assistance | NS

NA

NA

NS

NS

NA | **Risk of Bias (low/high/unclear):**
Selection Bias: (low) randomized 1:1 by interactive voice and web response system.
Performance Bias: (high) open-label.
Detection Bias: (unclear) No details provided.
Attrition Bias:(low) Overall attrition was higher for D (13%) vs. G (8%). Analysis was done on the ITT with LOCF for missing data.
Reporting Bias:(low) Study protocol followed and outcomes reported as specified.

Applicability:
Patient: Predominately white patients who were insulin-naïve on background OADs.
Intervention: Patients started on 10 units and titrated to target. Mean insulin doses were similar at the end of treatment for both therapies.
Comparator: Glargine is an appropriate comparator.
Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful.
Setting: Eight countries and 106 sites. |

7. Garber, et al.[7] PG, OL, NI, RCT Phase 3	1. Insulin degludec Qday (D)* 2. Insulin glargine Qday (G)* *Doses titrated to achieve a FBG of 70.2-90.0 mg/dL once weekly *Concomitant mealtime insulin aspart *± metformin and/or pioglitazone Duration 52 weeks	Demographics: Mean age: 59 years Male: 54% Baseline A1c: 8.3% BMI: 32 kg/m^2 White: 83% Black 10% Asian: 6% Key Inclusion Criteria: - **T2DM** - Age ≥18 years - A1c 7-10% - BMI ≤40 kg/m^2 - Prior insulin use for ≥3 months ± OAD Key Exclusion Criteria: - GLP-1 receptor agonists or rosilglitazone within 3 months of screening - Significant CVD - Uncontrolled HTN, - Impaired hepatic or renal function -Proliferative retinopathy or maculopathy	ITT: 1. 744 2. 248 PP: 1. 694 2. 233 Attrition: 1. 7% 2. 6%	Primary Outcome: Change in A1c from baseline: D: -1.10% G: -1.18% ETD 0.08% (95% CI, -0.05 to 0.21%; p-value not given) Secondary Outcome: A1c <7.0%: D 49% G 50% p-value not given	NA NA	Nocturnal hypoglycemia*: D 40% G 47% RR 0.75 (95% CI, 0.58 to 0.99; p=0.0399) Severe hypoglycemia**: D 5% G 4% p-value not given Injection site reactions: D 4% G 3% p=NS Weight gain from baseline: D +3.6 kg G +4.0 kg p-value not given Early D/C due to AE: D 4.0% G 4.0% p-value not given * Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am ** Severe hypoglycemia – hypoglycemia requiring assistance	7/14 NA NS NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 3:1 by a central interactive voice or web response system. Performance Bias: (high) open-label. Detection Bias: (unclear) Data handlers were masked to treatment allocation until dataset was unlocked for analysis. Attrition Bias:(low) Overall attrition was similar. Analysis was done on the ITT with LOCF for missing data. Reporting Bias:(low) Study protocol followed and outcomes reported as specified. **Applicability**: Patient: Patients with a history of insulin use and approximately 13-year history of T2DM; 60% on metformin, 6% on pioglitazone. Intervention: Mean insulin doses were similar at the end of treatment for both therapies. Comparator: Glargine is an appropriate comparator. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: Twelve countries and 123 sites.

| 8. Meneghini, et al.[8]

PG, OL, NI, RCT

Phase 3 | 1. Insulin degludec Qday Forced-Flex (D FF)*^

2. Insulin degludec Qday (D)*

3. Insulin glargine Qday (G)*

*Doses titrated to achieve a FBG of 70.2-90.0 mg/dL once weekly

*± metformin and/or pioglitazone

Duration 26 weeks

^Forced Flex dosing was rotating morning and evening dosing regimens to allow for 8-40 hours between doses | Demographics:
Mean age: 56 years
Male: 54%
Baseline A1c: 8.4%
BMI: 29.6 kg/m^2
White: 67%
Black: 2%
Asian: 30%

