CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks

Final Report

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Institute for Clinical and Economic Review

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

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The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at http://www.ctaf.org

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List of Acronyms Used in this Report

AE	Adverse event
AG	Alpha-glucosidase
BI	Budget impact
BMI	Body mass index
BSCA	Blue Shield of California
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DHCS	Department of Health Care Services
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase 4
FDA	Food and Drug Administration
GDP	Gross domestic product
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
ICER	Incremental cost-effectiveness ratio
LCD	Local coverage determination
MAC	Medicare Administrative Contractor
MACE	Major adverse cardiac events
MI	Myocardial infarction
NCD	National coverage determination
NCPE	National Centre for Pharmacoeconomics
NHE	National health expenditures
NPH	Neutral protamine Hagedorn (insulin)
PBM	Pharmacy benefit manager
PDP	Part D Plan (Medicare)
PICOTS	Population(s), Intervention(s), Comparator(s), Outcome(s), Timing, Setting(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk or rate ratio
SAE	Serious adverse event
SF-36	Short form 36 (health survey)
SGLT-2	Sodium-glucose cotransporter-2
TZD	Thiazolidinedione
UHC	UnitedHealthcare
UKPDS	United Kingdom Prospective Diabetes Study
USPSTF	United States Preventive Services Task Force

Executive Summary

Background

The Centers for Disease Control and Prevention (CDC) estimates that 29.1 million Americans have diabetes and 1.7 million adults are newly diagnosed with diabetes mellitus (DM) each year.[1] The majority of people with diabetes (~95%) have type 2 diabetes, which is characterized by resistance of tissues in the body to the effects of insulin, a hormone that helps move glucose from the bloodstream into cells in the body where it is needed to provide energy. The remaining 5% of patients have type 1 diabetes, in which an auto-immune process destroys cells in the pancreas that produce insulin, leading to more dramatic increases in blood glucose levels. The metabolic effects associated with elevated blood glucose (hyperglycemia) lead over time to increased risks for premature heart disease, strokes, blindness, peripheral nerve damage, and kidney failure.

To treat diabetes, approximately 6 million Americans use insulin therapy as part of their treatment plan to control their blood glucose level.[1] Current guidelines for managing DM of either type recommend target pre-prandial (pre-meal) blood glucose values of 80 to 130 mg per deciliter, peak post-prandial (after meal) blood glucose values <180 mg per deciliter, and hemoglobin A1c (HbA1c) levels of ≤7.0%.[2] Several large clinical trials have demonstrated the benefits of intensive management of blood glucose in reducing the likelihood of downstream complications. However, intensive management, particularly with insulins, has also been associated with an increased risk of hypoglycemia (a drop in blood glucose to abnormally low levels). Untreated, episodes of severe hypoglycemia can lead to seizure, coma, and even death. Even when treated, severe hypoglycemia may increase the risk of myocardial infarction or stroke over the long term.[3,4]

Topic in Context

In summarizing the contextual considerations for appraisal of a health care intervention, we seek to highlight the four following specific issues:

- Is there a particularly high burden/severity of illness?
- Do other acceptable treatments exist?
- Are other, equally or more effective treatments nearing introduction into practice?
- Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

As mentioned above, chronically uncontrolled hyperglycemia leads to a wide range of adverse health outcomes including retinopathy, nephropathy, neuropathy, and cardiovascular disease. These complications result in significant morbidity and mortality for patients with diabetes.

Fortunately, many treatment options exist, including a variety of oral agents that act to increase the body's sensitivity to insulin in patients with type 2 DM. As the disease progresses, however, management of blood glucose becomes more complex, and many patients require insulin to complement treatment. Earlier forms of insulin were relatively short-acting, requiring multiple injections per day and careful coordination with mealtimes to minimize the risk of hyper- and hypoglycemic episodes.

Hypoglycemic episodes are the major adverse event associated with insulin therapy. Severe hypoglycemia is defined as an event that requires the assistance of another person to administer carbohydrate, glucagon, or some other form of resuscitation; as described above, severe episodes are associated with significant short- and long-term morbidity and even immediate death in some circumstances. Nonsevere events are typically defined as those with a blood glucose level <70 mg/dL, and they may or may not produce bothersome but transient symptoms (e.g., palpitations, sweating). These nonsevere events can occur during the day or at night (i.e., nocturnal hypoglycemia). The health effects of nonsevere hypoglycemia are less well-understood. Some studies have suggested that these events may be correlated with lower productivity and fatigue,[5] while others have recorded instances of QT prolongation and arrhythmia.[6,7] However, the transient episodes associated with nonsevere hypoglycemia have not been persuasively linked to adverse long-term health effects.

Long-acting insulins

To address the disadvantages of frequent injections and hypoglycemia often associated with shorter-acting insulins, long-acting insulins have been developed to meet the background (or "basal") insulin needs of patients with DM. The first long-acting insulin, neutral protamine Hagedorn (NPH) insulin, has a delayed onset, reaching its peak within six to seven hours. At least two injections per day are still needed, however, and insulin levels remain variable during the day. Insulin glargine U100 (Lantus®, Sanofi) and insulin detemir (Levemir®, Novo Nordisk) are newer long-acting insulins with longer half-lives that allow for once-a-day dosing. Randomized trials have demonstrated that patients treated with glargine or detemir require fewer injections and have fewer hypoglycemic episodes that those treated with NPH.[8] Insulin glargine is the dominant long-acting insulin in the current marketplace; it was among the five best-selling pharmaceuticals in 2014, with worldwide sales in excess of $8 billion.[9]

Most patients with type 2 DM, particularly those starting insulin use for the first time, are able to achieve adequate glucose control by using long-acting insulins alone or in combination with oral agents. This treatment approach is commonly known as a "basal-only" regimen. But for all patients with type 1 DM, and for those with poorly-controlled or advanced type 2 DM, long-acting insulins are usually used in combination with a short-acting insulin to create a "basal-bolus" regimen.

Patients with type 2 DM who require basal-bolus regimens commonly need much higher doses of long-acting insulin than patients on basal-only regimens.

Insulin degludec (Tresiba®, Novo Nordisk A/S)

Insulin degludec is a new, long-acting insulin for use in both type 1 and type 2 DM. It has a half-life of approximately 25 hours and can be detected in the blood for at least five days after the last dose. The long half-life allows for flexible dosing once a day to maintain a steady level in the blood stream. Insulin degludec comes in two formulations: U100, which contains 100 units of insulin per milliliter and U200, which contains 200 units per milliliter. The more concentrated formulation is designed to meet the needs of patients with type 2 diabetes and large insulin requirements.

Insulin degludec was initially reviewed by the Food and Drug Administration (FDA) in November 2012. Approval was not granted at that time because of evidence suggesting a higher rate of major adverse cardiovascular events (MACE) with insulin degludec versus comparator therapy (see "Harms" below for detailed information). Results of an interim analysis of an ongoing trial to measure MACE were subsequently presented to the FDA by the manufacturer, and approval was granted in September 2015. Data from this interim analysis have not been made public so as not to compromise the integrity of the ongoing study.

In this review, we sought to assess the comparative clinical effectiveness and comparative value of use of insulin degludec relative to that of other long-acting insulins (i.e., insulin glargine, insulin detemir) in patients with type 1 and type 2 diabetes.

Comparative Clinical Effectiveness

The primary evidence base for evaluation comes from eight industry-sponsored Phase III randomized controlled trials (RCTs) comparing insulin degludec to another long-acting insulin. We excluded one trial comparing insulin degludec to a non-insulin comparator, the oral agent sitagliptin. There were four primary reports for randomized trials of degludec as basal-only therapy for patients with type 2 DM,[10-13] one for degludec as part of a basal-bolus regimen in patients with type 2 DM,[14] and three for degludec basal-bolus therapy for patients with type 1 DM.[15-17] One trial used insulin detemir as the active control;[15] the remaining seven trials used insulin glargine U100 as the control. Follow-up was either six or 12 months in these studies. All trials were deemed to be of fair quality because they employed an open-label design that allowed patients and clinicians to know which insulin was being used. Key study characteristics can be found in Appendix Table F1, organized by study population of interest (i.e., type 1 DM, type 2 DM basal-only, type 2 DM basal-bolus). An abbreviated version of Appendix Table F1 is presented as Table ES1.

Table ES1. Overview of Studies

Author/Year	N	Follow-up, months	Degludec Formulation	Comparator	Mean Age, years	Sex, % Female	DM Duration, years
Type 1 DM							
Heller 2012	629	12	U100	Glargine U100	43	41	19
Davies 2014	456	6	U100	Detemir	41	48	14
Mathieu 2013	493	6	U100	Glargine U100	44	42	19
Type 2 DM Basal-Only							
Zinman 2012	1,030	12	U100	Glargine U100	59	38	9
Gough 2013	460	6	U200	Glargine U100	58	47	8
Onishi 2013	435	6	U100	Glargine U100	59	46	12
Meneghini 2013	687	6	U100	Glargine U100	56	46	11
Type 2 DM Basal-Bolus							
Garber 2012	984	12	U100	Glargine U100	59	46	14

All of the studies were designed as "non-inferiority" trials with HbA1c level as the primary outcome. The goal of the studies was to demonstrate with adequate statistical significance that insulin degludec was not inferior in reducing HbA1c to other long-acting insulins already approved by the FDA. Published guidance from the FDA on measuring outcomes in diabetes trials was used to define non-inferiority, which was a difference of no more than 0.4% in statistical comparisons of HbA1c across treatment groups. The studies achieved this goal by adjusting the basal insulin dose to achieve a fasting morning glucose level between 70 and 90 mg/dL. Insulin dose adjustment was performed weekly using a pre-specified algorithm by personnel blinded to treatment assignment. It is noteworthy that the target fasting glucose level is lower than that usually recommended for tight glucose control.

Rates of overall, severe, and nocturnal hypoglycemia, defined as above, were compared in these studies using traditional statistical techniques.

Results

Clinical Benefits

In all eight RCTs, insulin degludec was found to be non-inferior to insulin glargine U100 or insulin detemir based on HbA1c levels at the end of each study. However, in six of eight trials the reduction in HbA1c was nominally less in the degludec group than in the comparator group; in Mathieu 2013, the greater reduction in HbA1c with glargine U100 was statistically significant, although the trial still met the non-inferiority boundary (see Table 2 in the full report). The other clinical benefit measured in some of the trials was quality of life (QOL), which was assessed using 10 physical and mental

health domains of the SF-36 (see Appendix Table F3) in five of the RCTs. QOL did not generally differ between treatment groups, which is not surprising given their equivalent clinical performance as well as similar rates of severe hypoglycemia (see "Harms" below). When differences in QOL were observed, the individual QOL domains showing benefit were not consistent across trials.

Harms

The total number of all adverse events was similar in the degludec groups and the glargine U100/detemir groups in the eight RCTs. The most common adverse events were headache, upper respiratory infections, and pharyngitis, and they were not significantly more common with degludec. There was no pattern of excess discontinuations due to adverse events in the degludec group in any of the trials. There was also no pattern of excess injection site reactions.

As described above, the adverse event of greatest concern with insulin therapy is hypoglycemia. There was an approximate 20% reduction in overall hypoglycemic episodes (i.e., severe and nonsevere) with insulin degludec in the type 2 DM trials, but this reached statistical significance only in the single basal-bolus trial (11.1 versus 13.6 episodes per year for insulin glargine U100; relative risk [RR] 0.82; 95% confidence interval [CI]: 0.69, 0.99). No statistical differences in total hypoglycemic episodes were observed in the type 1 DM trials.

Only one of the type 2 DM trials showed a statistically-significant difference in the rate of severe hypoglycemia between insulin degludec and the control arm. This was the BEGIN Once Long trial (basal-only therapy for type 2 DM), which showed an annual rate of 0.003 events for insulin degludec versus 0.023 for insulin glargine U100 (RR 0.14; 95% CI: 0.03, 0.70). No reductions in severe hypoglycemic events were observed in the trials among patients with type 1 DM, in whom the risk of severe hypoglycemia is much higher (0.2 to 0.4 events per person-year).

Nocturnal but nonsevere hypoglycemic episodes were reported at rates of 0.2 - 1.8 events per year in the type 2 DM trials and 4-6 events per year in the type 1 DM trials. Across all eight RCTs, there was a consistent 25% to 35% reduction in nocturnal hypoglycemia with insulin degludec versus glargine U100/detemir, although results of a patient-level meta-analysis indicated statistically-significant differences during the treatment period only among patients with type 2 DM.[18] This reduction in nocturnal hypoglycemia appears to be the primary distinguishing feature of degludec compared with glargine U100 or detemir.

There are several concerns about the reliability of the hypoglycemia results. First, a non-standard definition of hypoglycemia was used: the ADA guidelines for clinical trials define confirmed hypoglycemia as < 70 mg/dL, but the trials used < 56 mg/dL. The more stringent definition in the trials decreases the number of hypoglycemic events, but increases the proportion of events that are likely to be clinically relevant. The trials were open label, which could have affected the reporting and adjudication of hypoglycemic events. Insulin degludec was always given in the evening, but

insulin glargine U100 was administered either in the morning or the evening at physician discretion, which could have influenced the timing of hypoglycemic events. The target fasting glucose level was lower than that typically used for tight glycemic control, which may have increased the incidence of hypoglycemia, though this should not cause differences between the two treatment groups. Finally, patients most at risk for hypoglycemic events (those with hypoglycemic unawareness or frequent hypoglycemic events) were excluded from the trials. The results of the trials should not be generalized to this clinically important subgroup of patients.

As described above, higher MACE rates for patients treated with insulin degludec were highlighted as a concern by the FDA when it initially declined to approve the drug in 2012 pending further data submission. The FDA included trials of insulin degludec or a combination of insulin degludec and short-acting insulin aspart (not currently available in the US) in its analysis, and found 70 MACE among the 5,794 patients receiving insulin degludec; 21 MACE were observed among the 3,461 participants randomized to a comparator (RR = 1.67; 95% CI: 1.01, 2.75). Based on these findings, the FDA requested additional data on MACE before reconsidering whether to approve degludec.[19] As noted in the ongoing studies section (see Appendix E), a double-blind randomized trial comparing degludec to insulin glargine U100 in more than 7,000 patients is scheduled to be completed in 2016; that trial should answer remaining questions about any increase in MACE with degludec compared to glargine U100. Interim data from this trial were submitted to the FDA prior to its decision to approve degludec in 2015, but these data have not been made public so as not to compromise the integrity of the ongoing study.

Controversies and Uncertainties

The primary source of uncertainty in the comparative net health benefit between insulin degludec and other treatment options is the paucity of peer-reviewed data on major adverse cardiovascular events with insulin degludec. In addition, because the major differentiating factor in favor of insulin degludec appears to be lower rates of nocturnal hypoglycemia, the lack of data on the clinical impact of these types of events is of concern. The nominally greater reductions in HbA1c in the comparator groups may partially explain the higher rates of hypoglycemic events in these groups, although the differences were small. In addition, the differential timing of the administration of the basal insulin dose may partially explain the differences in nocturnal hypoglycemia rates.

Comparative Clinical Effectiveness: *Summary and Comment*

We find that the evidence for insulin degludec provides moderate certainty of a small comparative net health benefit in comparison to insulin glargine U100/detemir in patients with type 2 diabetes on basal-only or basal-bolus insulin regimens, based on “non-inferior” glycemic control and consistent findings of reduced nocturnal hypoglycemia. There is greater uncertainty in patients with type 1 diabetes, as no consistent and statistically-significant reductions in hypoglycemia were demonstrated in available meta-analyses. In addition, any potential benefits must be balanced by

residual concerns about potentially higher rates of major adverse cardiovascular events in all subpopulations and the nominally lesser reduction in HbA1c in the degludec group in 6/8 of the trials. With this risk in mind, and the resulting possibility (<10% in our estimation) that insulin degludec is actually harmful overall compared to other treatment options, we judge the current body of evidence on the comparative clinical effectiveness of insulin degludec to be "promising but inconclusive" using the ICER Evidence Rating Matrix.

Other Benefits or Disadvantages

Compared with some long-acting insulin preparations, the longer half-life of insulin degludec may allow for more stable steady-state levels of the medication with late or inconsistent timing of administration, but that same benefit likely applies to the new U300 formulation of insulin glargine (Toujeo®, Sanofi). Insulin degludec appears to offer no additional benefits or disadvantages beyond the outcomes measured in the clinical trials.

Comparative Value

To assess the incremental costs per outcomes achieved, we conducted a cost-effectiveness analysis (CEA) using a lifetime simulation model of diabetes comparing outcomes and costs of degludec versus glargine U100 (the most commonly used comparator) in representative populations of patients with type 1 and type 2 DM. For our analyses, we used a validated diabetes natural history model based on risk estimates from the long-term United Kingdom Prospective Diabetes Study (UKPDS).[20] Our analysis of long-term cost-effectiveness was designed to capture and reflect the significant differences in patient characteristics, insulin dosing requirements, and corresponding treatment costs across type 1 DM, type 2 DM basal-only, and type 2 DM basal-bolus subpopulations. We employed a payer perspective and focused on direct health care costs only.

Given that the clinical effectiveness of insulin degludec has been evaluated through non-inferiority study designs, we assumed no comparative clinical benefit of insulin degludec other than reductions in the rate of hypoglycemia. For severe hypoglycemic events, we assigned lower quality of life and higher costs; for nonsevere hypoglycemia, we assumed only a relatively small impact on quality of life. In neither case was hypoglycemia assumed to affect length of life.

Outputs from the cost-effectiveness model were also used to inform a population-based analysis of the one- and five-year potential budgetary impact of insulin degludec at a national level. Potential budgetary impact included estimates of costs saved from averted hypoglycemic events and was calculated assuming an uptake pattern for insulin degludec if covered for the FDA-labeled indications without payer or provider efforts to restrain utilization. Based on long-term incremental cost-effectiveness ratios and a threshold for potential budget impact related to net health care cost growth at the national level, we also define a "value-based price benchmark" for insulin degludec

for each subpopulation and for a weighted average of all eligible patients with DM. Details on methods and inputs for all analyses can be found in the full report and appendices.

Incremental Costs per Outcomes Achieved: *Results*

Results of the base-case analysis are shown in Table ES2. We present the results on quality-adjusted life-years (QALYs) in two strata: 1) QALYs related to the "background" clinical outcomes and life expectancy of patients in each of the three diabetes subpopulations; and 2) QALYs specifically arising from changes in rates of hypoglycemic events. As can be seen in the table, since the impact on Hb1Ac of degludec and glargine U100 were assumed to be indistinguishable, the background QALYs do not differ between degludec and glargine U100 in any of the patient subpopulations. For patients with type 1 DM, since the evidence base did not demonstrate significant differences in rates of *any* type of hypoglycemia, the total QALYs did not differ between the two treatments. Because the list price of degludec is higher than the price for glargine U100, degludec was equally effective and more expensive, i.e., "dominated."

Rates of nonsevere hypoglycemia did differ between groups in the trials among patients with type 2 DM. As illustrated in the table, this resulted in higher overall QALYs for patients treated with degludec versus those treated with glargine U100. Rates of severe hypoglycemia, however, were not assumed to differ between treatments, and since only severe hypoglycemia was assumed to generate additional health care costs, the costs associated with hypoglycemia did not differ between treatments within each of the three patient subpopulations.

For type 2 DM patients in the basal-only population, the benefits in quality of life produced a very small overall increase in QALYs: 0.034, or approximately two weeks of quality-adjusted life expectancy. Total costs were approximately $12,000 higher for degludec, producing an estimated cost/QALY ratio of approximately $353,000 compared to insulin glargine U100.

Costs were highest in the type 2 DM basal-bolus population, as these patients have the greatest insulin needs. The incremental cost-effectiveness ratio for degludec versus glargine U100 in this group was approximately $167,000/QALY, far lower than that for the basal-only population. This improved cost-effectiveness is a result of a much larger benefit in quality of life from reduced hypoglycemia (0.237 QALYs) in this more hypoglycemia-prone population along with a modest increase in lifetime costs ($39,498).

Table ES2. Base-Case Clinical and Economic Outcomes*

		Type 1 DM†		Type 2 DM Basal-only		Type 2 DM Basal-bolus	
		QALY	Total Costs	QALY	Total Costs	QALY	Total Costs
Insulin glargine U100	UKPDS	16.818	$95,777	11.971	$108,794	11.603	$214,453
	Hypoglycemia		†	-0.192	$815	-1.292	$2,952
	Total			11.779	$109,609	10.312	$217,405
Insulin degludec	UKPDS	16.818	$99,594	11.971	$120,816	11.603	$253,951
	Hypoglycemia		†	-0.158	$815	-1.055	$2,952
	Total			11.813	$121,631	10.549	$256,903
Increment (insulin degludec – insulin glargine U100)				0.034	$12,022	0.237	$39,498
Cost/QALY			†		$353,020		$166,644

NOTE: UKPDS refers to projected clinical outcomes and costs regardless of insulin treatment, according to calculations in the UKPDS outcomes model.

* Future costs and QALYs are discounted 3% a year.

† No base-case could be calculated for type 1 DM patients, as there were no significant differences in any type of hypoglycemia.

Sensitivity Analyses

We performed sensitivity analyses on several input parameters. Not surprisingly, given the dependence on differences in rates of hypoglycemia in the model, results were very sensitive to the relative rate of hypoglycemic events for insulin degludec compared to insulin glargine U100 as well as the disutility associated with these events. For example, if insulin degludec was assumed to be 20% more effective in reducing rates of all severe and nonsevere hypoglycemia, cost-effectiveness would improve to approximately $174,000 for type 2 DM basal-only patients and $87,000 per QALY for the type 2 DM basal-bolus population. This alternative assumption would also mean that degludec would produce incremental clinical benefits for patients with type 1 DM, with an estimated cost-effectiveness ratio of $2,481 per QALY gained.

Threshold Analyses

The annual cost of insulin degludec required to achieve commonly-cited thresholds for the cost per QALY gained are presented by threshold and diabetes population in Table ES3. To achieve a cost-effectiveness ratio of $150,000 per QALY gained, the annual cost would need to decrease by 8% to a cost of $5,025 for type 2 DM basal-only patients, and by 2% to an annual cost of $14,498 for patients in the type 2 DM basal-bolus population that requires much higher doses of insulin. Greater discounts would be required to achieve a cost-effectiveness ratio of $100,000 per QALY gained (10% and 7%, respectively) or $50,000 per QALY gained (12% and 13%, respectively).

While the annual cost at list price for type 1 DM is presented in the table for completeness, there are no prices that would achieve common cost-effectiveness thresholds given our model assumption of no difference in clinical outcomes between degludec and glargine U100 for these patients. The annual cost of insulin glargine U100 in type 1 DM was therefore used as a reference price for cost-effectiveness in this population.

Threshold prices are also presented for a combined population of all type 1 and type 2 DM patients, weighted by anticipated population size (see Potential Budgetary Impact below). For this total population, discounts of 8-12% would be required from the weighted list price of $7,800 for a year's treatment to achieve cost-effectiveness thresholds of $50,000 - $150,000 per QALY gained.

Table ES3. Threshold Analysis for Annual Cost of Insulin Degludec, by Subpopulation

ICER	Type 1 DM	Type 2 DM Basal-only	Type 2 DM Basal-bolus	Total (Weighted Average)
$50,000/QALY	$2,688*	$4,801	$12,878	$6,850
$100,000/QALY	$2,688*	$4,914	$13,683	$7,006
$150,000/QALY	$2,688*	$5,025	$14,498	$7,154
List Price Annual Cost	$2,873	$5,486	$14,765	$7,800

*Insulin glargine U100 cost as reference price; thresholds could not be calculated, as no clinical differences were assumed for the base-case.
ICER: Incremental cost-effectiveness ratio

Potential Budgetary Impact Model: *Results*

We calculated the potential budget impact of insulin degludec across all candidate populations for treatment. Using national statistics to estimate the prevalence of DM in the 2015 US population and published analyses from claims data to estimate the proportion of different types of insulin regimens used, we estimated that there are approximately 549,000 type 1 DM patients using basal-bolus insulin, 3.5 million type 2 DM patients using basal-only insulin, and 1.55 million type 2 DM patients on basal-bolus insulin regimens.

Based on several criteria, we estimated that the theoretical "unmanaged" uptake of insulin degludec would lead to approximately 10% of eligible patients using the drug by year five following its introduction. We chose this "low" uptake assumption because insulin degludec is one of several long-acting insulins available on the US market, and a new concentrated formula of insulin glargine (U300, Toujeo®) shares many of the same characteristics. In addition, on December 16, 2015, the FDA approved a "follow-on" form of insulin glargine (Basaglar®).[21] Finally, other forms of insulin delivery (e.g., continuous pumps) and a variety of other anti-diabetic agents for type 2 DM compete for market share.

Table ES4 presents our analysis of the potential budgetary impact of insulin degludec in the US population, assuming the uptake pattern described above. As in the cost-effectiveness analysis, annual costs were estimated based on average daily dosing seen in the insulin degludec clinical trials for each of the three subpopulations of interest. Results are presented for both one-year and five-year time horizons. An estimated 112,000 individuals in the U.S. would receive insulin degludec in the first year. After one year of treatment, with net annual costs of $1,276 per patient, one-year budget impact is estimated to be $143 million.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 560,000 persons taking insulin degludec. Across this timeframe, the weighted budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $3,733 per patient. Total budgetary impact in the US over five years is estimated at approximately $2.09 billion, with an annualized average budget impact of approximately $418.3 million.

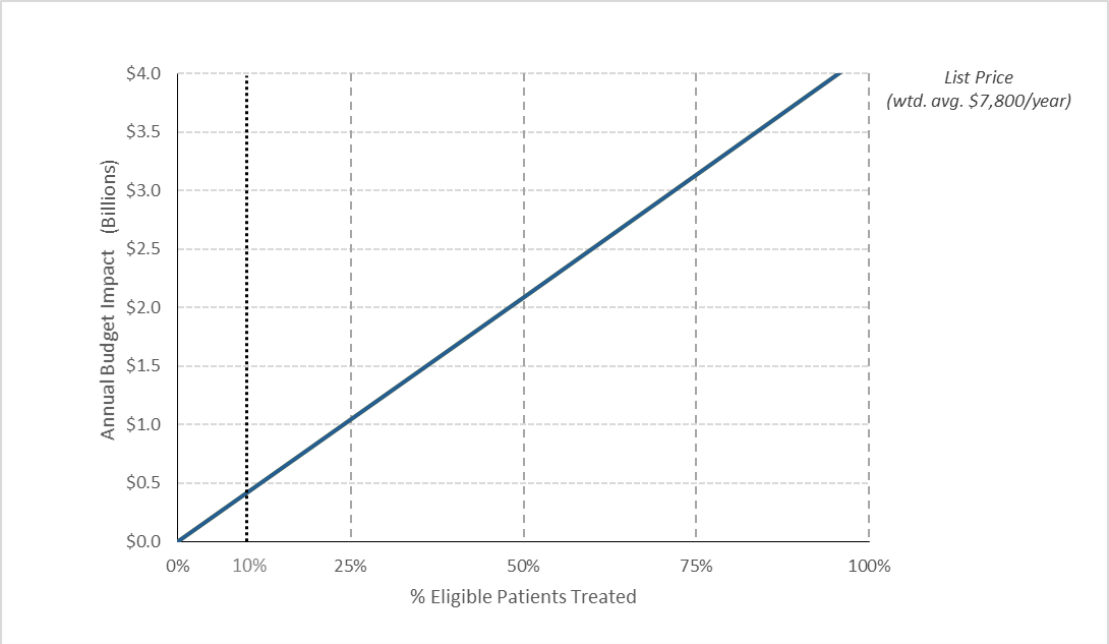
Table ES4. Potential Budget Impact (BI) of Insulin Degludec Based on Assumed Patterns of Uptake

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
Insulin Degludec	Eligible Population (millions)	Number Treated (thousands)	Annual BI per Patient ($)*	Total BI (millions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Average BI per year (millions)
Type 1 DM	0.55	10.98	$183	$2.0	54.9	$538	$5.9
Type 2 DM Basal-only	3.50	70.04	$815	$57.1	350.1	$2,365	$165.6
Type 2 DM Basal-bolus	1.55	31.04	$2,704	$83.9	155.2	$7,950	$246.8
Total	5.60	112.06	$1,276	$143.0	560.3	$3,733	$418.3

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figure ES1 below demonstrates different potential budget impact levels associated with different pricing and patient uptake assumptions. As shown in the figure, based on the weighted list price trend line (with a weighted average drug cost of $7,800/year) and our assumed uptake of 10%, potential budget impact is well below an annual threshold of $904 million that ICER uses as a level commensurate with national growth targets for overall health care costs. On a national basis, the annualized potential budget impact for insulin degludec at list price would rise to $1.05 billion if 25% of eligible patients are treated and would be approximately $4.2 billion if 100% of eligible patients are treated. Approximately 22% of eligible patients could be treated before the budget impact threshold is crossed.

Figure ES1. Potential Budget Impact for Insulin Degludec at Different Uptake Assumptions



Note: Solid line represents the annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug.

Value-Based Price Benchmarks

As shown in Table ES5, we could not calculate prices linked to a long-term cost-effectiveness range for type 1 DM patients, as there were no assumed clinical differences between insulin degludec and insulin glargine U100 in our primary analyses. Therefore, the value-based price benchmark for insulin degludec for this subpopulation would be the same price as its comparator treatment, i.e., the reference price. The annual cost of insulin glargine U100, assuming the profile of type 1 DM patients used in our analysis, is $2,688 annually. This cost is included in our calculations of an overall price benchmark across the three diabetes subpopulations of interest.

The annual cost for insulin degludec to meet a cost-effectiveness range of $100,000-$150,000/QALY is the price range that ICER designates as a long-term "care value" price. The "care value" price range for treatment of type 2 DM patients on basal-only regimens is $4,914 to $5,025/year, and that for treatment of type 2 DM patients receiving basal-bolus therapy is $13,683 to $14,498/year. Applying this range of prices/unit across the combined type 1 and type 2 DM population (with an estimated average weight across the entire population of 87 kg and incorporation of the type 1 DM reference price) produces a long-term care value price range of $7,006 to $7,154/year. Across all subpopulations, the potential budget impact of insulin degludec is not estimated to exceed ICER's short-term (five-year) threshold linked to national health care cost growth targets.

Therefore, the ICER value-based price benchmark for insulin degludec, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $7,006 to $7,154 per year, which corresponds to a per-unit price from $0.265/unit to $0.271/unit. This price represents an 8-10% discount from the weighted average cost per year.

Table ES5. Value-based Price Benchmarks for Insulin Degludec

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Exceeds Potential Budget Impact Threshold?	Value-Based Price Benchmark
Type 1 DM (n=54,889)	$2,688/year*	$2,688/year*	No	N/A
Type 2 DM Basal-only (n=350,183)	$4,914/year	$5,025/year	No	$4,914 to $5,025/year
Type 2 DM Basal-bolus (n=155,202)	$13,683/year	$14,498/year	No	$13,683 to $14,498/year
Total (n=560,274)	$7,006/year	$7,154/year	No	$7,006 to $7,154/year

Comparative Value: *Summary and Comment*

Based on currently-available evidence and the non-inferiority design of major clinical trials, use of insulin degludec appears to confer small net health benefits in comparison to insulin glargine U100 in patients with type 1 or type 2 diabetes mellitus. Where benefits exist, they are limited to episodes of nocturnal hypoglycemia. At the current wholesale acquisition cost, the estimated cost-effectiveness of insulin degludec exceeds commonly-cited thresholds. However, achieving levels of value more closely aligned with patient benefit would require relatively modest discounts (8-10%) from the current list price. Across all subpopulations, the potential budget impact of insulin degludec is not estimated to exceed ICER's short-term (five-year) threshold linked to national health care cost growth targets.

1. Background

1.1 Introduction

Background

The Centers for Disease Control and Prevention (CDC) estimates that 29.1 million Americans have diabetes and 1.7 million adults are newly diagnosed with diabetes mellitus (DM) each year.[1] The majority of the population with diabetes (~95%) has type 2 diabetes, which is characterized by resistance of tissues in the body to the effects of insulin. The remaining 5% of patients have type 1 diabetes in which the body's immune system destroys the cells in the pancreas that produce insulin and is characterized by very low levels of insulin production. The direct medical costs of diabetes were estimated to be $176 billion in 2012.[1] Diabetes is characterized by elevated blood glucose, which over time leads to premature heart disease, strokes, blindness, and kidney failure. Approximately six million Americans use insulin therapy as part of their treatment plan to control their blood glucose level.[1] Insulin degludec (Tresiba®, Novo Nordisk) is a new, long-acting insulin for use in both type 1 and type 2 DM.

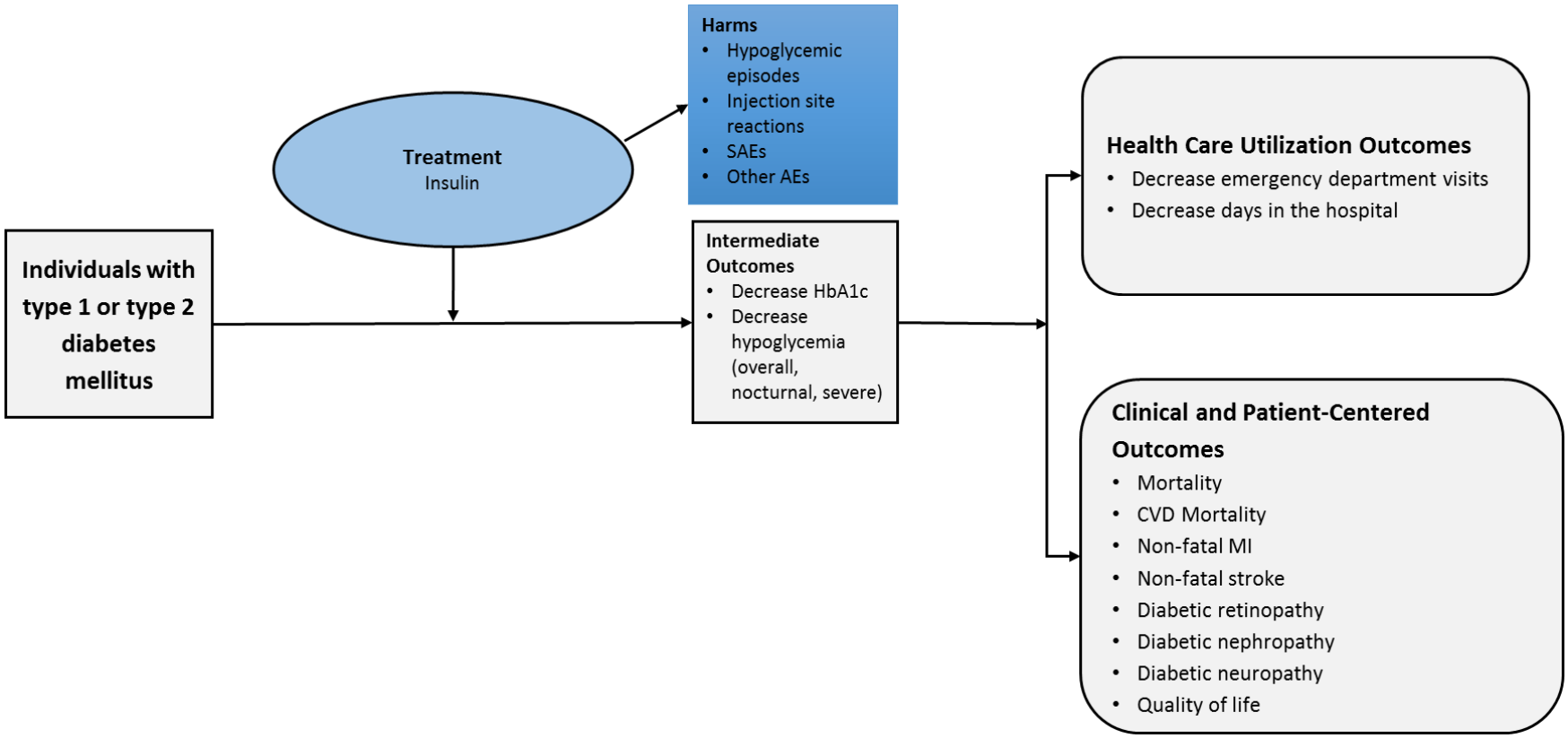
Scope of the Assessment

The scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.[22] Evidence was culled from Phase III randomized controlled trials (RCTs) and comparative cohort studies as well as high-quality systematic reviews and meta-analyses where available. We also included real world observational data that met certain quality criteria (e.g., sample retention, consecutive patients, clearly-defined entry criteria). The majority of the pivotal randomized trials submitted for Food and Drug Administration (FDA) approval of insulin degludec use a non-inferiority design compared to available insulin therapy. Both arms of the trials adjust insulin dosing to achieve pre-breakfast blood glucose levels of 70-90 mg/dL and to have equivalent hemoglobin A1c (HbA1c) levels.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.

Figure 1. Analytic Framework: Diabetes Management with Insulin



Note: SAEs: serious adverse events; AEs: adverse events; CVD: cardiovascular disease; MI: myocardial infarction

Populations

The population of focus for this review included adults ages 18 years and older with type 1 or type 2 DM. We considered type 1 and type 2 DM as separate populations. Within the population of individuals with type 2 DM, we considered patients on basal-only insulin regimens separately from patients on basal-bolus regimens.

Interventions

The intervention of interest was insulin degludec (Tresiba®, Novo Nordisk).

Comparators

The primary comparator was long-acting insulin (i.e., insulin glargine, insulin detemir).

Outcomes

This review examined clinical and health care utilization outcomes related to diabetes. Listed below are the outcomes of interest:

- Macrovascular outcomes (myocardial infarction, stroke, death from cardiovascular disease)
- Microvascular outcomes (retinopathy, nephropathy, neuropathy)
- DM-related hospitalizations and emergency department visits
- Hypoglycemic events (overall, nocturnal, and severe)
- HbA1c as a measure of glycemic control
- Other clinical parameters (e.g., weight, blood pressure, lipids)
- Measures of functional status, and/or health-related quality of life
- Short- and long-term complications and adverse events of treatment
- Costs and cost-effectiveness of insulin degludec

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

2. The Topic in Context

Diabetes Mellitus

There are two distinct forms of diabetes: type 1 diabetes mellitus (DM), characterized by lack of insulin production, and type 2 DM, characterized by insulin resistance. An estimated 29.1 million people in the United States are known to have DM.[1] Current guidelines for managing DM of either form recommend target pre-prandial (pre-meal) blood glucose values of 80 to 130 mg per deciliter, peak post-prandial (after meal) blood glucose values <180 mg per deciliter, and HbA1c (HbA1c) levels of ≤7.0%.[2]

Management of blood glucose is critical to minimizing the risk of downstream disease-related complications. Chronically uncontrolled hyperglycemia leads to a wide range of adverse health outcomes including retinopathy, nephropathy, neuropathy, and cardiovascular disease. These complications result in significant morbidity and mortality for patients with diabetes. Strategies to prevent or reduce the occurrence of secondary diabetic complications have been intensively studied.

Intensive management of glucose levels

Two large RCTs have demonstrated that intensive management of blood glucose levels reduces the rate of diabetic complications compared with conventional management. However, intensive management was also associated with a three-fold increase in the rates of severe hypoglycemic events. Intensive management of DM consists of three or more daily injections of insulin, use of an insulin pump, or use of oral agents to achieve normoglycemia.

The Diabetes Control and Complications Trial.

The Diabetes Control and Complications Trial (DCCT) randomized 1,441 patients with insulin-treated diabetes to either intensive management or conventional therapy.[3] The primary endpoint was diabetic retinopathy. Secondary outcomes included renal, neurologic, cardiovascular, and neuropsychological outcomes and adverse effects associated with the treatment regimens. Patients in the DCCT had a mean age of 27 years and were followed for an average of 6.5 years. At baseline, the median HbA1c level was 8.9%. In the intensive treatment arm, HbA1c dropped to a median of about 7% while patients in the usual care group maintained a median HbA1c of 9%.

Patients without retinopathy at baseline who received intensive glucose management had a 76% (95% confidence interval [CI]: 62%, 85%) reduction in retinopathy compared to patients randomized to usual care. Among participants with retinopathy at baseline who were randomized to intensive therapy, there was a 54% (95% CI: 39%, 66%) reduction in progression of retinopathy. Furthermore,

intensive therapy significantly reduced the risk of microalbuminuria (39%), albuminuria (54%), and clinical neuropathy (60%). The incidence of major cardiovascular and peripheral vascular events was low as expected in this young cohort (0.5 events per 100 person-years vs. 0.8 events; relative risk [RR] 0.59; 95% CI: 0.32, 1.10).

However, intensive therapy was also associated with more than a three-fold increased risk of severe hypoglycemia, defined as an episode with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and was associated with a blood glucose level <50 mg/dl or prompt recovery after therapy for hypoglycemia. The rate of severe hypoglycemia was 62 episodes per 100 person-years in the intensive therapy group versus 19 episodes per 100 person-years in the usual care group. During five years of follow-up, 60% of patients in the intensive therapy group experienced at least one severe hypoglycemic event and 36% experienced three or more.

The United Kingdom Prospective Diabetes Study.