Key Inclusion Criteria:
- **T2DM**
- Age ≥18 years
- A1c 7-11% if prior OAD use
- A1c 7-10% if prior basal insulin ± OADs
- BMI ≤40 kg/m^2
- Prior use of either insulin ±OADs

Key Exclusion Criteria:
- GLP-1 receptor agonists, rosilglitazone, DPP-4 inhibitors or α-glucosidase inhibitors within 3 months of screening
- Significant CVD
- Uncontrolled HTN,
- Impaired hepatic or renal function
- Severe, recurrent hypoglycemia
- Hypoglycemia unawareness
- Cancer | ITT:
1. 229
2. 228
3. 230

PP:
1. 211
2. 207
3. 210

Attrition:
1. 8%
2. 9%
3. 9% | Primary Outcome:
Change in A1c from baseline:
D FF: - 1.28%
D: -1.07%
G: -1.26%

D FF vs. G:
ETD 0.04% (95% CI, -0.12 to 0.20%; p-value not given)

D FF vs. D:
ETD -0.13% (95% CI, -0.29 to 0.03%; p-value not given)

Secondary Outcome:
A1c <7.0%:
D FF: 38.9%
G: 43.9%
p=0.34

D FF: 38.9%
D: 40.8%
p=0.99 |

NA

NA

NS

NS | Nocturnal hypoglycemia*:
D FF 13%
D 11%
G 21%

D FF vs. G: p=NS
D FF vs. D: p=NS

Severe hypoglycemia**:
D FF 0.87%
D 0.88%
G 0.87%
p-value not given

Injection site reactions:
D FF 1.3%
D 3.5%
G 1.7%
p-value not given

Early D/C due to AE:
D FF 0.87%
D 0.44%
G 0.87%
p-value not given

* Nocturnal hypoglycemia – confirmed glucose readings < 56 mg/dL between the hours of 1 am and 5:59 am

** Severe hypoglycemia – hypoglycemia requiring assistance |

NS
NS

NA

NA

NA | **Risk of Bias (low/high/unclear):**
Selection Bias: (low) randomized 1:1:1 by an interactive voice/web response system.
Performance Bias: (high) open-label.
Detection Bias: (unclear) Data handlers were masked to treatment allocation until dataset was unlocked for analysis.
Attrition Bias:(low) Overall attrition (9%) was similar. Analysis was done on the ITT with LOCF for missing data.
Reporting Bias:(low) Study protocol followed and outcomes reported as specified.

Applicability:
Patient: Patients with a 10-year history of T2DM with 58% previously on OAD and 39% with prior insulin use; 91% were on metformin and 66% were on sulfonylureas. Patients continued their prior OAD use during the trial.
Intervention: Mean insulin doses were similar at the end of treatment for both therapies.
Comparator: Glargine is an appropriate comparator.
Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful.
Setting: Fourteen countries and 69 sites. |

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; D/C = discontinuations; DPP-4 = dipeptidyl peptidase-4; ETD = estimated treatment difference; FAS = ?; GLP-1 = glucagon-like peptide-1; EER = estimated rate ratio; FBG = fasting blood glucose; HTN = hypertension; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; OAD = oral antidiabetic drugs; OR = odds ratio; OL = open-label; PP = per protocol; Qday = once daily; RR = relative risk; SAE = serious adverse events; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones.

References:

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use
TRESIBA safely and effectively. See full prescribing information for
TRESIBA.

TRESIBA® (insulin degludec injection), for subcutaneous use
Initial U.S. Approval: 2015

--------------------INDICATIONS AND USAGE----------------------------
TRESIBA is a long-acting human insulin analog indicated to improve
glycemic control in adults with diabetes mellitus (1).

Limitations of Use:
Not recommended for treating diabetic ketoacidosis.