The United Kingdom Prospective Diabetes Study (UKPDS) enrolled 3,867 patients with a new diagnosis of type 2 DM who had persistent elevation of fasting blood glucose (between 110 and 270 mg/dL) after three months of dietary treatment.[4] The study compared intensive glycemic management with medications (goal fasting blood glucose <108 mg/dL) to conventional management: diet therapy alone until fasting blood glucose levels were greater than 270 mg/dL. The primary outcome was the incidence of any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, myocardial infarction, angina, heart failure, stroke, peripheral vascular disease, renal failure, amputation, retinopathy, blindness, or cataract extraction). Secondary outcomes included diabetes-related death and all-cause mortality. Patients in the UKPDS had a mean age of 53 years and were followed for a median of 10 years. At baseline the median HbA1c level was 7.1%. In the intensive treatment arm, HbA1c was maintained at about 7% during follow-up while patients in the usual care group increased to a median HbA1c of 7.9%.

Patients in the intensive management group had a 12% lower risk of any diabetes-related endpoint (95% CI: 1%, 21%) compared to patients randomized to conventional management. The intensive management group also had a non-significant 10% reduction in diabetes-related death (p=0.34) and a non-significant 6% reduction in all-cause mortality (p=0.44). The most significant factor was a reduction in microvascular endpoints with a 25% reduction (95% CI: 7%, 40%).

As in the DCCT, there was a significant two- to three-fold increased risk of severe hypoglycemic events. The rate of severe hypoglycemia was 1.8 episodes per 100 person-years in the intensive therapy group treated with insulin and 1.2 episodes per 100 person-years in the intensive therapy group treated with oral therapy, versus 0.7 episodes per 100 person-years in the usual care group.

Post-hoc observational analyses in both the DCCT and UKPDS suggest that there is a continuous reduction in microvascular and macrovascular complications of diabetes: for every 1% lowering of HbA1c from greater than 10% down to 6%, there is a corresponding reduction in complications of between 12-43%. There was no clear threshold below which benefits stopped accruing.

Hypoglycemia

The American Diabetes Association (ADA) Workgroup on Hypoglycemia established standards for defining and reporting hypoglycemia in 2005 to advise the FDA on how hypoglycemia should be used as an endpoint in studies, and the Workgroup reaffirmed the standards in 2013.[23,24] Severe hypoglycemia is an event that requires the assistance of another person to administer carbohydrate, glucagon, or some other form of resuscitation. Documented symptomatic hypoglycemia is an event with typical symptoms of hypoglycemia (palpitations, sweating, tremor, confusion) associated with a measured plasma glucose level of ≤70 mg/dL. Asymptomatic hypoglycemia is an event without symptoms of hypoglycemia that is associated with a measured plasma glucose level of ≤70 mg/dL.[23,24] The Workgroup suggested that a 10 to 20% reduction in severe hypoglycemic events and a 30% reduction is all hypoglycemic events by a new drug, device, or management strategy would be considered clinically significant.

Severe hypoglycemic episodes were the major adverse events associated with intensive therapy in both the DCCT and the UKPDS. Untreated severe hypoglycemic episodes may result in confusion, coma, seizures, and even death. In the ACCORD trial, participants with type 2 DM randomized to intensive control were more likely to die from any cause (5% vs. 4%; RR 1.22; 95% CI: 1.01, 1.46).[25] The increase in mortality was primarily due to cardiovascular deaths that may have been triggered by severe hypoglycemia.

Recurrent hypoglycemia can result in hypoglycemic unawareness, which puts patients at increased risk for severe hypoglycemia during intensive therapy for diabetes.[24] Recurrent hypoglycemia has been hypothesized to cause chronic cognitive impairment, but there were no differences in detailed neurocognitive testing after 18 years in participants with type 1 DM in the DCCT who had frequent hypoglycemia compared to those without frequent hypoglycemia.[24] Similarly, for patients with type 2 DM in the ACCORD trial, there was no difference in cognitive function over time in those in the intensive therapy group compared to the standard therapy group even though the intensive therapy group experienced three times the rate of hypoglycemic events.[24] Hypoglycemia is associated with a decrease in quality of life and with mood disorders (depression, anxiety), though there is controversy about whether the association represents cause-effect or effect-cause.[24]

Long-acting insulins

Long acting insulins are designed to meet the background or basal needs for insulin. The first long acting insulin, neutral protamine Hagedorn (NPH) insulin, has a delayed onset reaching its peak

within six to seven hours. At least two injections a day are needed to provide 24-hour coverage, and insulin levels are variable throughout the day, which increases the risk for both hypoglycemic and hyperglycemic episodes. Insulin glargine U100 (Lantus®, Sanofi) and insulin detemir (Levemir®, Novo Nordisk) are newer long-acting insulins with longer half-lives that allow for once-a-day dosing. Randomized trials demonstrate that patients treated with glargine U100 or detemir have improved glycemic control, require fewer injections, and have fewer hypoglycemic episodes than those treated with NPH.[26,27]

Insulin degludec (Tresiba®, Novo Nordisk)

Insulin degludec is a novel long-acting analog of human insulin intended to meet the basal insulin needs of patients with type 1 and type 2 DM. It has a half-life of approximately 25 hours and can be detected in the blood for at least five days after the last dose. The long half-life allows for flexible dosing once a day to maintain a steady level in the blood stream. Insulin degludec comes in two formulations: U100, which contains 100 units of insulin per milliliter and U200, which contains 200 units per milliliter. The more concentrated formulation is designed to meet the needs of patients with type 2 diabetes and large insulin requirements.

3. Summary of Coverage Policies

To understand the insurance landscape for long-acting insulins, we reviewed the publicly available coverage policies and formularies of the Centers for Medicare & Medicaid Services (CMS), California Department of Health Care Services (DHCS), Aetna, Anthem, CIGNA, Humana, UnitedHealthcare (UHC), Health Net, Blue Shield of California (BSCA), and CVS/caremark. We supplemented our search for coverage policy on insulin degludec with summaries of existing policies for insulins detemir, glargine U100 and U300 (Toujeo®, Sanofi), and NPH insulin (Humulin N®, Eli Lilly; Novolin N®, Novo Nordisk) as a model for coverage for long- and intermediate-acting insulins.

CMS has not issued a National Coverage Determination (NCD) and Medicare Administrative Contractors (MAC) have not issued a Local Coverage Determination (LCD) for long- and intermediate-acting insulins in California. The California DHCS does not currently list insulin degludec or insulin glargine U300 in their contract drug list; insulin glargine U100 is included.[28]

Each of the national private payers listed above offers a Medicare Part D Plan (PDP) that covers long- and intermediate-acting insulins. Humana is the only payer that currently lists insulin degludec in a PDP formulary, and places it at the third tier.[29,30] All of the payers included in our survey list insulin glargine U100 at the third tier of their PDPs with the exception of Anthem, which places it at the second tier.[29-40]

Private payers have also begun to include insulin degludec in their employment-based insurance plans. Aetna and Health Net list insulin degludec at the third tier of the majority of their formularies, and Anthem requires patients to attempt therapy with either insulin glargine U100 or insulin detemir for one month before authorizing coverage.[39,41] Anthem, Cigna, and Humana generally do not include insulin degludec in their formularies, but list it at the third tier in some drug lists.[40,42,43] Of those payers, only Humana has a publicly available prior authorization policy, and they payer requires that patients attempt treatment or demonstrate intolerance to insulin glargine (U100 and U300 concentrations) and insulin detemir before coverage will be granted.[44] Blue Shield of California does not include insulin degludec in their formularies, but will cover the drug at the third tier based on medical necessity.[45] We were unable to locate any publicly available coverage documents pertaining to insulin degludec from UHC.

All of the payers included in our review cover insulin glargine U100 at the second tier of their commercial formularies with the exception of UHC, which lists the drug at the third tier, and Aetna, which places it at the second and third tier with equal frequency across plans

Payer coverage policies are summarized in Table 1 and described in detail in Appendix C.

Table 1. Representative Public and Private Payer Policies for Long- and Intermediate-acting Insulins (Medicare Part D Plans Excluded)

	Medi-Cal	Aetna	Anthem	Cigna	Humana	UHC	Health Net	BSCA	CVS
Insulin degludec									
Tier	--	3	3	3	NF	--	3	NF	NS
Step Therapy	--	Yes	No	No	--	--	No	--	--
PA	--	No	No	Yes	Yes	--	No	--	--
Insulin glargine U300									
Tier	--	3	3	3	NF	--	2	NF	NS
Step Therapy	--	Yes	No	No	No	--	No	--	--
PA	--	Yes	No	Yes	No	--	No	--	--
Insulin glargine U100									
Tier	NS	2, 3	2	2	2	3	2	2	NS
Step Therapy	--	Yes	No	No	No	No	No	--	--
PA	--	Yes	No	No	No	No	No	--	--
Insulin detemir									
Tier	NS	2	2	2	2	1	2	2	NS
Step Therapy	--	No	No	No	No	No	No	--	--
PA	See appendix C	No	No	No	No	No	No	--	--
NPH insulins (intermediate acting)									
Tier	NS	Humulin N: 2 Novolin N: 3	Humulin N: 2 Novolin N: 2	Humulin N: 2 Novolin N: 2, NF	Humulin N: 2 Novolin, N: 3, 4	Humulin N: 1 Novolin N: 3	Humulin N: 2 Novolin N: 3	Humulin N: 2 Novolin N: NF	Humulin N: NF Novolin N: NS
Step Therapy	--	Humulin N: No Novolin N: Yes	No	No	Humulin N: No Novolin N: Yes	Humulin N: No Novolin N: Yes	No	--	--
PA	--	Humulin N: No Novolin N: Yes	No	No	No	No	No	--	--

--: Not mentioned in coverage policy; PA: prior authorization; NF: non-formulary; NS: not specified

Note: The information in this table is extracted from publicly available documents as of January 18, 2016, and meant to summarize broad trends within and across payer coverage policies. The drugs included in the above table may be included at a higher or lower tier in a small number of plans offered by a payer. For a more detailed summary of individual payer policies, refer to Appendix C.

4. Comparative Clinical Effectiveness

4.1 Overview

Evidence was abstracted from Phase III RCTs of individuals ages 18 years and older with either type 1 or type 2 DM treated with insulin degludec. The comparator treatment was another long-acting insulin (insulin glargine U100 or insulin detemir). Our review focused on clinical benefits (e.g., glucose control assessed by HbA1c as a surrogate for microvascular and macrovascular complications of diabetes and quality of life) as well as potential harms (hypoglycemia and drug-related adverse events).

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on insulin degludec for DM followed established best methods used in systematic review research.[46] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[47] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

The timeframe for our search spanned the period from January 1990 to the most recently published data available and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, conference abstracts, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithm are available in Appendix Table A2.

Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described above. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study. We excluded trials that evaluated non-standard dosing such as every-other-day insulin degludec or "flex" dosing that alternates morning and nighttime dosing (alternating eight and 40 hours between doses) unless the trials also included an arm with usual daily dosing of the basal insulin.

We also included FDA documents related to insulin degludec. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Of note, a combination of insulin degludec and shorter-acting insulin aspart has also been studied and approved by the FDA, but as of this writing there are no public announcements suggesting that this combination will be marketed in the US. These studies were therefore excluded from the assessment.

Data Extraction and Quality Assessment

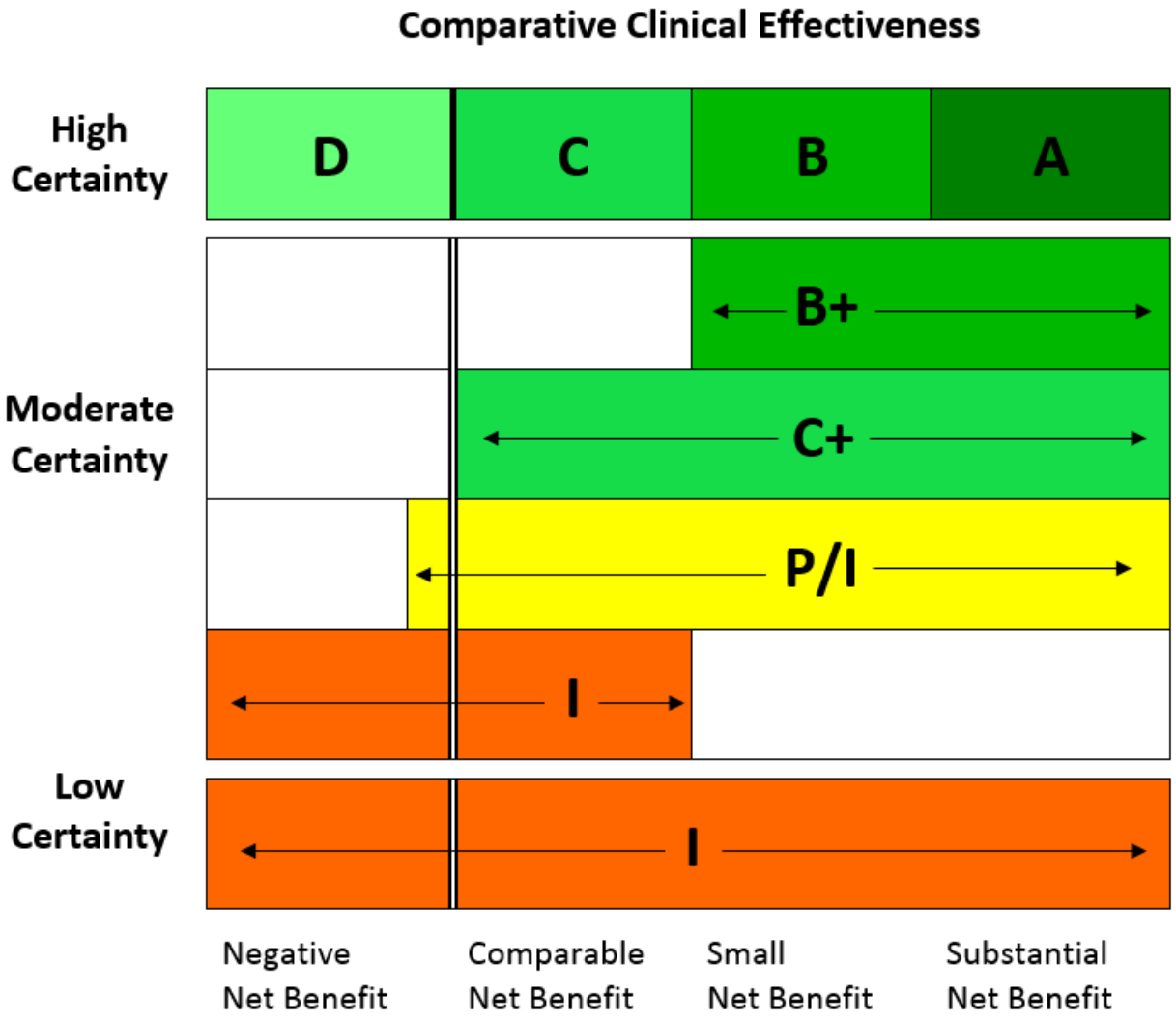
Our data extraction and review process is detailed in Appendix F, and Tables F1 through F4 are summary tables. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[48]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[49]

Figure 2. ICER Evidence Rating Matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"**-** High certainty of a comparable net health benefit
D="Negative"**-** High certainty of an inferior net health benefit
B+="Incremental or Better" **–** Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" **-** Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **–** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias represented by general or specific study designs used in the assessment of each intervention. Given the emerging nature of the evidence base for these newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies identified provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

When appropriate, we performed formal meta-analysis to generate pooled estimates of treatment effects for the outcomes of interest.

4.3 Results

Included Studies

The literature search for insulin degludec identified 203 potentially relevant references (see Appendix Figure A1), of which eight randomized trials met our inclusion criteria. There were four primary reports for randomized trials of basal-only insulin therapy for patients with type 2 DM,[10-13] one for basal-bolus insulin in patients with type 2 DM,[14] and three for basal-bolus insulin therapy for patients with type 1 DM.[15-17] Insulin aspart was the short acting insulin used for bolus therapy in all of the clinical trials. One trial used the more concentrated U200 formulation of degludec;[10] the remaining seven trials used the U100 formulation. One trial used insulin detemir as the active control;[15] the remaining seven trials used insulin glargine U100 as the control. Several studies have additional publications of extended follow-up,[50-55] but they are not the focus of this review. Details of the included studies are summarized in Appendix Tables F1 through F4.

The search identified four observational studies reporting on the real-world experience of patients in countries with earlier approval of insulin degludec.[56-59] They are smaller studies than the RCTs with shorter duration of follow-up, and thus do not add appreciably to the evidence. They do support the utility of degludec in real-world practice.

Scanning of the ClinicalTrials.gov site to identify additional studies completed more than two years ago that would have met our inclusion criteria but have not been published revealed no such studies (see Appendix E for ongoing studies).

Key Studies

All of the studies were designed as non-inferiority trials with HbA1c level as the primary outcome. The goal of the studies was to demonstrate that insulin degludec was not inferior to other long-acting insulins already approved by the FDA for the treatment of diabetes. In order to demonstrate non-inferiority, the upper bound of the 95% confidence interval for the change in HbA1c level between the two groups could be no more than 0.4%. The studies achieved this goal by adjusting the basal insulin dose to achieve a fasting morning glucose level between 70 and 90 mg/dL. Insulin dose adjustment was performed weekly using a pre-specified algorithm by personnel blinded to treatment assignment. It is noteworthy that the target fasting glucose level is lower than that usually recommended for tight glucose control.

Type 1 Basal-Bolus Therapy

The BEGIN Type 1 Long trial[16] was an open label RCT of 629 patients with type 1 DM ages 18 years and older (mean age 43 years, 41% female, duration of DM 19 years, average HbA1c 7.7%) with an HbA1c less than 10%. It is the largest and longest trial for this patient population. The participants were randomized in a 3:1 fashion to insulin degludec or glargine U100 (both with bolus insulin aspart) and followed for 12 months. The change in HbA1c level was similar in both groups (-0.4% degludec, -0.4% glargine U100; difference 0.01%; 95% CI: -0.14%, 0.12%), which met the non-inferiority limit. There were no significant differences in the overall rate of hypoglycemia or severe hypoglycemia, although both were nominally higher in the insulin degludec group (42.5 vs. 40.2 per person year total; 0.21 vs. 0.16 severe). As in the other trials, the rate of nocturnal hypoglycemia was lower in the degludec group (4.4 per person year vs. 5.9 per person year; RR 0.75; 95% CI: 0.59, 0.96).

Type 2 Basal-Only Therapy

The BEGIN Once Long trial[13] was an open label RCT of 1,030 patients with type 2 DM ages 18 years and older (mean age 59 years, 38% female, duration of DM 9 years, average HbA1c 8.2%) with an HbA1c between 7% and 10%. It is the largest and longest trial for this patient population. The participants were randomized in a 3:1 fashion to insulin degludec or glargine U100 and followed for 12 months. The change in HbA1c level was similar in both groups (-1.1% degludec, -1.2% glargine U100; difference 0.09%; 95% CI: -0.04%, 0.22%), which met the non-inferiority limit. There were no significant differences in the overall rate of hypoglycemia or severe hypoglycemia, but the rate of nocturnal hypoglycemia was lower (0.25 per person year vs. 0.39 per person year; RR 0.64; 95% CI: 0.42, 0.98).

Type 2 Basal-Bolus Therapy

The BEGIN Basal-Bolus Type 2 trial[14] was an open label RCT of 984 patients with type 2 DM ages 18 years and older (mean age 59 years, 46% female, duration of DM 14 years, average HbA1c 8.3%) with an HbA1c between 7% and 10%. It is the only trial for this patient population. The participants were randomized in a 3:1 fashion to basal insulin degludec or glargine U100 with bolus insulin aspart and followed for 12 months. The change in HbA1c level was similar in both groups (-1.1% degludec vs. -1.2% glargine U100; difference 0.08%; 95% CI: -0.05%, 0.21%), which met the non-inferiority limit. There was no significant difference in the rate of severe hypoglycemia, but the rates of all hypoglycemia (11.1 per person year vs. 13.6 per person year; RR 0.82; 95% CI: 0.69, 0.99) and nocturnal hypoglycemia (1.4 per person year vs. 1.8 per person year; RR 0.75; 95% CI: 0.58, 0.99) were statistically-significantly lower with degludec. It is worth noting that the rates of hypoglycemia were five to 10 times higher in patients with type 2 DM treated with basal-bolus therapy compared with basal-only therapy (see Appendix Table F3).

Quality of Individual Studies

As noted above, we used criteria from USPSTF to rate the quality of the trials. Based on these criteria, we considered all of the trials to be of fair quality. The primary decrement to quality was the lack of blinding of both the patients and investigators. The lack of blinding could bias patient-reported outcomes such as quality of life in favor of the degludec because patients randomized to degludec would know that they were receiving the newer therapy. It could also influence co-interventions and adherence. The central adjudication committees were masked to treatment assignment, but there could have been ascertainment bias on the part of the study staff. The manufacturer argued that masking in insulin studies is not practical or safe because of the need to individualize dosage and dose titration in the trial and because there are not identical injectable pen systems for the drugs used in the trials. In general, the study arms were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition occurred during follow-up except in the BEGIN FLEX Type 1 trial, which had more adverse event related withdrawals in the degludec group.[17]

Clinical Benefits

The primary clinical benefit of insulin therapy is glucose control, which is summarized by the HbA1c level. Table 2 shows the difference in the decrease in HbA1c levels of insulin degludec versus the control insulin.

Table 2. Difference in Change in Hemoglobin A1c Level

Trial	Comparator	Change in HbA1c* (Degludec – Comparator)
Type 1 DM		
Heller 2012	Glargine U100	-0.01% (-0.14 to 0.12)
Davies 2014	Detemir	-0.09% (-0.23 to 0.05)
Mathieu 2013	Glargine U100	0.17% (0.04 to 0.30)
Type 2 DM Basal-only		
Zinman 2012	Glargine U100	0.09% (-0.04 to 0.22)
Gough 2013	Glargine U100	0.04% (-0.11 to 0.19)
Onishi 2013	Glargine U100	0.11% (-0.03 to 0.24)
Meneghini 2013	Glargine U100	0.2 (NR)
Type 2 DM Basal-bolus		
Garber 2012	Glargine U100	0.08% (-0.05 to 0.21)

* A negative number indicates greater reduction with degludec and a positive number indicates a greater reduction with the comparator insulin.

In all eight trials, the upper bound of the 95% confidence interval was less than 0.4%, which means that degludec was non-inferior to the comparator using the *a priori* definition of non-inferiority. However, in six of eight trials the reduction in HbA1c was nominally less in the degludec group than in the comparator group (a positive between group change in Table 2). In Mathieu 2013, the greater reduction in HbA1c with glargine U100 compared with degludec was statistically significant, although the trial still met the non-inferiority boundary. In Meneghini 2013, the between-group difference may also be statistically significant, but this comparison was not reported in the published report or in the FDA briefing document. The trials all documented non-inferiority, but this does not rule out the possibility that glycemic control with degludec was slightly worse than that of the comparator.

The other benefit measured in at least some of the trials was quality of life, as assessed using 10 domains of the SF-36 (see Appendix Table F3). The quality of life results were not presented in detail in any of the trials. There were no significant differences between treatment groups in two trials, a significant difference in favor of degludec in one domain in one trial, and a significant difference in favor of degludec in two domains in two trials. However, the domains showing benefit were not consistent across trials. In addition, the benefits in favor of degludec were small (less than two points on 100 point scales with five to 10 point differences considered clinically significant). A meta-analysis of the SF-36 results from three of the studies in the type 2 DM population found significant improvements in Bodily Pain (1.10 points; 95% CI: 0.22, 1.98), Physical Health (0.66 points; 95% CI; 0.04, 1.28), and Vitality (0.081 points; 95% CI: 0.01, 1.59).[60] The same investigators mapped the SF-36 results from six of the randomized trials to the EuroQoL-5D utility scale (range -0.59 to 1.00; negative is worse than death, 1.00 is perfect health) and found a small increase in quality of life with degludec compared to glargine U100 (0.005 points; 95% CI: 0.0006, 0.009).[61]

These small improvements in self-reported quality of life may be biased in favor of degludec because the trials were all open label, so the participants on degludec knew that they had been randomized to the newer treatment.

Harms

The total number of adverse events was similar in the degludec groups and the glargine U100/detemir groups in the eight RCTs (see Appendix Table F4). The most common adverse events were headache, upper respiratory infections, and pharyngitis, and they were not significantly more common with degludec. There was no pattern of excess discontinuations due to adverse events in the degludec group in any of the trials. There was also no pattern of excess injection site reactions.

The adverse event of greatest concern with insulin therapy is hypoglycemia. As highlighted in the Topic in Context section above, severe hypoglycemic events can be life threatening and are the major barrier to tight blood glucose control in DM. There was no consistent pattern for overall hypoglycemic events or severe hypoglycemic events (see Table 3 and Appendix Table F3). One of the eight trials reported a statistically-significant decrease in total hypoglycemic events (BEGIN Basal Bolus Type 2: RR 0.82; 95% CI: 0.69, 0.99), although a decrease of similar magnitude was seen in most of the trials of patients with type 2 DM. The BEGIN Once Long trial showed a marked reduction in severe hypoglycemic events with insulin degludec, but this was not reproduced in any of the other trials of degludec. The annual incidence of severe hypoglycemic events was remarkably low in the degludec group in that trial (0.003 events per person year). No reduction in severe hypoglycemic events was observed in the trials among patients with type 1 DM in whom the risk of severe hypoglycemia is much higher (0.2 to 0.4 events per person-year in the degludec arms of the three trials). There was a consistent 25% to 35% reduction in nocturnal hypoglycemia across all of the trials. This reduction in nocturnal hypoglycemia appears to be the primary distinguishing feature of degludec compared with glargine U100 or detemir.

Table 3. Rates of Confirmed Hypoglycemic Events

Trial	Degludec (per person year)	Comparator (per person year)	RR (95% CI)
Type 1 DM			
Heller 2012	42.5	40.2	1.07 (0.89, 1.28)
Davies 2014	45.8	45.7	0.98 (0.80, 1.20)
Mathieu 2013	88.3	79.7	NR, but >1
Type 2 DM Basal-only			
Zinman 2012	1.5	1.9	0.82 (0.64, 1.04)
Gough 2013	1.2	1.4	0.86 (0.58, 1.28)
Onishi 2013	3.0	3.7	0.82 (0.60, 1.11)
Meneghini 2013	3.6	3.5	NR, but > 1
Type 2 DM Basal-bolus			
Garber 2012	11.1	13.6	0.82 (0.69, 0.99)

NR: Not reported

Novo Nordisk sponsored a pre-planned meta-analysis pooling patient level data on hypoglycemic events from the seven RCTs with glargine U100 as the control long-acting insulin.[18] The results for the entire treatment period of the trials are summarized in Table 4 below. There were no significant differences in the summary rate ratios of hypoglycemia among patients with type 1 DM in the trials although there was a trend towards fewer nocturnal hypoglycemic events and more total and severe hypoglycemic events among patients treated with insulin degludec. There were significantly lower rates of total, nocturnal, and severe hypoglycemic events in patients with type 2 DM receiving only basal insulin, but the estimate for severe hypoglycemia is likely an error because it is identical to the rate ratio reported in one of the four trials (Zinman 2012) and there were no differences in the rates of severe hypoglycemic events in the other three trials. Only one trial (Garber 2012) compared degludec to glargine U100 in patients with type 2 DM treated with basal-bolus insulin. In that patient population, there were significantly lower rates of total and nocturnal hypoglycemia with degludec, but there was a trend towards a higher rate of severe hypoglycemia.

Table 4: Summary Estimates for the Rate Ratios for Hypoglycemia of Degludec Compared with Glargine U100

Patient Population	Total Hypoglycemia Rate Ratio (95% CI)	Nocturnal Hypoglycemia Rate Ratio (95% CI)	Severe Hypoglycemia Rate Ratio (95% CI)
Type 1 DM	1.10 (0.96, 1.26)	0.83 (0.69, 1.00)	1.12 (0.68, 1.86)
Type 2 DM Basal-only	0.83 (0.70, 0.98)*	0.64 (0.48-0.86)*	0.14 (0.03, 0.70) †
Type 2 DM Basal-bolus	0.82 (0.69, 0.99)*	0.75 (0.58, 0.99)*	>1.0

* p<0.05

† Likely an error. It is identical to an outlier from one trial only. The meta-analysis does not report that the other trials were excluded.

There are several concerns about the reliability of the hypoglycemia results. First, a non-standard definition of hypoglycemia was used: the ADA guidelines for clinical trials define confirmed hypoglycemia as < 70 mg/dL, but the trials used < 56 mg/dL. The more stringent definition in the trials decreases the number of hypoglycemic events, but increases the proportion of events that are likely to be clinically relevant. The trials were open label, which could have affected the reporting and adjudication of hypoglycemic events. Insulin degludec was always given in the evening, but insulin glargine U100 was administered either in the morning or the evening at physician discretion, which could have influenced the timing of hypoglycemic events. The target fasting glucose level was lower than that typically used for tight glycemic control, which may have increased the incidence of hypoglycemia, though this should not cause differences between the two treatment groups. Finally, patients most at risk for hypoglycemic events (those with hypoglycemic unawareness or frequent hypoglycemic events) were excluded from the trials. The results of the trials should not be generalized to this clinically important subgroup of patients.

Major adverse cardiovascular events (MACE) were incompletely reported in the published trials but were highlighted as a concern by the FDA when they initially declined to approve insulin degludec in 2012. The FDA included all trials of insulin degludec in its analysis and found 70 MACE among the 5,794 patients randomized to insulin degludec or the combination of degludec and aspart; 21 MACE were observed among the 3,461 participants randomized to the comparator (RR 1.67; 95% CI: 1.01, 2.75). The FDA requested additional data on MACE prior to approval. As noted in the ongoing studies section, a double-blind RCT comparing degludec to glargine U100 in more than 7,000 patients is scheduled to be completed in 2016; that trial should answer remaining questions about any increase in MACE with degludec compared to glargine U100. Interim data from this trial were submitted to the FDA to assist in their 2015 approval decision, but these data have not been made public so as not to compromise the integrity of the ongoing study.

Controversies and Uncertainties

The primary source of uncertainty is the paucity of peer-reviewed data on MACE with insulin degludec. In addition, because the major differentiating factor in favor of insulin degludec appears to be lower rates of nocturnal hypoglycemia, the lack of data on the clinical impact of these types of events is of concern. The nominally greater reductions in HbA1c in the comparator groups may partially explain the higher rates of hypoglycemic events in these groups, although the differences were small. In addition, the differential timing of the administration of the basal insulin dose may partially explain the differences in nocturnal hypoglycemia rates. Finally, severe hypoglycemia is rare, so the estimates for the relative rates comparing insulin degludec to glargine U100 are somewhat unstable.

Summary

We find that the evidence for insulin degludec provides moderate certainty of a small comparative net health benefit in comparison to insulin glargine U100/detemir in patients with type 2 diabetes on basal-only or basal-bolus insulin regimens, based on "non-inferior" glycemic control and consistent findings of reduced nocturnal hypoglycemia. There is greater uncertainty in patients with type 1 diabetes, as no consistent and statistically-significant reductions in hypoglycemia were demonstrated in available meta-analyses. In addition, any potential benefits must be balanced by residual concerns about potentially higher rates of major adverse cardiovascular events in all subpopulations and the nominally lesser reduction in HbA1c in the degludec group in six of eight of the trials. With this risk in mind, and the resulting possibility (<10% in our estimation) that insulin degludec is actually harmful overall compared to other treatment options, we judge the current body of evidence on the comparative clinical effectiveness of insulin degludec to be "promising but inconclusive" using the ICER Evidence Rating Matrix.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

Insulin degludec appears to offer no unique benefits or disadvantages compared with available long-acting insulin preparations. Its long half-life should allow for more stable steady state levels of the medication with late or inconsistent timing of administration, but that same benefit likely applies to the new U300 formulation of insulin glargine.

6. Comparative Value

6.1 Overview

To assess the incremental costs per outcomes achieved, we conducted a cost-effectiveness analysis (CEA) using a validated and published simulation model of diabetes outcomes and costs (United Kingdom Prospective Diabetes Study Outcomes Model version 2 [UKPDS OM2])[20] in representative cohorts of patients with type 1 DM and type 2 DM. We estimated the incremental cost-effectiveness of insulin degludec relative to insulin glargine U100 (the comparator in all but one of the major clinical trials) using drug cost estimates derived from current prices and estimates of rates of hypoglycemia and other clinical parameters from relevant trial data.

We also used outputs from this model to inform a population-based analysis of the one- and five-year budgetary impact of insulin degludec (see section 6.4). Budgetary impact was assessed using assumed levels of uptake over these timeframes and included assessment of drug costs as well as cost savings from averted hypoglycemic episodes. We define a "value-based price benchmark" for insulin degludec based on a calculated threshold for policy intervention to manage the costs of a new pharmaceutical.

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of Insulin Degludec

Evans et al. (2014)[62]

Evans and colleagues evaluated the cost-effectiveness of insulin degludec compared to insulin glargine U100 in insulin-eligible type 2 DM patients. They used meta-analysis data from three clinical trials to model the costs and effects of treatment over a 12-month time horizon, from a UK National Health Service perspective. Their model produced estimated cost-effectiveness ratios of £13,078 ($19,666) using a disutility per hypoglycemic event, to £15,795 ($23,752) per quality-adjusted life-year (QALY) gained using utilities derived from SF-36 scores. Incremental cost-effectiveness did not vary greatly in most sensitivity analyses but was more sensitive to variations in the rate of severe hypoglycemia, and whether patients experienced a benefit from flexible dosing. Limitations of this model included reliance on short-term clinical trials, did not project beyond a one-year time horizon, and did not include any adjustment for the multiple competing risks that exist in a diabetes population (e.g., death due to cardiovascular complications of diabetes).

Ericsson et al. (2013)[63]

Ericsson and colleagues evaluated the cost-effectiveness of insulin degludec compared to insulin glargine U100 in type 1 DM patients, type 2 DM patients on basal-only therapy, and type 2 DM patients on basal-bolus therapy. They used data collected for Swedish diabetes patients and a meta-analysis of data from insulin degludec clinical trials to model the costs and effects of treatment over a one-year time horizon. Cost-effectiveness ratios were estimated as SEK 19,766 ($2,804), SEK 10,082 ($1,430) and SEK 36,074 ($5,118) per QALY gained in patients with type 1 DM, and in patients with type 2 DM on basal-only and basal-bolus regimens, respectively. Limitations of this model include that it relied on a patient questionnaire for recall of hypoglycemic events, as well as the short-term time horizon and issues of competing risks described above.

National Centre for Pharmacoeconomics (2015)[64]

Ireland's National Centre for Pharmacoeconomics (NCPE) reviewed a cost-utility analysis of insulin degludec versus insulin glargine U100 provided by Novo Nordisk that used hypoglycemic event rate as the primary efficacy measure in type 1 DM patients and type 2 DM patients using a basal-only regimen along with oral agents. Their model estimated the disutility for different hypoglycemia events over a one-year time horizon, using an international time trade-off survey of the general population. The cost per QALY gained was estimated as €6,284 ($8,015) for type 1 DM patients and €3,010 ($3,839) for type 2 DM basal-only patients. NCPE's review noted that the analysis mainly considered only the effects on hypoglycemia, and that results were sensitive to the disutility estimates used, for which there was variability in the literature. The NCPE Review Group preferred lower estimates for hypoglycemic event rates and their associated costs and disutilities, which resulted in cost-effectiveness estimates of €50,697/QALY ($64,665/QALY) for type 1 DM patients and €108,203/QALY ($138,014/QALY) for type 2 DM basal-only patients, both of which exceeded the group's threshold for considering an intervention to be cost-effective.

6.3 Incremental Costs per Outcome Achieved

Cost-Effectiveness Model: Methods

Model Structure

We used the existing UKPDS OM2[20] to assess the cost-effectiveness of insulin degludec relative to insulin glargine U100. The UKPDS OM2 is "a patient-level epidemiological model for a target population of adults aged 30 and over with any duration of diabetes" that allows one to model differential treatment effects on a platform that represents the typical trajectory for diabetes patients.[20] The model was used to calculate the net costs, health benefits, and incremental cost-

effectiveness ratios (ICERs). Separate analyses were conducted for patients with type 1 DM and type 2 DM. Although the UKPDS evaluated patients with type 2 DM only, a type 1 DM cohort was modeled by setting age and other patient characteristics to be consistent with those reported in the type 1 DM insulin degludec trials.

Because the major trials of insulin degludec utilized non-inferiority designs, comparisons of glycemic control and corresponding extrapolations to downstream clinical events (e.g., micro- and macrovascular complications) were not the primary focus of this analysis. Rather, we used this model to present a realistic trajectory for the clinical and economic outcomes associated with type 1 and type 2 DM. Our analysis focused on the avoidance of hypoglycemic episodes and other adverse events, along with associated costs (e.g., emergency department visits and/or hospitalizations) and corresponding reductions in health-related quality of life. The UKPDS OM2 does not include hypoglycemia as an outcome; we therefore incorporated hypoglycemia, including costs and disutilities for each such event, in a separate sub-model, following the general techniques used in recent Canadian Agency for Drugs and Technologies in Health (CADTH) reports.[65]

The UKPDS OM2 also allows for the inclusion of effects on other important clinical parameters, such as weight change and blood pressure. We conducted alternative analyses in which we allowed differences between insulin degludec and insulin glargine U100 that were observed in clinical trials to be used in the model, regardless of whether they were statistically-significant (see Outcomes below).

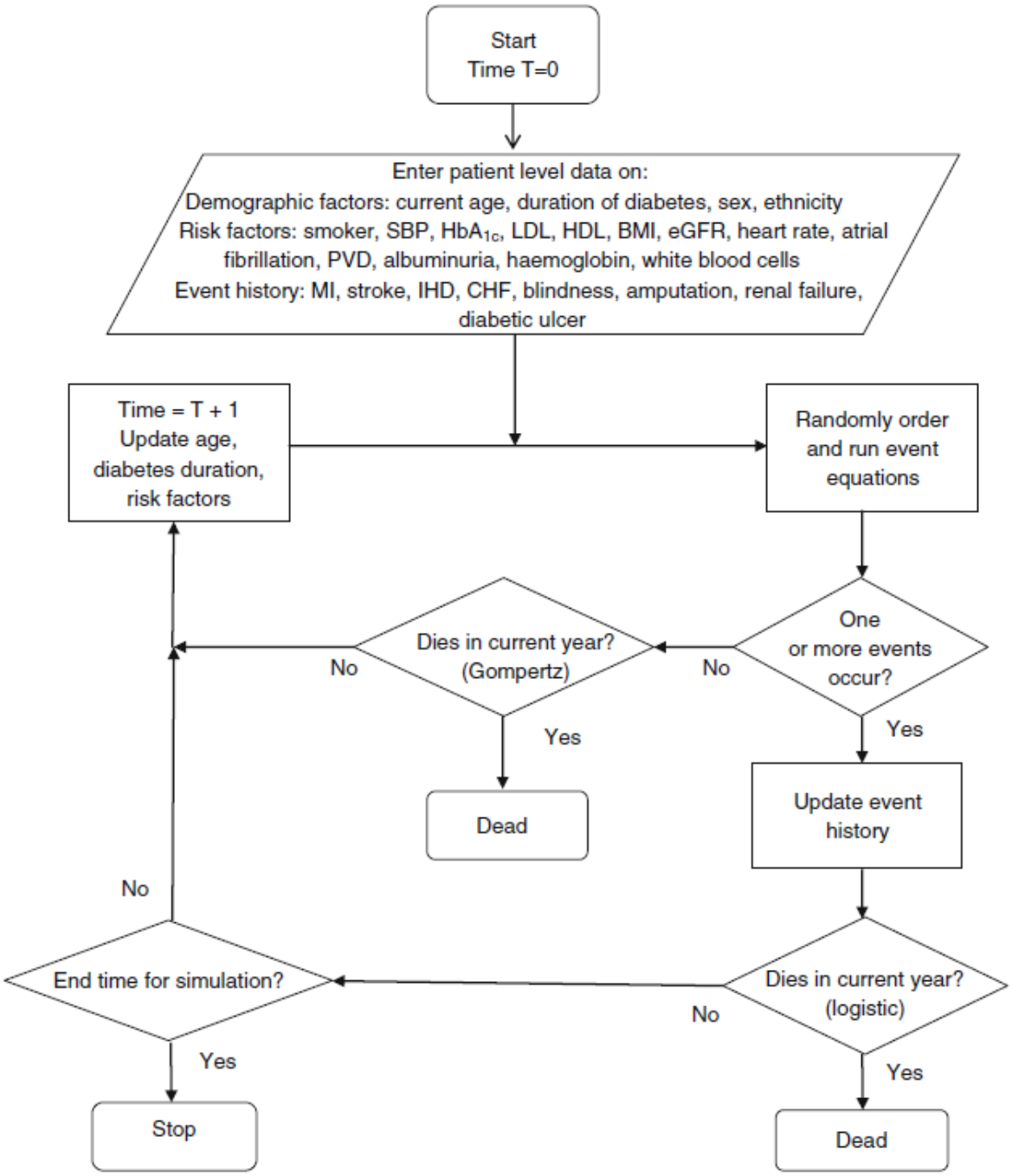
Model Schematic

The general model structure is depicted in Figure 3. The model allows for population-level input on baseline characteristics and changes in demographic and clinical risk factors at one-year intervals over patients' lifetimes.