-----------------DOSAGE AND ADMINISTRATION--------------------------
- Individualize dose based on type of diabetes, metabolic needs, blood
  glucose monitoring results and glycemic control goal (2.1, 2.2, 2.3, 2.4).
- Rotate injection sites to reduce the risk of lipodystrophy (2.1).
- Do not dilute or mix with any other insulin or solution (2.1).
- Administer subcutaneously once daily at any time of day (2.2).
- Do NOT perform dose conversion when using the TRESIBA U-100 or U-
  200 FlexTouch pens. The TRESIBA U-100 and U-200 FlexTouch pens
  dose window shows the number of insulin units to be delivered and NO
  conversion is needed (2.2).

-----------------DOSAGE FORMS AND STRENGTHS-------------------
TRESIBA is available in the following package sizes:
- 100 units/mL (U-100): 3 mL FlexTouch® (3).
- 200 units/mL (U-200): 3 mL FlexTouch® (3).

----------------------CONTRAINDICATIONS----------------------------
- During episodes of hypoglycemia (4).
- Hypersensitivity to TRESIBA or one of its excipients (4).

--------------------WARNINGS AND PRECAUTIONS----------------------
- *Never share* a TRESIBA FlexTouch pen between patients, even if the
  needle is changed (5.1).
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under
  close medical supervision and increase frequency of blood glucose
  monitoring (5.2).

35 - *Hypoglycemia:* May be life-threatening. Increase monitoring with
36   changes to: insulin dosage, co-administered glucose lowering
37   medications, meal pattern, physical activity; and in patients with renal
38   impairment or hepatic impairment or hypoglycemia unawareness (5.3,
39   5.4, 6.1).
40 - *Hypoglycemia due to medication errors:* Accidental mix-ups between
41   insulin products can occur. Instruct patients to check insulin labels before
42   injection. DO NOT transfer TRESIBA into a syringe for administration as
43   overdosage and severe hypoglycemia can result (5.4).
44 - *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy,
45   including anaphylaxis, can occur. Discontinue TRESIBA, monitor and
46   treat if indicated (5.5).
47 - *Hypokalemia:* May be life-threatening. Monitor potassium levels in
48   patients at risk for hypokalemia and treat if indicated (5.6).
49 - *Fluid retention and heart failure with concomitant use of*
50   *Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart
51   failure; consider dosage reduction or discontinuation if heart failure
52   occurs (5.7).

53 ---------------------------ADVERSE REACTIONS----------------------------
54 Adverse reactions commonly associated with TRESIBA are:
55 - hypoglycemia, allergic reactions, injection site reactions, lipodystrophy,
56   pruritus, rash, edema and weight gain (6.1).

57 **To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk**
58 **at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

59 ---------------------------DRUG INTERACTIONS----------------------------
60 - *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may
61   be needed; closely monitor blood glucose (7).
62 - *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and*
63   *reserpine):* Signs and symptoms of hypoglycemia may be reduced or
64   absent (7).

65 **See 17 for PATIENT COUNSELING INFORMATION and FDA-**
66 **approved patient labeling.**
67   **Revised: 09/2015**

Author: K. Sentena, Pharm.D.   Date: March 2016

Insulins

Goal:
- Restrict certain insulin products to specified patient populations to ensure appropriate and safe use.

Length of Authorization:
> Up to 12 months

Requires PA:
- Non-preferred insulins
- All pre-filled insulin pens, cartridges and syringes

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP
3. Is the request for an Insulin Pen or Cartridge?	Yes: Go to #4	No: Go to #5
4. Is the insulin being administered by the patient or a non-professional caregiver AND any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is on 40 units or less of insulin per day • The patient is a child less than 18 years of age	Yes: Go to #5	No: Pass to RPh; deny for medical appropriateness

Approval Criteria

5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a copay • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee	Yes: Inform prescriber of covered alternatives in class. Approve insulin pens/cartridges for up to 12 months (other preferred products do not require PA)	No: Approve for up to 12 months