Hypoglycemia events and costs were estimated via a separate submodule (see Figure 4). Hypoglycemia event rates per year, broken out into mild/moderate daytime, mild/moderate nocturnal, and severe, were modeled using estimates obtained during the overall treatment period from a patient-level meta-analysis of the insulin degludec clinical trials.[18] We derived rates of daytime events by subtracting rates of severe and nocturnal events from overall rates.

Each hypoglycemia event was assigned an associated cost and disutility, which was recorded and summarized over the model's time horizon, with appropriate discounting applied. These cost and utility estimates were then combined with those from the UKPDS OM2 to produce our final cost and QALY estimates.

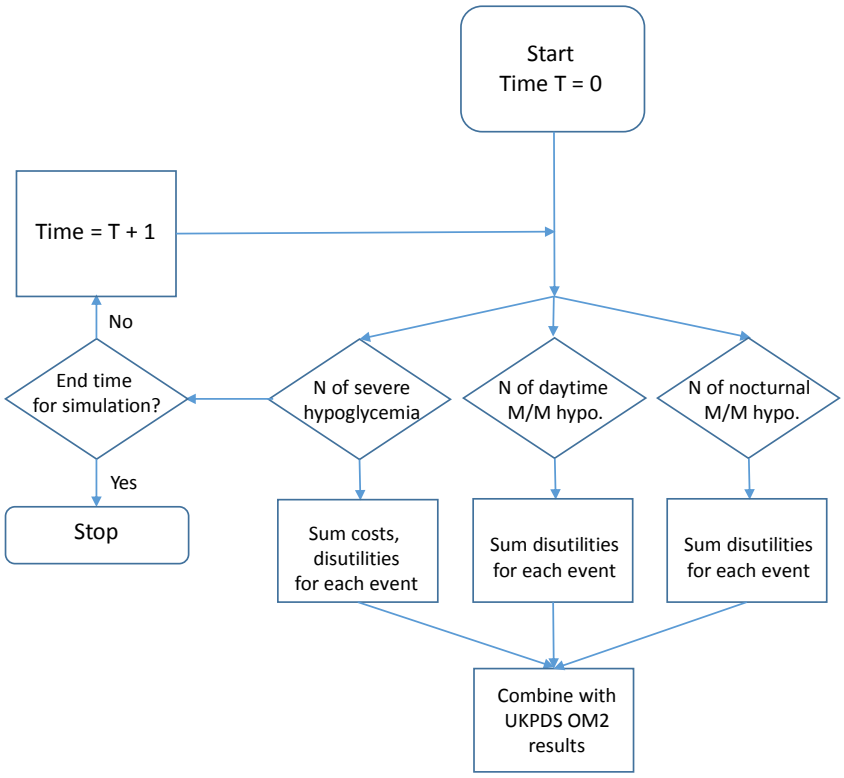
Figure 3. Model Schematic for UKPDS OM2[20]



Note: BMI: body mass index, CHF: congestive heart failure, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, IHD: ischemic heart disease, LDL: low-density lipoprotein, MI: myocardial infarction, PVD: peripheral vascular disease, SBP: systolic blood pressure

From: Hayes et al., Diabetologia, 2013 [20]

Figure 4. Model Schematic for Hypoglycemia Submodule



Note: M/M: mild/moderate

Model Parameters

Target Populations

The populations of focus for the economic analyses included adults ages 18 years and older with type 1 DM or type 2 DM, considered as separate populations. Within the population of individuals with type 2 DM, we considered patients taking basal-only insulin separately from patients taking basal-bolus insulin. Demographic and clinical characteristics of each of these groups were taken from the relevant insulin degludec trials and are shown in Table 5.

Table 5. Model Cohort Characteristics*

Population	Type 1 DM	Type 2 DM Basal-only	Type 2 DM Basal-bolus §
Age (years)	43 (14)	58 (9.8)	59
Female (%)	44%	44%	46%
Race (%)	White 81%, Black 1.5% Asian 16% Other 1.5%	White 70%, Black 7% Asian 21% Other 2%	White 83%, Black 9% Asian 6% Other 1%
Weight (kg)	76.1 (15.9)	86.1 (19.1)	93
Height (meters)	1.717†	1.683†	1.705†
BMI (kg/m2)	25.8 (3.9)	30.4 (5.2)	32
Diabetes duration (years)	17.5 (12.0)	10.8 (7.0)	10.8‡
HbA1c (%)	7.8 (1.0)	8.3 (0.8)	8.3
LDL cholesterol (mg/dL)	96	94	97
HDL cholesterol (mg/dL)	61	44	47
Systolic BP (mm Hg)	120‡	133	133‡
Heart rate (bpm)	80‡	80	80‡
WBC (x 10^9/L)	7.5‡	7.5‡	7.5‡
Hemoglobin (g/dL)	16[66]	16‡	15.5‡
eGFR (mL/min/1.73m^2)	90‡	90‡	90‡

* From mean (standard deviation) unless otherwise noted

† Calculated; ‡ Assumed; § From a single study in this population: BEGIN Basal-Bolus Type 2[14]

Interventions & Comparators

The intervention of interest was insulin degludec for the treatment of type 1 DM and type 2 DM. The primary comparator was insulin glargine U100, as this was the predominant comparator in available trial data. In the model, individuals received the intervention (insulin degludec or insulin glargine U100) at the outset and were then followed over their lifetimes. We did not assume any insulin switching or other changes to therapy.

Time Horizon

The time horizon for the cost-effectiveness analysis was lifetime, extrapolated up to 70 years from the short-term trial results (six to 12 months).

Perspective

Analyses were conducted from the payer perspective, with cost estimates limited to direct medical costs only (e.g., costs of intervention, as well as diabetes management and complications). Direct

costs to patients (e.g., transportation) and time costs (e.g., productivity losses) were not included, and any potential increases in future lifetime productivity resulting from successful treatment were not quantified.

Costs

The costs of insulin degludec and insulin glargine U100 were estimated based on published wholesale acquisition costs for each medication,[67,68] multiplied by the mean body weights of trial patients (see Table 5) and the mean ending doses for each drug in the trials (see Table 6), stratified by population (i.e., type 1 DM and type 2 DM basal-only and basal-bolus). The health care costs of severe hypoglycemia were based on a published estimate of resource use from Leese et al.[69] and costs from a report using the Alberta case-costing database[70] as reported by CADTH,[71] converted to 2014 US dollars; no additional health care costs were assumed to occur for either daytime or nocturnal hypoglycemia. Costs of complications (both at time of event and in subsequent years) mainly followed those used in a 2014 New England Comparative Effectiveness Public Advisory Council (CEPAC) report on type 2 DM, with costs for ischemic heart disease, myocardial infarction, stroke, amputation, blindness, and renal failure from Zhuo et al.,[72] for heart failure from Heidenreich et al.,[73] and for ulcer from Rice 2013,[74] as shown in Appendix Table G1. All costs were updated to 2014 USD as necessary using the medical component of the Consumer Price Index.

Table 6. Treatment-Related Parameters*

Input	Degludec	Glargine U100
Type 1 DM Population		
Ending dose (mean U/kg)	0.35	0.39
Hypoglycemic events (per person-year)	NS* (42.5†)	NS (40.2†)
Nocturnal	NS* (4.4†)	NS (5.9†)
Severe	NS* (0.21†)	NS (0.16†)
HbA1c post-treatment (%)	7.4 (7.4†)	7.4 (7.297†)
Weight (kg)	77.9†	77.7†
Type 2 DM Basal-Only		
Ending dose (mean U/kg)	0.59	0.60
Hypoglycemic event (per person-year)	RR 0.83* (1.6†)	1.9†
Nocturnal	RR 0.64* (0.25†)	0.39†
Severe	NS (0.01†)	NS (0.02†)
HbA1c post-treatment (%)	7.1 (7.151†)	7.1 (7.03†)
Weight (kg)	88.1†	87.7†
Type 2 DM Basal-bolus		
Ending dose, basal + bolus (mean U/kg)	1.47	1.43
Hypoglycemic events (per person year)	RR 0.82** (11.15†)	13.6
Nocturnal	RR 0.75** (1.35†)	1.8
Severe	NS** (0.06†)	NS (0.05†)
HbA1c post-treatment (%)	7.4 (7.2†)	7.4 (7.1†)
Weight (kg)	96.6†	97.0†

NS: not significant, U: units

* From Ratner 2013; ** From Garber 2012; † Values used in scenario analysis

Utilities

The model included utility weights for diabetes (without hypoglycemia), hypoglycemia events, and complications. We used the default values in the UKPDS OM2 for the baseline utility for diabetes, as well as the utility decrements for all complications except hypoglycemia events (see Appendix Table G2). For some complications, disutilities were assumed to occur in subsequent years, as well as at the time of the event, as shown in Appendix Table G2. Disutility for hypoglycemia events was based on values recommended in a recent review by Beaudet et al.,[75] which proposed using values adapted from a study by Currie et al. published in 2006.[76] Beaudet et al. converted the utility values from Currie et al. into annual value estimates of -0.012 per major hypoglycemia event and -0.004 per minor hypoglycemia event. There is precedent for such a conversion, as the unadjusted values from Currie et al. have been considered to be overstated by both CADTH and the National Institute

for Health and Care Excellence (NICE)[71] – applying the unadjusted value from Currie et al. of 0.047 for severe hypoglycemia over one year would be equivalent to losing 17 days of life in that year. We used the value for major events as our estimate of disutility for severe hypoglycemia. We used the Beaudet adjustment to account for the transient nature of even severe events.

The utility decrement for minor hypoglycemia was assumed to apply to mild and moderate hypoglycemia events but was modified to account for differing utilities associated with daytime and nocturnal mild/moderate events. To do so, we used evidence from a time trade-off survey conducted by Evans et al., which found a 63% higher disutility associated with nonsevere nocturnal hypoglycemia events compared to daytime events.[77] While this was a multi-country evaluation, we opted to use the pooled rather than U.S.-specific estimate based on the authors' observation that responses were consistent across geographies and that hypoglycemia-related disutility appears to be "comparable and independent of healthcare system differences."[77] We applied the 63% differential to the -0.004 disutility per minor hypoglycemia event to obtain the disutility values for daytime and nocturnal mild/moderate hypoglycemia events that are shown in Table 7. Estimates specific to the UKPDS model, as well as the costs of diabetes-related complications, can be found in Appendix Tables G1 and G2.

Discount Rate

Both costs and QALYs were discounted at 3% per year in the cost-effectiveness analysis. The budget impact analysis was conducted using undiscounted costs.

Table 7. Select Model Parameters

Annual Drug Costs (2014 $)				
Input	**Type 1 DM**	**Type 2 DM Basal-only**	**Type 2 DM Basal-bolus**	**Source**
Insulin degludec	2,873	5,486	14,765*	Calculated
Insulin glargine U100	2,688	4,686	12,063*	Calculated
Utility Values				
Input	**Base-case**	**Range of Values**		**Source**
Diabetes (initial utility)	0.807			Alva 2014 (UKPDS OM2 default value)[78]
Daytime mild/moderate hypoglycemia	-0.003042	-0.00076	-0.02357	Beaudet 2014[75] (Currie 2006)[76]
Nocturnal mild/moderate hypoglycemia	-0.004958	-0.00124	-0.038426	Adapted from Beaudet 2014[75]
Severe hypoglycemia	-0.012	-0.005	-0.020	Adapted from Beaudet 2014[75]

*Based on basal-bolus dosing.

Outcomes

In annual intervals in the UKPDS OM2, individuals may experience diabetes-related complications, as well as death from diabetes-related and non-diabetes-related causes. Mortality rates and age-based increase in overall mortality were based on the UKPDS OM2 default risk equations. Importantly, as there are as yet no publicly-available data from the DEVOTE trial to inform any conclusions regarding the relative risk of MACE events with insulin degludec vs. insulin glargine U100, such effects were not incorporated into the model.

Given that the majority of evidence was from non-inferiority trials, the model assumed equivalent HbA1c levels in each treatment arm. The primary outcome of interest for these analyses was the change in rates of hypoglycemic events (overall, nocturnal, and severe), and any subsequent effects on health, resource utilization, and costs. We used the results for the entire treatment period in Table 3 of the pre-planned, pooled meta-analysis by Ratner to estimate the effect on hypoglycemic episodes, with one exception.[18] No meta-analysis was performed for severe hypoglycemic episodes in the population of type 2 DM patients on basal-only insulin regimens. Ratner appears to report only the finding from Zinman[13] (which was an outlier for the rate of severe hypoglycemic events) and did not include the other three basal-only trials. In addition, there are not sufficient data from the reports of the other three trials for us to conduct our own meta-analysis, although rates of severe hypoglycemia did not differ in these three trials. Our base-case analysis assumed that there were no differences in hypoglycemia rates unless the difference was shown to be statistically significant in this meta-analysis of the trial results. Rates of hypoglycemia events are shown in Table 6.

Our definitions of hypoglycemia followed those used in the clinical effectiveness review. Specifically, severe hypoglycemia was defined as an event that required the assistance of another person to administer carbohydrate, glucagon, or some other form of resuscitation. Hypoglycemia was any documented plasma glucose <56 mg/dL or whole blood glucose <50 mg/dL, including severe hypoglycemia. Nocturnal hypoglycemia was any hypoglycemic event occurring between midnight and 6 AM. Other adverse events or outcomes were not included in the primary analyses, as none were found to differ significantly in the clinical effectiveness review. However, we did include point-estimate differences in hypoglycemia event rates, HbA1c levels, and body weight in a separate scenario analysis (see Appendix Table G3).

Data on cardiovascular outcomes with insulin degludec are not expected to be available until summer 2016. There has been some speculation that a flexible dosing schedule for insulin degludec could lead to better adherence to insulin treatment, but due to lack of available evidence, this effect was not modeled in primary analyses.[79]

Sensitivity Analyses

We conducted deterministic, one-way sensitivity analyses, in which key model parameters were allowed to vary across assumed ranges to determine the impact on cost-effectiveness findings. A tornado diagram was used for illustrative purposes in these analyses. We evaluated the effect of uncertainty in specific model inputs, focusing on intervention-specific uncertainties and characteristics of the patient population. Given the limited amount of clinical trial data currently available, we varied estimates by adjusting the reduction in hypoglycemia, the cost per hypoglycemia event, the effect of hypoglycemic events on quality of life, and the costs of insulin degludec.

Our base-case assumed equality for all non-hypoglycemia outcomes measured in the trials, given the non-inferiority design and lack of statistically significant differences in those outcomes. However, as described above, we conducted a separate scenario analysis in which point-estimate differences in hypoglycemia event rates, HbA1c levels, and body weight were incorporated into the model, whether statistically significant or not.

Finally, a threshold analysis was also conducted for the price of insulin degludec, to determine the price point needed to reach $50,000/QALY, $100,000/QALY and $150,000/QALY thresholds within each population of interest.

Cost-Effectiveness Model: Results

Results of the base-case analysis are shown in Table 8. Because there were no significant differences in rates of any type of hypoglycemia in the type 1 DM population, we were unable to calculate a base-case cost-effectiveness ratio for this group. Also, while rates of nonsevere hypoglycemia differed between groups in the type 2 trials, rates of severe hypoglycemia (the only type of hypoglycemic event assumed to generate health care costs) did not. As illustrated in the table, this resulted in QALY differences by insulin type but identical costs. For type 2 DM patients on basal-only insulin therapy, our base-case assumptions resulted in a cost/QALY ratio of approximately $353,000 for insulin degludec compared to insulin glargine U100. While total cost differences were relatively small (~$12,000), the utility benefit from reductions in nocturnal or daytime hypoglycemia also was small (0.034, or approximately two weeks of quality-adjusted life expectancy). For type 2 DM patients on basal-bolus insulin therapy, the ratio was approximately $167,000/QALY, as a larger difference in lifetime costs (~$40,000) was offset to a greater extent by a larger hypoglycemia benefit (0.237, or three months of quality-adjusted life expectancy).

Table 8. Base-Case Clinical and Economic Outcomes*

		Type 1 DM†		Type 2 DM Basal-only		Type 2 DM Basal-bolus	
		QALY	Total Costs	QALY	Total Costs	QALY	Total Costs
Insulin glargine U100	UKPDS	16.818	$95,777	11.971	$108,794	11.603	$214,453
	Hypoglycemia		†	-0.192	$815	-1.292	$2,952
	Total			11.779	$109,609	10.312	$217,405
Insulin degludec	UKPDS	16.818	$99,594	11.971	$120,816	11.603	$253,951
	Hypoglycemia		†	-0.158	$815	-1.055	$2,952
	Total			11.813	$121,631	10.549	$256,903
Increment (insulin degludec – insulin glargine U100)				0.034	$12,022	0.237	$39,498
Cost/QALY			†		$353,020		$166,644

NOTE: UKPDS refers to projected clinical outcomes and costs regardless of insulin treatment, according to calculations in the UKPDS outcomes model.

* Future costs and QALYs are discounted 3% a year.

† No base-case could be calculated for type 1 DM patients, as there were no significant differences in hypoglycemia.

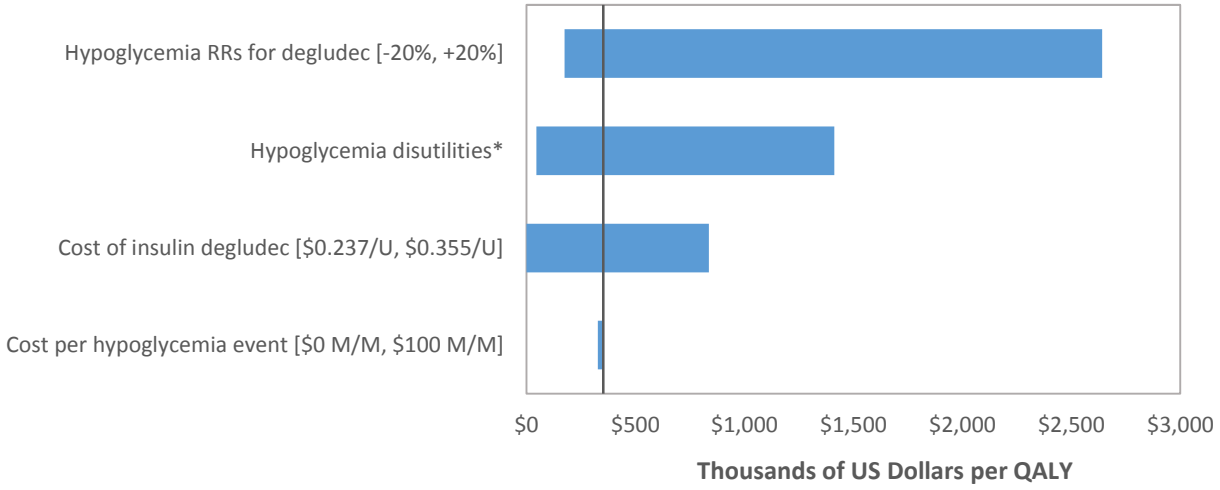
Sensitivity Analyses

We performed sensitivity analyses on several input parameters (see Figures 5A and 5B). The model was very sensitive to the relative rate of hypoglycemia events for insulin degludec compared to insulin glargine U100 as well as the disutility associated with these events. If the relative rates were assumed to be 20% higher than those in the base-case (i.e., insulin degludec was less effective in reducing hypoglycemia events), the cost per QALY gained would increase to approximately $2.6 million in type 2 DM patients on basal-only regimens, and to approximately $1.5 million for type 2 DM patients on basal-bolus regimens. The cost per QALY gained would decrease to approximately $174,000 and $87,000 for type 2 DM patients on basal-only and basal-bolus regimens, respectively, if relative rates were assumed to be 20% lower than in the base-case. In addition, insulin degludec would no longer be dominated (i.e., equal or lower effectiveness and higher costs) by insulin glargine U100, with an estimated cost-effectiveness ratio of $2,481/QALY gained. In all other sensitivity analyses, insulin degludec continued to be dominated by insulin glargine U100.

We also varied the disutilities associated with hypoglycemia events, using the range of values presented in Table 7 above. Disutilities for daytime mild/moderate, nocturnal mild/moderate, and severe hypoglycemia events were varied together according to the upper and lower bounds of this range. If we assumed the upper bounds, the incremental number of QALYs lost increased by a factor of approximately 7.75, causing the incremental cost-effectiveness ratio of insulin degludec to decrease to $45,551 per QALY gained in type 2 DM patients on basal-only therapy, and to $21,502

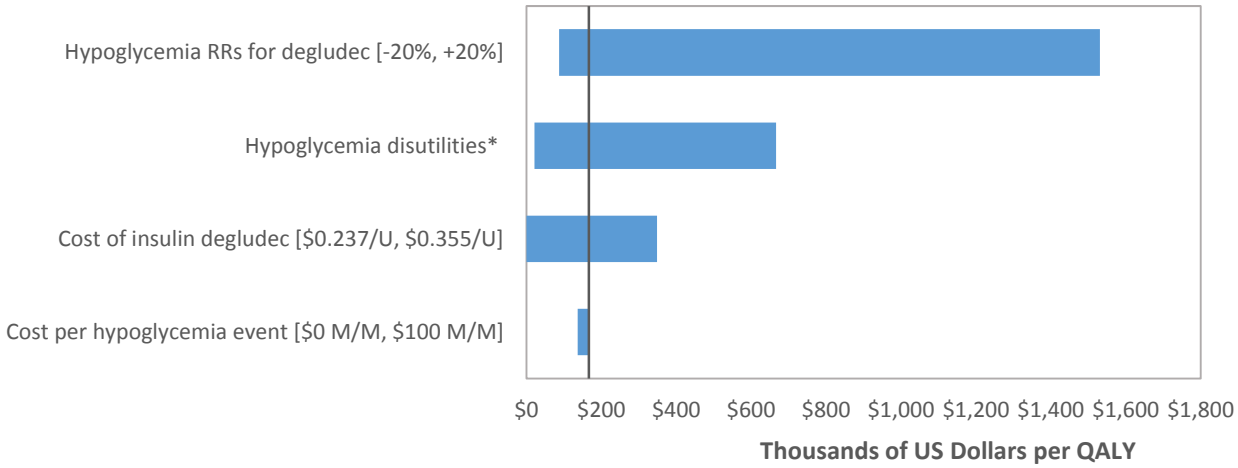
in type 2 DM patients on basal-bolus therapy. If we assume the lower bounds, the incremental cost-effectiveness ratio would increase to approximately $1.4 million per QALY gained in type 2 DM patients on basal-only regimens, and to $666,575 per QALY gained in type 2 DM patients on basal-bolus regimens. If the cost of insulin degludec were increased to $0.355 per unit, the estimated cost per QALY would increase to $837,276 in type 2 DM patients on basal-only regimens, and to $348,543 in type 2 DM patients on basal-bolus regimens. Varying the cost per mild/moderate hypoglycemic event (from no cost in the base-case to $100 per mild/moderate event) did not change the cost per QALY substantially, decreasing it to $327,614 in type 2 DM patients on basal-only regimens and $137,178 in type 2 DM patients on basal-bolus regimens.

Figure 5A. One-Way Sensitivity Analysis Results: Tornado Diagram (Type 2 DM Basal-only Patients)



*Hypoglycemia disutilities varied from -0.02357 to -0.00076 for daytime mild/moderate hypoglycemia, -0.038426 to -0.00124 for nocturnal mild/moderate hypoglycemia, and -0.020 to -0.005 for severe hypoglycemia.

Figure 5B. One-Way Sensitivity Analysis Results: Tornado Diagram (Type 2 DM Basal-bolus Patients)



*Hypoglycemia disutilities varied from -0.02357 to -0.00076 for daytime mild/moderate hypoglycemia, -0.038426 to -0.00124 for nocturnal mild/moderate hypoglycemia, and -0.020 to -0.005 for severe hypoglycemia.

Scenario Analysis

We also conducted an analysis in which we allowed point-estimate differences between treatment groups in available clinical trials to be input for hypoglycemia rates, HbA1c, and weight changes, regardless of whether the rates differed statistically between groups. In this scenario, insulin degludec was dominated compared to insulin glargine U100 in type 1 DM patients (i.e., insulin degludec produced fewer QALYs at a higher cost) (see Appendix Table G3). The estimated incremental cost per QALY for the type 2 DM basal-only group increased to over $800,000/QALY, while that for the type 2 DM basal-bolus group increased to approximately $180,000/QALY.

Threshold Analyses

The annual cost of insulin degludec required to achieve commonly-cited thresholds for the cost per QALY gained are presented by threshold and diabetes population in Table 9. To achieve a cost-effectiveness ratio of $150,000 per QALY gained, the annual cost would need to decrease to $5,025 and $14,498 in the type 2 DM basal-only and basal-bolus populations respectively, which represent 8% and 2% discounts respectively. Greater discounts would be required to achieve a cost-effectiveness ratio of $100,000 per QALY gained (10% and 7% respectively) or $50,000 per QALY gained (12% and 13% respectively).

While the annual cost at the list price for type 1 DM is presented in the table for completeness, there are no prices that would achieve common cost-effectiveness thresholds given the base-case

assumption of no differences in clinical benefit or harm between groups. The annual cost of insulin glargine U100 in type 1 DM was therefore used as the reference price for this population.

Threshold prices are also presented for all three populations combined, weighted by anticipated population size (see Section 6.4). Discounts of 8-12% would be required from the weighted list price of $7,800 to achieve cost-effectiveness thresholds of $50,000 - $150,000 per QALY gained.

Table 9. Threshold Analysis for Annual Cost of Insulin Degludec, by Subpopulation

ICER	Type 1 DM	Type 2 DM Basal-only	Type 2 DM Basal-bolus	Total (Weighted Average)
$50,000/QALY	$2,688*	$4,801	$12,878	$6,850
$100,000/QALY	$2,688*	$4,914	$13,683	$7,006
$150,000/QALY	$2,688*	$5,025	$14,498	$7,154
Annual Cost at List Price	$2,873	$5,486	$14,765	$7,800

*Insulin glargine U100 cost as reference price; thresholds could not be calculated, as no clinical differences were assumed for the base-case.

6.4 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total budgetary impact of insulin degludec based on assumed patterns of product uptake. We then combined consideration of the price range between cost-effectiveness thresholds of $100,000 to $150,000 per QALY with potential budget impact to calculate value-based price benchmarks. The budgetary impact analyses assumed a specific product uptake rate over the five-year period. We also developed a value-based price benchmark for insulin degludec in each of the populations of interest (type 1 DM and type 2 DM basal-only and basal-bolus); this benchmark represents a policy trigger for managing the cost of new interventions with a budgetary impact that exceeds the level of growth in the overall US economy.

Budget Impact Model: Methods

We used the same model employed for the cost-effectiveness analyses to estimate potential total budgetary impact. Potential budgetary impact was defined as the total incremental cost of the therapy for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted hypoglycemia events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time.

We calculated budget impact by including the entire candidate populations for treatment: patients with type 1 DM on basal-bolus regimens, patients with type 2 DM on basal-only regimens, and

patients with type 2 DM on basal-bolus regimens. To estimate the size of the potential candidate population for insulin degludec, we first applied the estimated prevalence of diabetes in the US in 2012[1] to the estimated 2015 US population.[80] Of the total US population (approximately 321.4 million), 0.40% were estimated to have type 1 DM (1.28 million) and 8.9% to have type 2 DM (27.85 million). We assumed that 100% of the type 1 DM population would be treated with insulin, and that 22.8% of type 2 DM patients would be on insulin.[81]

An analysis of diabetes treatment patterns using claims data[82] found that 42.7% of type 1 DM patients initiating insulin therapy used a basal-bolus regimen, with the remainder on alternative insulin regimens (such as insulin pumps or premixed insulin). The same analysis found that 53.7% of type 2 DM patients were on a basal-only regimen and 23.8% on a basal-bolus regimen, with the remainder on alternative insulin regimens. Applying these proportions to the projected 2015 US population, we estimated approximately 549,000 type 1 DM patients on basal-bolus insulin, 3.5 million type 2 DM patients on basal-only insulin, and 1.55 million type 2 DM patients on basal-bolus insulin regimens.

ICER's methods for estimating budget impact and calculating value-based benchmark prices are described in detail elsewhere. Briefly, our calculations assume that the utilization of new drugs or devices occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug/device uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate unmanaged uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year five); 2) high (50% uptake by year five); 3) intermediate (25% uptake by year five); and 4) low (10% uptake by year five). In this analysis, we assumed a low uptake pattern for insulin degludec. We made this assumption because insulin degludec is one of several long-acting insulins available on the US market, and a new concentrated formula of insulin glargine (U300, Toujeo) shares many of the same characteristics. In addition, other forms of insulin delivery (e.g., continuous pumps) and a variety of other anti-diabetic agents for type 2 DM compete for market share.

The resulting population size after five years, assuming an estimated 10% uptake, was approximately 55,000 for type 1 DM, 350,000 for type 2 DM basal-only, and 155,000 for type 2 DM basal-bolus. For consistency, uptake was assumed to occur in equal proportions across the five-year timeframe, and we adjusted net costs to account for this. For example, in this population estimated to have a 10% five-year uptake, 2% of patients would be assumed to initiate therapy each year. Patients initiating therapy in year one would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of the five-year costs.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug (or device) approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs (or devices) to total health care spending. Calculations are performed as shown in Table 10.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 10. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS National Health Expenditures (NHE), 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS NHE, Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact and the Value-based Price Benchmark

We combine consideration of the potential budget impact with the threshold prices presented above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug. This price benchmark begins with the price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug would exceed the potential budget impact threshold (i.e., $904 million). If the potential budget impact does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

Budget Impact Model: Results

Table 11 presents the budgetary impact of five years of insulin degludec in the candidate population, assuming the uptake patterns previously described. Results from the budget impact model showed that, with the uptake pattern assumptions mentioned above, an estimated 112,055 individuals in the U.S. would receive insulin degludec in the first year. Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 560,000 persons taking insulin degludec for one or more years. Across this timeframe, the weighted budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $538 per type 1 DM patient, $2,365 per type 2 DM basal-only patient, and $7,950 per type 2 DM basal-bolus patient. Total budgetary impact over five years is approximately $2.09 billion, with an average budget impact per year of approximately $418.3 million. This annualized potential budget impact is only 46% of the budget impact threshold of $904 million for a new drug.

Table 11. Potential Budget Impact (BI) of Insulin Degludec Based on Assumed Patterns of Uptake

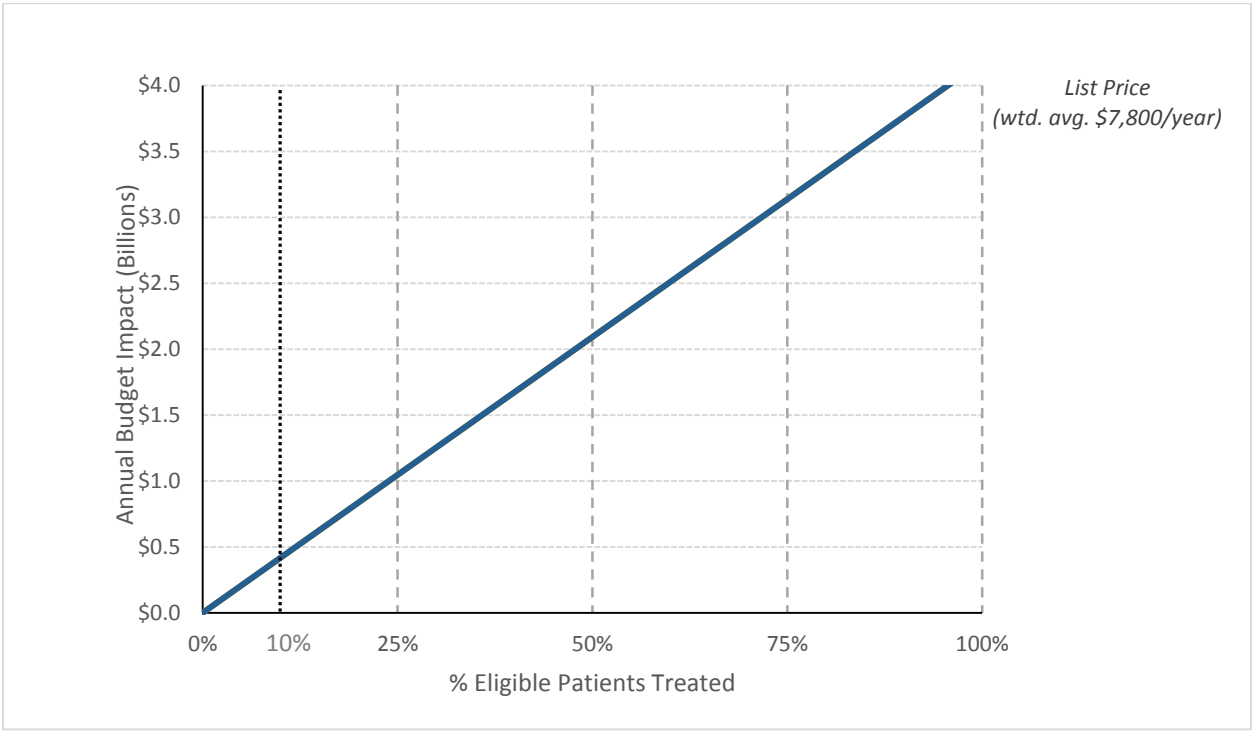
		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
Insulin Degludec	Eligible Population (millions)	Number Treated (thousands)	Annual BI per Patient ($)*	Total BI (millions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Average BI per year (millions)
Type 1 DM	0.55	10.98	$183	$2.0	54.9	$538	$5.9
Type 2 DM Basal-only	3.50	70.04	$815	$57.1	350.1	$2,365	$165.6
Type 2 DM Basal-bolus	1.55	31.04	$2,704	$83.9	155.2	$7,950	$246.8
Total	5.60	112.06	$1,276	$143.0	560.3	$3,733	$418.3

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figure 6 provides findings of multiple analyses that give perspective on the relationship between varying possible drug costs, uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored line demonstrates how quickly the annual budget impact increases with increasing percentages of patients treated at the list price used in this analysis (i.e., weighted average annual cost of $7,800/year for insulin degludec). Note that results are not presented according to prices that would meet common cost-effectiveness thresholds, as such prices were not available for the type 1 DM population (because of assumed clinical equivalence between insulin degludec and insulin glargine U100).

As can be seen in Figure 6, based on the weighted list price trend line (with a weighted average drug cost of $7,800/year), budget impact at an assumed uptake of 10% is well below an annual threshold of $904 million to meet national growth targets. On a national basis, the annualized potential budget impact for insulin degludec at list price is $418.3 million at our assumed uptake of 10%, would rise to $1.05 billion if 25% of eligible patients are treated, and would be approximately $4.2 billion if 100% of eligible patients are treated. Approximately 22% of eligible patients could be treated before the budget impact threshold is crossed.

Figure 6. Potential Budget Impact for Insulin Degludec at Different Uptake Assumptions



Note: Solid line represents the annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug.

6.5 Value-based Price Benchmark

Our value-based prices benchmarks for insulin degludec are provided in Table 12. As noted in the ICER methods document, the value-based price benchmark for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained, without exceeding the $904 million budgetary impact threshold for new drugs. We could not calculate long-term "care value" prices for type 1 DM patients, as there were no assumed clinical differences between insulin degludec and insulin glargine U100 in our primary analyses. Therefore, the value-based price benchmark for insulin degludec for this subpopulation would be the same price as its comparator treatment, i.e., the reference price. The annual cost of insulin glargine U100, assuming the profile of type 1 DM patients used in our analysis, is $2,688 annually. This cost is included in our calculations of an overall price benchmark across the three diabetes subpopulations of interest.

As shown in Table 12, the price range in type 2 DM patients on basal-only regimens based on cost-effectiveness thresholds ($4,914 to $5,025/year) is lower than the annual cost for these patients using list price for insulin degludec ($5,486/year), as would be expected given that our analyses indicated a cost/QALY higher than $150,000 for this intervention at the list price. Similarly, the price range in type 2 DM patients on basal-bolus regimens based on cost-effectiveness thresholds ($13,683 to $14,498/year) is lower than the annual cost based on list price for insulin degludec ($14,765/year), as our analyses indicated a cost/QALY slightly higher than $150,000 for this intervention at the list price. A weighted average of these prices gives us a price range of $7,607 to $7,934/year for type 2 DM patients, which corresponds to a per-unit price from $0.265/unit to $0.271/unit. Including type 1 DM patients and applying this range of prices/unit across all eligible populations (with a weighted average weight of 87 kg), gives a weighted average price range of $7,006 to $7,154/year.

As noted previously, the budgetary impact of insulin degludec does not exceed our stated threshold when annualized over a five-year time horizon. The price of insulin degludec that could be charged and not exceed the $904 million annual benchmark is higher than the price range that would achieve $100,000 to $150,000 per QALY gained. Details of the budget impact threshold price analysis can be found in Appendix Table G4.

Therefore, the ICER value-based price benchmark for insulin degludec, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $7,006 to $7,154 per year, which corresponds to a per-unit price from $0.265/unit to $0.271/unit. This price represents an 8-10% discount from the weighted average cost per year.

Table 12. Value-based Price Benchmarks for Insulin Degludec

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Exceeds Potential Budget Impact Threshold?	Value-Based Price Benchmark
Type 1 DM (n=54,889)	$2,688/year*	$2,688/year*	No	N/A
Type 2 DM Basal-only (n=350,183)	$4,914/year	$5,025/year	No	$4,914 to $5,025/year
Type 2 DM Basal-bolus (n=155,202)	$13,683/year	$14,498/year	No	$13,683 to $14,498/year
Total (n=560,274)	$7,006/year	$7,154/year	No	$7,006 to $7,154/year

*Using insulin glargine U100 cost as reference price.

6.6 Summary and Comment

Findings from our analysis suggest that the long-term care value of insulin degludec exceeds commonly-cited cost-effectiveness thresholds. Care value varied by subpopulation; patients with type 2 DM receiving basal-only regimens had a care value estimate >$350,000, as benefits from reductions in nocturnal hypoglycemia were very modest in this group. In contrast, while insulin dosing requirements and corresponding treatment costs were greatest in patients with type 2 DM receiving basal-bolus treatment, care value was more favorable ($167,000/QALY) due to a more pronounced reduction in nocturnal hypoglycemia in a population with a higher baseline risk for these events. We could not evaluate the long-term care value of insulin degludec in type 1 DM patients, as we found no data suggesting statistically- and/or clinically-significant improvement in outcomes versus insulin glargine U100.

Under an assumption that insulin degludec would have a 10% uptake in the candidate population for long-acting insulin, its annual potential budget impact would be approximately $420 million, well below ICER's annual budget impact threshold of $904 million. In addition, relatively modest discounts (8-10%) would be needed to better align the price of insulin degludec with patient value.

We note several limitations to our analysis. Most important, given the non-inferiority nature of the trials, our results were quite sensitive to the relative rates of hypoglycemia events, as well as the disutility associated with these events. Longer-term follow-up studies would be useful in determining the relative risk of different types of hypoglycemia events for insulin degludec compared to insulin glargine U100 over different treatment time horizons. In addition, there remains a need for determining the long-term impact of both severe and nonsevere hypoglycemic episodes, so that the impact of these events on clinical outcomes, costs, and quality of life can be better quantified. As with any evidence base for recently-approved interventions, there is limited long-term data on the effects of insulin degludec, requiring the assumption that the effects

observed in the short-term efficacy trials will continue over a lifetime horizon and will remain constant over that time. In reality, insulin dosing needs change for patients with diabetes over time, as does the use of additional anti-diabetic agents; these changes will likely affect the trajectory of glycemic control and risk of hypoglycemia.

The UKPDS OM2 model was used to model the clinical and economic trajectory for patients with both type 1 and type 2 DM, even though the risk equations are derived based on type 2 experience alone. While we attempted to model the type 1 population based on a realistic baseline profile, we recognize that disease progression and pathology for this population was not adequately reflected. However, no material differences in clinical outcome between insulin degludec and insulin glargine U100 were observed among type 1 patients in available clinical trials, so model results and our conclusions are most relevant for the type 2 basal-only and basal-bolus populations.

The costs of managing hypoglycemia may have been underestimated, as our use of the payer perspective required only that we estimate the costs of severe episodes (i.e., those requiring 3rd-party intervention). However, no differences between treatment groups in the rates of severe hypoglycemia were observed in any of the diabetes populations of interest in our model, and estimates of the costs of nonsevere episodes are highly variable and have been debated intensely in the literature.[5-7]

We used wholesale acquisition costs for medication costs because of lack of transparency regarding the magnitude and pervasiveness of potential discounts, which are usually not publicly available or even determined at the time we conducted our analysis (shortly after FDA approval); in addition, the purpose of our analysis is in part to determine the level of discount that may be required to achieve certain thresholds for both short- and long-term value. Finally, for the budget impact analyses, our assumed levels of market uptake by five years were based on reasoned assumptions, and actual uptake may vary from these estimates. However, we also present the potential budget impact across a wide range of uptake possibilities in our budget impact analysis.

In summary, based on currently-available evidence and the non-inferiority design of major clinical trials, use of insulin degludec appears to confer small net health benefits in comparison to insulin glargine U100 in patients with type 1 or type 2 DM. Where benefits exist, they are limited to episodes of nocturnal hypoglycemia. At the current wholesale acquisition cost, the estimated cost-effectiveness of insulin degludec exceeds commonly-cited thresholds. However, achieving levels of value more closely aligned with patient benefit would require relatively modest discounts (8-10%) from the current list price. Across all subpopulations, the potential budget impact of insulin degludec is not estimated to exceed ICER's short-term (five-year) threshold linked to national health care cost growth targets.

7. Summary of the Votes and Considerations for Policy

7.1 About the CTAF Process

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Panel members typically serve for two or more years and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of the CTAF Panel and ground the conversation in the interpretation of the published evidence, they are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation, and they help form recommendations with the CTAF Panel on ways the evidence can be applied to policy and practice.

At each meeting, after the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

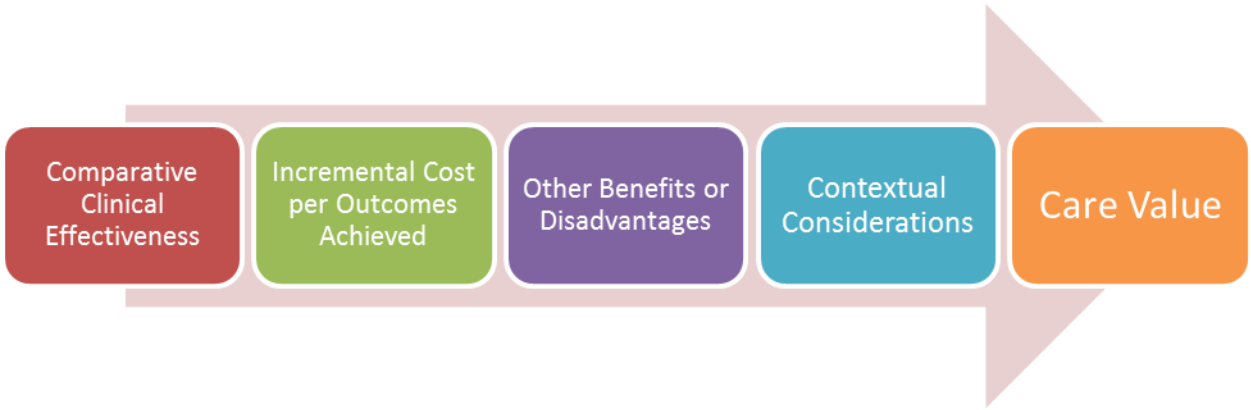
At the February 12, 2016 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the use of insulin degludec for the treatment of type 1 and type 2 diabetes mellitus (DM). Following the evidence presentation and public comments, the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of insulin degludec. These questions are developed by the ICER research team for each assessment, with input from the CTAF Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. The voting results are presented below, along with comments reflecting considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and votes related to value, the CTAF Panel makes use of a value assessment framework with four different components of *care value*, a concept which represents the long-term

perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, other benefits or disadvantages, and contextual considerations regarding the illness or therapy.

Once the CTAF Panel makes an overall assessment of care value as low, intermediate, or high considering these four components, they then explicitly consider the affordability of the intervention under review in assessing *provisional health system value* as low, intermediate, or high (see Figure 7 and Figure 8, as well as the detailed explanation that follows).

Figure 7. Care Value Framework



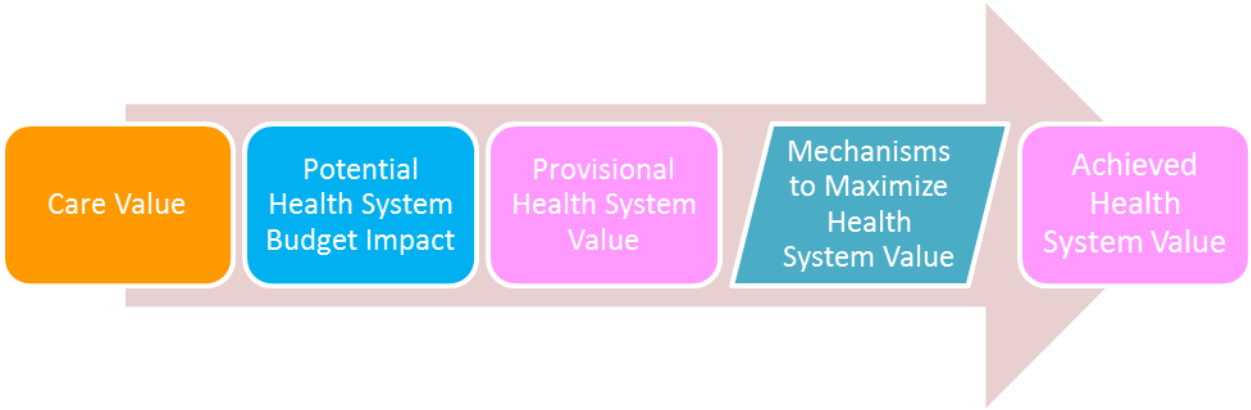
There are four elements to consider when deliberating on care value:

1. ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.
2. ***Incremental cost per outcomes achieved*** is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a "cost per outcome achieved." Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of incremental costs per outcomes achieved, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios of incremental costs per outcomes achieved.

3. ***Other benefits or disadvantages*** refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include mechanisms of treatment delivery that require many fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.
4. ***Contextual considerations*** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

In assessing provisional health system value, the CTAF Panel is asked to vote whether interventions represent a "high," "intermediate," or "low" value.

Figure 8. Health System Value Framework



1. ***Potential Health System Budget Impact*** is the estimated *net* change in *total* health care costs over a 5-year time-frame.
2. ***Provisional "Health System Value"*** represents a judgment integrating consideration of the long-term care value of a new intervention with an analysis of its potential short-term budget impact if utilization is unmanaged. The CTAF Panel votes reflect a judgement on the provisional health system value of an intervention.

3. ***Mechanisms to Maximize Health System Value*** is an action step, ideally supported by enhanced early dialogue among manufacturers, payers, and other stakeholders.
4. ***Achieved Health System Value*** is the real-world result of health care stakeholder efforts to maximize the value of a given intervention.

Usually, the care value and the provisional health care system value of an intervention or approach to care will align, whether it is "high," "intermediate," or "low." For example, a treatment that is judged to represent high care value from the perspective of per-patient costs and benefits will almost always represent a high health system value as well. But health system value also takes into consideration the short-term effects of the potential budget impact of a change in care across the entire population of patients. Rarely, when the additional per-patient costs for a new care option are multiplied by the number of potential patients treated, the short-term budget impact of a new intervention of intermediate or even high care value could be so substantial that the intervention would be "unaffordable" unless the health system severely restricts its use, delays or cancels other valuable care programs, or undermines access to affordable health insurance for all patients by sharply increasing health care premiums. Under these circumstances, unmanaged change to a new care option could cause significant harm across the entire health system, in the short-term possibly even outweighing the good provided by use of the new care option itself.

Provisional health system value builds upon the judgment of care value by integrating consideration of the potential short-term budget impact of a new intervention, a figure highly dependent upon an estimation of the potential uptake of the new drug across the entire population. In the ICER framework, the theoretical basis for the budget impact threshold is based on societal willingness to pay. This foundation rests upon the assumption that society would prefer health care costs to grow at a rate that does not exceed growth in the overall national economy. ICER has used estimates based on data from the World Bank, the Centers for Medicare & Medicaid Services (CMS), and other public sources to calculate a budget impact threshold for individual new drugs or devices that would identify those whose potential budget impact would contribute significantly to excessive health care cost growth.

It should be noted that if, after considering potential budget impact, a health intervention judged to have high care value receives a judgment of "low" provisional health system value from the CTAF Panel, this does not imply that the health system should not adopt the intervention; rather, the vote indicates that policy makers should consider implementing mechanisms related to patient selection, step therapy, pricing, and/or financing to ensure that the short-term budget impact of a high care value intervention does not lead to more harm than good. CTAF votes on provisional health system value will therefore serve an important function by highlighting situations when policymakers need to take action and work together to align care value with health system value.

7.2 Summary of the Votes

1. For patients with type 1 diabetes mellitus (DM), is the evidence adequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100?

   CTAF Panel Vote: 0 Yes (0%) 16 No (100%)

   Comment: Members of the CTAF panel judged the clinical trials for insulin degludec to be insufficiently rigorous to demonstrate superiority to insulin glargine U100. The predominant concerns among the panel were that all available studies were both unblinded and reliant on patient-reported outcomes, which could bias the results in favor of the newer intervention; that data on major adverse cardiovascular events (MACE) from an ongoing clinical trial, though available to the FDA, are not yet accessible to the public to preserve the integrity of the study; that insulin dose time was variable across both arms of the clinical trials; and that the trials set atypically low fasting blood glucose targets, thus capturing fewer hypoglycemic events than would have been observed using fasting blood glucose targets from real-world clinical practice. Additionally, the trials excluded patients with hypoglycemic unawareness or frequent hypoglycemia, a subgroup of patients that would experience greater benefits from a reduction in hypoglycemic events.

2. Given the available evidence for patients with type 1 DM, what is the care value of treatment with insulin degludec vs. treatment with insulin glargine U100?

   Comment: A care value vote was not taken because the CTAF Panel voted that the evidence was inadequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100 for patients with type 1 DM.

3. Given the available evidence for patients with type 1 DM, what is the provisional health system value of treatment with insulin degludec vs. treatment with insulin glargine U100?

   Comment: A provisional health system value vote was not taken because the CTAF Panel voted that the evidence was inadequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100 for patients with type 1 DM.

4. For patients with type 2 DM who are on basal-only insulin regimens, is the evidence adequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100?

CTAF Panel Vote: 1 Yes (6%) 15 No (94%)

Comment: The CTAF Panel voiced concerns similar to those expressed during the votes on question one, namely that the trial design was inadequate to demonstrate the superiority of insulin degludec to insulin glargine U100, data on MACE are currently unavailable to the public, and that fasting blood glucose targets differed from those used in real-world practice. One panelist who judged that the evidence was adequate felt that the trials sufficiently demonstrated that insulin degludec reduces the incidence of hypoglycemia compared to insulin glargine U100.

5. Given the available evidence for patients with type 2 DM who are on basal-only insulin regimens, what is the care value of treatment with insulin degludec vs. treatment with insulin glargine U100?

   Comment: A care value vote was not taken because the CTAF Panel voted that the evidence was inadequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100 for patients with type 2 DM on basal-only regimens.

6. Given the available evidence for patients with type 2 DM who are on basal-only insulin regimens, what is the provisional health system value of treatment with insulin degludec vs. treatment with insulin glargine U100?

   Comment: A provisional health system value vote was not taken because the CTAF Panel voted that the evidence was inadequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100 for patients with type 2 DM on basal-only regimens.

7. For patients with type 2 DM who are on basal-bolus insulin regimens, is the evidence adequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100?

   CTAF Panel Vote: 2 Yes (13%) 14 No (88%)

   Comment: When examining the data for patients with type 2 DM on basal-bolus regimens, the CTAF panel voiced the same concerns that they stated during the votes on questions one and four.

8. Given the available evidence for patients with type 2 DM who are on basal-bolus insulin regimens, what is the care value of treatment with insulin degludec vs. treatment with insulin glargine U100?

Comment: A care value vote was not taken because the CTAF Panel voted that the evidence was inadequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100 for patients with type 2 DM on basal-bolus regimens.

9. Given the available evidence for patients with type 2 DM who are on basal-bolus insulin regimens, what is the provisional health system value of treatment with insulin degludec vs. treatment with insulin glargine U100?

   Comment: A provisional health system value vote was not taken because the CTAF Panel voted that the evidence was inadequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100 for patients with type 2 DM on basal-bolus regimens.

7.3 Roundtable Discussions and Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion about the use of insulin degludec and the management of diabetes with a Policy Roundtable that included two clinical experts, a medical director for a public payer, and a medical director from a private payer. The policy roundtable discussion with the CTAF Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown in Table 13, and conflict of interest information for all meeting participants can be found in Appendix H.

Table 13. Policy Roundtable Participants

Neal Kohatsu, MD, MPH	Medical Director, California Department of Health Care Services
Elizabeth Murphy, MD, DPhil	Chief, Endocrinology and Metabolism Division and Director of Diabetes Center for High Risk Populations, San Francisco General Hospital; Professor of Clinical Medicine, UCSF
Manuel Quiñones, MD	Internal Medicine and Diabetology, Healthcare Partners - Anaheim
Tony Van Goor, MD, MMM, CPE, FACP	Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California

The roundtable discussion was facilitated by Jed Weissberg, MD, Senior Fellow at ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

- Given the CTAF Panel's judgment that current evidence is inadequate to demonstrate that insulin degludec is superior to insulin glargine U100, payers should consider using utilization management tools to regulate the uptake of insulin degludec.

- The policy roundtable discussed that before spending money on expensive, long-acting insulins, it is important to ensure that patients have access to basic testing and treatment supplies; therefore, payers should consider a streamlined administrative process that eases access to these supplies for an appropriate subset of patients. An informal poll of the CTAF Panel revealed that most clinicians had witnessed the obstacles and challenges patients face when trying to obtain even basic supplies such as testing strips. Without basic testing supplies, it is difficult to ensure that standard of care is met. For patients that require frequent glucose testing, clinicians noted that there is a substantial administrative burden to obtain coverage for these supplies.

Providers

- Clinicians should work with individual patients to determine targets for glycemic control. Relaxed targets for glycemic control may be appropriate for patients who experience frequent hypoglycemic episodes.

- Providers should consider use of insulins with full-day coverage for patients who have difficulty adhering to insulin-based treatment regimens. Clinicians on the Panel and Policy Roundtable highlighted the reality that some patients may skip insulin dosing purposely, whether because of treatment fatigue, convenience, or financial hardship. These patients can include those with mental illness, the homeless, and those who are of lower socioeconomic status. Clinicians on the policy roundtable stated that their primary goal with these patients is to prevent hospitalization, and treatment options that allow for more flexible dosing schedules, specifically long-acting insulins with complete day coverage, may lead to fewer complications and hospitalizations.

Patients

- Patients should discuss the relative effectiveness of available insulins with their providers and be aware that newly approved insulins may not have evidence to clearly demonstrate their superiority to other insulins already on the market.

- Patients should also discuss evidence on effectiveness with their providers before switching to a more expensive medication. It is especially important for patients of limited financial

means to understand whether the cost impact of switching insulins is worth any potential health benefit the new insulin would provide.

- Although newer long-acting insulins may allow for flexible dosing schedules, clinicians still recommend that patients aim to keep insulin administration time as consistent as possible as a best practice.

Manufacturers

- In order to provide the evidence needed by patients, clinicians, and payers, manufacturers should ensure that future trials be double-blinded and powered to detect meaningful clinical differences in objective outcomes such as severe hypoglycemia and HbA1c, as opposed to surrogate and/or non-standardized subjective outcomes.

- Although the FDA specifies that non-inferiority trial design is adequate for approval, manufacturers should seek other trial designs when competing therapies are available in the marketplace, as non-inferiority studies do not provide sufficient information to patients, payers, or clinicians in their determinations of treatment to use or reimburse.

- Future developmental trials for diabetes drugs should use widely-accepted thresholds for hypoglycemia (plasma glucose <70 mg/dL) as opposed to the lower thresholds used in the clinical trials for insulin degludec (<56 mg/dL). This change will ensure that trial evidence is more applicable to real-world practice.

- Future developmental trials should be conducted among patients with severe or frequent hypoglycemia, a clinically important group that was excluded from the trials summarized in the ICER review. As a result of this subgroup's exclusion, one payer on the policy roundtable shared that they were waiting for more data and post-approval trial outcomes prior to placing insulin degludec on the formulary.

Researchers

- Further study is required to better understand the long-term effects of hypoglycemia, including non-severe events. While there are a variety of approaches to manage hypoglycemia and other DM symptoms, ranging from newer insulins with longer half-lives and steadier pharmacokinetics like insulin degludec; to the use of insulin in combination with other diabetes medications; to the adjustment of HbA1c goals; to ensuring that good standard of care is met, there are still many unanswered questions regarding the effects of hypoglycemia. Further research is needed to better understand:

    - The short- and long-term health effects of hypoglycemic episodes
    - The decrement in quality of life associated with hypoglycemia

- Further research is needed to determine insulin degludec's effectiveness relative to other insulins, particularly for patients with type 1 DM. Current clinical evidence is insufficient to demonstrate consistent or statistically significant reductions in hypoglycemic events for this patient population.

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This is the first CTAF review of insulin degludec.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

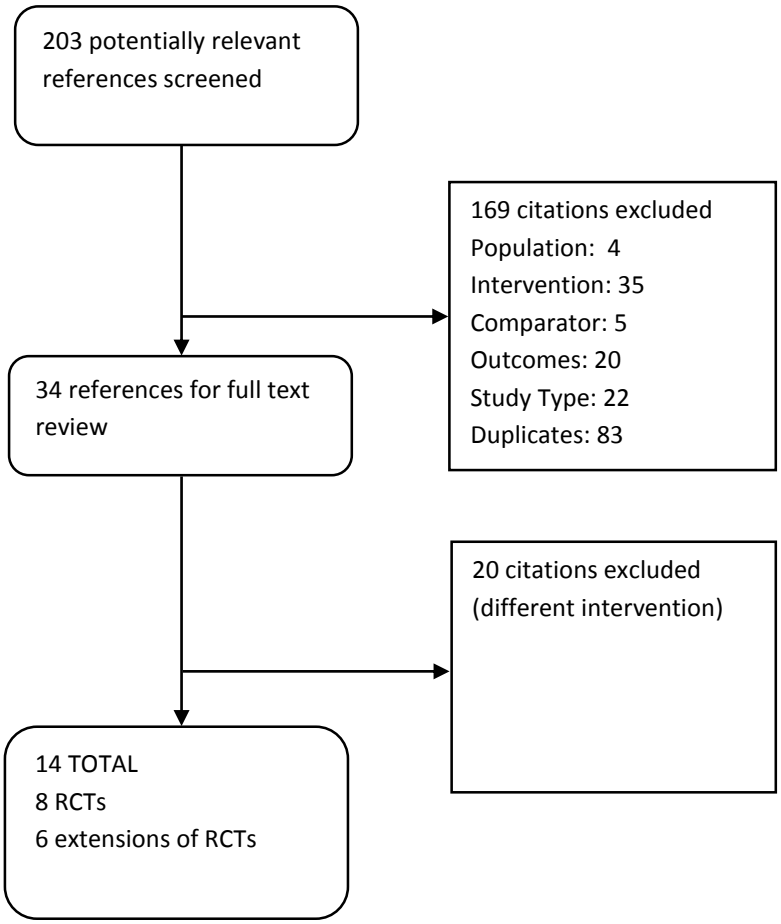
Table A2. Search Strategies for Insulin Degludec

PUBMED
Degludec – 188 articles
Limits: Randomized Controlled Trial, Systematic Review, Meta-analyses – 52 articles

EMBASE
Degludec AND [randomized controlled trial]/lim
Results: 48

Cochrane
Degludec – 112 articles
Limit to Trials – 103 articles

Figure A1. PRISMA flow Chart Showing Results of Literature Search for insulin Degludec



Appendix B. Clinical Guidelines

American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE), 2016

https://www.aace.com/publications/algorithm

The AACE/ACE guidelines recommend a HbA1c target of ≤6.5% for patients without serious concurrent illness and low risk of hypoglycemia, but notes that targets of >6.5% may be appropriate for patients with serious concurrent illness and at risk for hypoglycemia. The guidelines additionally remark on the importance of avoiding hypoglycemia, noting that several large RCTs have shown that type 2 DM patients with a history of one or more severe hypoglycemic events have a death rate two to four times higher than patients without the same history.

Lifestyle modification is recommended as a first-line therapy for type 2 DM. Patients who require pharmacological therapy and are unable to achieve HbA1c <7.5% after three months of monotherapy with metformin or other first-line agent should add of a second agent to treatment. In order of decreasing preference, the second agent should be a glucagon-like peptide-1 (GLP-1) receptor agonist, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, dipeptidyl peptidase 4 (DPP-4) inhibitor, thiazolidinedione (TZD), basal insulin, colesevelam, bromocriptine QR, alpha-glucosidase (AG) inhibitors, and sulfonylureas/glinides. If HbA1c does not decrease below 7.5% after three months of dual therapy with one of the aforementioned second agents, triple therapy is recommended following a similar hierarchy (DPP-4 inhibitors are moved below basal insulin). Treatment for asymptomatic patients with HbA1c >9.0% should begin at the dual or triple therapy level. Symptomatic patients should be treated with insulin (with or without other agents). TZD, basal insulin, and sulfonlyureas/glinides should be used with caution due to their associated risks.

The guidelines note that basal insulin analogs are preferred over NPH insulin because they produce a flat response for approximately 24 hours. Physicians should consider discontinuing or reducing the use of sulfonylureas after adding basal insulin to a patient's regimen. Patients who are unable to achieve glycemic control goal after the addition of basal insulin should initiate prandial control through the addition of a GLP-1 receptor agonist, SGLT-2 inhibitor, or a DPP-4 inhibitor; or through the addition of a prandial insulin dose of 50% basal insulin analog and 50% prandial analog. NPH, regular, and premixed insulin are noted to be less desirable than insulin analogs.

In a description of the principles behind the guidelines statement for the treatment of type 2 DM, the authors note that priority was given to minimizing the risk of hypoglycemia due to safety, adherence, and cost considerations, further explaining that "safety and efficacy should be given higher priorities than initial acquisition cost of medications per se since cost of medications is only a small part of the total cost of care of diabetes."

American College of Physicians (ACP), 2012

http://annals.org/article.aspx?articleid=1033354

The ACP recommends determining HbA1c goals based on individual patient assessment but notes that goals of less than 7.0% are reasonable for many patients. The ACP guidelines recommend lifestyle modification as a first-line treatment for type 2 DM. Patients who require pharmacologic therapy should begin with metformin alone, adding a second agent when lifestyle changes and metformin alone do not bring the patient to a reasonable HbA1c target. They do not offer specific preference as to which agents may be most suitable as second-line options.

American Diabetes Association (ADA), 2016

http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf

The ADA recommends that patients with type 1 DM be treated with multiple-dose insulin injections per day of basal and prandial insulin, or by continuous subcutaneous insulin infusion, and that most patients should receive insulin analogs to lower the risk of hypoglycemia.

The ADA recommends an HbA1c goal of less than 7.0% for many adults with type 2 DM but notes that a goal of 6.5% is appropriate for patients without significant hypoglycemia or other adverse effects of treatments. A goal of HbA1c <8.0% should be considered for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, many comorbidities, or who have been unable to achieve goals with education and appropriate pharmacological care.

Lifestyle modification should be the first line of therapy for most patients with type 2 DM. Patients with type 2 DM requiring pharmacological intervention should begin with metformin monotherapy, unless contraindicated. Patients with recent diagnoses of type 2 DM who are symptomatic and have elevated blood glucose levels or HbA1c should be considered for insulin therapy, with or without other agents. Similarly, physicians should add a second-line agent (i.e. oral agent, GLP-1 receptor agonist, basal insulin) to metformin therapy for patients who are unable to achieve HbA1c control after three months of non-insulin monotherapy. If the second-line agent chosen is insulin, the ADA recommends that physicians begin with basal insulin alone. If a patient is unable to achieve control with the basal insulin, the further addition of a rapid-acting insulin or a change to premixed insulin is recommended. If neither of the latter two strategies are effective at controlling a patient's diabetes, two or more rapid insulin injections should be considered (i.e., basal-bolus therapy). The ADA encourages patient-centered approaches to drug selection that take efficacy, cost, side effects, weight, comorbidities, risk of hypoglycemia, and patient preferences into account.

The ADA guidelines additionally note that higher concentrations of insulin such as insulin glargine U300 and insulin degludec U200 allow higher doses of insulin to be administered in smaller volumes, but are more expensive and may be more complicated for patients to properly dose.

American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD), 2012

http://care.diabetesjournals.org/content/35/6/1364.full

The ADA recommends a HbA1c target of 7.0% for most patients to reduce the incidence of microvascular disease. HbA1c targets of 6.0% to 6.5% may be appropriate for patients with short disease duration, long life expectancy, or the absence of significant cardiovascular disease if the targets are reachable without significant hypoglycemia. For patients with a history of hypoglycemia, low life expectancy, advanced complications, significant comorbidity, or who have difficulty reaching HbA1c goals despite education and appropriate pharmacological management, targets of 7.5% to 8.0% may be appropriate.

The ADA/EASD guidelines recommend the addition of either a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin for dual therapy regimens if the patient does not reach their individualized HbA1c target after three months of monotherapy with metformin (or an alternative first-line medication, in patients unable to tolerate metformin). They do not offer a suggested hierarchy for second-line prescription but instead emphasize that the decision should be based on individual patient factors and drug characteristics. Patients with HbA1c >9.0% should begin treatment the dual-therapy level or with insulin therapy due to the low probability of their achieving control through monotherapy. If HbA1c control is not achieved after three months at the dual therapy level, triple-therapy may be initiated. If therapy that includes basal insulin fails to achieve control after three to six months, insulin strategies comprising multiple daily injections should be explored.

Basal insulin may be considered as first-line therapy if the patient is significantly hyperglycemic and/or symptomatic. Either NPH insulin, insulin glargine, or insulin detemir may be used, though the guidelines note that the latter two options are associated with lower incidence of nocturnal hypoglycemia and insulin detemir is associated with lower weight gain. These potential benefits for insulin detemir and glargine are moderated by their increased cost. Patients whose insulin secretory capacity is reduced may require the addition of short-acting prandial insulin.

International Diabetes Federation (IDF), 2012

http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf

The IDF guidelines recommend that patients attempt to reach HbA1c levels below 7.0% to reduce the risk of complications and note that lower goals are appropriate for patients who are able to reach them safely and easily. Higher goals should be considered for patients with comorbidities or who experience hypoglycemia.

The guidelines recommend basal insulin used when sulfonylureas, rapid-acting insulin secretagogues, AG inhibitors, DPP-4 inhibitors, or TZD no longer result in glucose control in combination with metformin. NPH insulin, insulin glargine, insulin detemir, and biphasic insulin are recommended. If control is not achieved with the aforementioned treatment strategy, basal-bolus insulin should be attempted.

US Department of Veteran Affairs (VA) / Department of Defense (DOD), 2010

http://www.healthquality.va.gov/guidelines/cd/diabetes/index.asp

The VA/DOD recommends that all patients with type 1 DM receive insulin replacement therapy.

The guidelines recommend setting individualized HbA1c goals but note that all patients with type 2 DM should target HbA1c levels below 9.0%. Patients with few or no microvascular complications, no major concurrent illness, and life expectancy of at least 10-15 years should set HbA1c goals of 7.0% or lower. Patients with type 2 DM of duration longer than 10 years, with comorbid conditions, and who require therapy with multiple pharmacologic agents including insulin should set HbA1c targets below 8.0%. Targets of 8.0% to 9.0% are appropriate for individuals with advanced microvascular complications, major comorbid illness, or life expectancy of fewer than five years. The VA/DOD recommends considering the risk of hypoglycemia when setting HbA1c goals for any patient.

Diet and exercise modification should be the first-line therapy in all patients with type 2 DM. Insulin should be considered for all patients with severe hyperglycemia. Metformin or a sulfonylurea should be used as a first-line pharmacological agents, and patients unable to tolerate either should attempt monotherapy with a TZD, AG inhibitor, meglitinide, DPP-4 inhibitor, or GLP-1 agonist. The VA/DOD recommends metformin with a sulfonylurea as the preferred combination therapy, with the same alternative therapies above listed as alternatives for patients unable to tolerate metformin of a sulfonylurea.

Intermediate- or long-acting insulins should be used as basal insulins, with insulin glargine and detemir reserved for patients who experience frequent or severe nocturnal hyperglycemia on NPH insulin. Regular insulin or short-acting insulin analogues should be added for patients who require prandial coverage.

National Institute for Health and Care Excellence (NICE), 2015

Type 1 DM

http://www.nice.org.uk/guidance/ng17

NICE recommends setting HbA1c goals of lower than 6.5% for patients with type 1 DM to minimize the risk of microvascular complications. Individualized targets should be set, however, based on a patient's daily activities, preferences, likelihood of complications, comorbidities, occupation, and risk of hypoglycemia.

The guidelines recommend that basal-bolus regimens be used as first-line treatment for adults with type 1 DM. Twice daily pre-mixed insulin, basal insulin-only, and bolus insulin-only are not recommended for patients with newly diagnosed type 1 DM, with insulin detemir listed as the first choice for basal insulin. However, NICE recommends keeping patients who are able to achieve agreed-upon targets on pre-existing regimens, even if they differ from the above options. Physicians should offer once-daily insulin glargine or insulin detemir for patients who are not amenable to twice-daily injections and should offer insulin glargine to patients who are unable to tolerate insulin detemir. Other insulin regimens should be considered only if the above recommendations do not achieve glucose control; when choosing an alternative treatment in this case, patient preference and acquisition cost should be considered.

Prandial injections of rapid-acting human or animal insulins are not recommended for type 1 DM patients; rapid-acting insulin analogues should be used instead. If multiple daily basal-bolus injections are not possible, patients should be offered twice-daily human mixed insulin regimens as an alternative. Patients who experience hypoglycemia when using premixed human insulin should be switched to a premixed insulin analog.

Type 2 DM

http://www.nice.org.uk/guidance/ng28/

NICE recommends that patients set a goal HbA1c of 6.5% if they are able to control type 2 DM through diet and lifestyle, or by diet, lifestyle, and a drug not associated with hypoglycemia. Adults on a drug associated with hypoglycemia should aim for a higher HbA1c goal of 7.0%. Patients who are unable to achieve control with a single drug and who have HbA1c of 7.5% or higher should be given counseling for diet, lifestyle, and treatment adherence with a goal of reaching HbA1c of 7.0%. Physicians should consider less stringent HbA1c goals on an individual basis for patients who are unlikely to achieve long-term risk-reduction benefits, are at high risk of hypoglycemia, or who have significant comorbidities.

The guidelines recommend the initiation of insulin therapy if a patient is unable to achieve agreed-upon HbA1c goals with metformin alone, and is subsequently unable to achieve control through dual therapy with metformin and a sulfonylurea, DPP-4 inhibitor, pioglitazone, sulfonylurea, or SGLT-2 inhibitor. Use of metformin should continue following the initiation of insulin therapy, and physicians should review whether the use of other blood glucose lowering therapies should continue. Patients should also be considered candidates for insulin therapy if they are unable to achieve control on therapy with two oral agents not including metformin.

NICE guidelines offer several options for initiating insulin therapy including NPH insulin twice daily, a combination of NPH and short-acting insulin (recommended for patients with HbA1c of 9.0% or greater), insulin detemir or glargine, or pre-mixed NPH insulin and short-acting insulin analogues. A patient should be switched to insulin detemir or glargine from NPH insulin if he or she has significant problems with hypoglycemia, cannot properly use the NPH insulin injection device, or would be able to reduce caregiver burden by decreasing the number of daily injections.

Canadian Agency for Drugs and Technology in Health (CADTH), 2013

https://www.cadth.ca/media/pdf/OP0512_Diabetes_RecsReport_2nd_3rd-line_e.pdf

CADTH recommends that sulfonylureas be added to metformin before attempting other options. NPH insulin should be added for patients who are unable to achieve control with metformin and a sulfonylurea; a DPP-4 inhibitor should replace NPH insulin when the latter is unsuccessful at achieving control.

Appendix C. Public and Representative Private Insurer Coverage Policies

Given insulin degludec's recent approval (September 2015), coverage policy may still be under development for many payers. We supplemented our search for coverage policy on insulin degludec with summaries of existing policies for insulins detemir, glargine (U100 and U300), and NPH insulin as a model for coverage for long-acting insulins.

National Public Payers

Centers for Medicare & Medicaid Services[28]

We were unable to find any National Coverage Determinations or Local Coverage Determinations pertaining to long-acting insulins from the Centers for Medicare & Medicaid Services (CMS).

Medi-Cal, California's Medicaid agency, covers insulin glargine U100, regular insulin, and NPH insulin, but requires authorization for insulin detemir except for claims with dates of service from July 1, 2006 through September 30, 2012. Beneficiaries wishing to receive continued coverage for insulin detemir must have had a claim for insulin detemir submitted and paid before September 30, 2012, and must not have not gone more than 100 days without a submitted and paid claim for the drug. Unless authorization is granted, full payment for insulin detemir is limited to three claims every 75 days; the fourth claim within that period will be reimbursed at drug ingredient cost only. Insulin degludec and insulin glargine U300 are not currently listed in the Medi-Cal Contract Drug List.

Medicare Part D

Coverage for long- and intermediate-acting insulins is provided through the Medicare Part D Plans (PDPs); variations among offered plans are described below.

Aetna[31-33]

Aetna does not currently list insulin degludec or insulin glargine U300 in any of their publicly available Medicare PDPs. The payer covers insulin detemir and Novolin N insulin at the third tier of its Medicare Rx Saver and Medicare Rx Premier PDPs (as of January 1, 2016, Aetna's Medicare Rx Premier PDPs are offered through Coventry Health, an Aetna subsidiary).[83] Insulin glargine U100 is covered at the third tier of Aetna's Medicare Rx Premier plans, and Humulin N is covered at the fourth tier of the Premier plan, subject to step-therapy requirements: a one-month trial of Novolin N insulin is required before coverage will be provided for Humulin N insulin.

Anthem[34]

Insulin degludec is not included in any of Anthem's PDPs. Anthem covers insulins detemir, glargine (U100 and U300), Humulin N, and Novolin N at the second tier in six out of the seven PDPs it offers. For its L5TC PDP, insulins glargine (U100 and U300) and Humulin N are covered at the third tier, insulin detemir is covered at the fourth tier, and Novolin N is excluded from the formulary.

CIGNA[37,38]

CIGNA covers insulins detemir, glargine (U100 and U300), and Humulin N at the third tier of its Rx Secure and Rx Secure-Extra PDPs. Novolin N insulin is excluded from the formulary.

Humana[40]

Humana includes insulins degludec, detemir, glargine (U100 and U300), Humulin N, and Novolin N at the third tier of most PDPs. All of the above insulins are covered at the third tier of the payer's Plus-5 and Plus-6 MAPD CSNP plans with the exception of subcutaneous solutions of insulin detemir U100, Humulin N, and Novolin N, which are covered at the second tier. All of the insulins listed above are covered at the second tier of Humana's Dual Eligible MMP PDP, with the exception of Humulin N, which is not included.

UnitedHealthcare[29,30]

UHC covers insulins detemir, glargine U100, and Humulin N at the third tier of its Medicare Rx Preferred and Medicare Rx Saver Plus PDPs. Insulin degludec, the U300 concentration of insulin glargine, and Novolin N are all excluded from the formularies.

Health Net[39]

Health Net does not list insulin degludec in any of its publicly available Medicare PDPs. The payer covers insulins detemir, glargine (U100 and U300), and Humulin N at the third tier of its Value formulary, while Novolin N is relegated to the fourth tier.

Blue Shield of California[35,36]

BSCA covers insulins detemir, glargine U100, and Humulin N at the third tier of its Medicare Basic and Enhanced plans. Insulin degludec, insulin glargine U300, and Novolin N are excluded from the formularies.

National Private Payers

Aetna[41]

Aetna covers insulin degludec at the third tier of the majority of its formularies, and the drug is generally subject to step therapy requirements that patients attempt either insulin glargine U100 or insulin detemir for one month.

Aetna covers insulin detemir at the second tier and insulin glargine U100 at the third tier of most of their plans. Some plans require patients attempt insulin detemir before authorization for insulin glargine will be granted. Insulin glargine U300 is usually covered at the third tier, Aetna generally requires a one-month trial of insulin detemir before granting authorization. Aetna covers NPH insulin, with Humulin N at the second tier and Novolin N at the third tier of most plans. Broadly, patients are required to attempt therapy with Humulin before moving to Novolin.

Anthem[42]

Anthem covers insulin degludec at the third tier of its four-tier Preferred Drug List, and excludes the drug from all other formularies. The payer covers NPH insulins, insulin glargine U100, and insulin detemir at the second tier of its drug lists. Insulin glargine U300 is relegated to the third tier of the payer's three- and four-tier National Plans and its four-tier preferred drug list, and it is excluded from the formulary for its California select drug list and its essential drug list.

Cigna[43]

Cigna covers insulin degludec and insulin glargine U300, subject to prior authorization, at the third tier of its Legacy plan and its Advantage and Value without DRT plans; the payer excludes the drug from all other formularies. Cigna covers insulin glargine U100 and Humulin N at the second tier of most of its formularies. The payer covers insulin detemir and Novolin N at the third tier of its Advantage and Value without DRT plans, at the second tier of its Legacy, Performance, and Standard plans, and excludes the drugs from its Advantage and Value plans. Insulin detemir and Humulin N are covered at the second tier of the payers Individual and Family plans for California, while all other insulins are excluded.

Humana[40,44]

Humana covers insulin degludec subject to prior authorization for patients who have previously been treated with or demonstrated intolerance to all concentrations of insulin glargine and insulin detemir. None of Humana's publicly available formularies, however, include insulin degludec, and we were unable to locate any publicly available documentation that resolved this apparent conflict.

Humana general covers Humulin N, insulin detemir, and insulin glargine U100 at the second tier of its drug lists. Novolin N is included at the third or fourth tier with equal frequency, and is subject to undescribed step therapy requirements in all cases. Humana generally excludes insulin glargine U300 from its formularies, but covers it at the second tier in two of its essential health benefits formularies. Novolin N is included with equal frequency at the third and fourth tier, and is subject to prior authorization.

UnitedHealthcare[84]

Insulin degludec and insulin glargine U300 are not currently listed on UnitedHealthcare's (UHC) publicly available drug list. UHC covers insulin detemir in the first tier of its prescription drug list and U100 insulin glargine U100 at the third tier. UHC places Humulin N vials in the first tier of its formulary, with the pen form relegated to the second tier. Novolin N is listed under the third (or fourth, in unspecified cases) tier of the UHC drug list, and is subject to prior authorization.

Regional Private Payers

Health Net[39]

Health Net lists insulin degludec at the third tier of its California Essential Rx and 3-Tier with Specialty drug lists; the drug is not listed in any other publicly available formularies. The payer places insulin glargine U100 and U300, insulin detemir, and Humulin N at the second tier of its two- and three-tier recommended drug lists as well as its California essential drug list. Novolin N is listed at the third tier of both California drug lists and its three-tier drug list and is subject to step therapy requirements; the insulin is not included in the payer's two-tier list.

Blue Shield of California[45]

Blue Shield of California (BSCA) excludes insulin degludec from their commercial formulary, although coverage may be granted at the third tier if the insulin is deemed to be medically necessary. The payer includes insulin detemir, insulin glargine U100, and Humulin N at the second tier of its commercial formulary. insulin glargine U300, Humulin N delivered via Kwikpen, and Novolin N are not included in the formulary but may be covered at the third-tier if determined to be medically necessary.

Pharmacy Benefit Managers

CVS/caremark[85]

CVS/caremark includes insulin degludec, insulin detemir, insulin glargine U100 and U300, and Novolin N on its Performance Drug List. Humulin N is not listed in the drug list.

Appendix D. Previous Systematic Reviews and Technology Assessments

We identified 11 systematic reviews of insulin degludec:

a. Dzygalo K, Golicki D, Kowalska A, Szypowska A. The beneficial effect of insulin degludec on nocturnal hypoglycaemia and insulin dose in type 1 diabetic patients: A systematic review and meta-analysis of randomised trials. *Acta Diabetologica.* 2015;52(2):231-238.

b. Einhorn D, Handelsman Y, Bode BW, Endahl LA, Mersebach H, King AB. Patients achieving good glycemic control (HbA1c <7%) experience a lower rate of hypoglycemia with insulin degludec than with insulin glargine: a meta-analysis of Phase 3A trials. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2015;21(8):917-926.

c. Freemantle N, Evans M, Christensen T, Wolden ML, Bjorner JB. A comparison of health-related quality of life (health utility) between insulin degludec and insulin glargine: A meta-analysis of phase 3 trials. *Diabetes, Obesity & Metabolism.* 2013;15(6):564-571.

d. Freemantle N, Meneghini L, Christensen T, Wolden ML, Jendle J, Ratner R. Insulin degludec improves health-related quality of life (SF-36(R)) compared with insulin glargine in people with Type 2 diabetes starting on basal insulin: A meta-analysis of phase 3a trials. *Diabetic Medicine: A Journal of the British Diabetic Association.* 2013;30(2):226-232.

e. Heller S, Mathieu C, Kapur R, Wolden ML, Zinman B. A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia. *Diabetic Medicine: A Journal of the British Diabetic Association.* 2015.

f. Monami M, Mannucci E. Efficacy and safety of degludec insulin: A meta-analysis of randomised trials. *Current Medical Research and Opinion.* 2013;29(4):339-342.

g. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: A pre-planned meta-analysis of phase 3 trials. *Diabetes, Obesity & Metabolism.* 2013;15(2):175-184.

h. Rodbard HW, Gough S, Lane W, Korsholm L, Bretler DM, Handelsman Y. Reduced risk of hypoglycemia with insulin degludec versus insulin glargine in patients with type 2 diabetes requiring high doses of basal insulin: A meta-analysis of 5 randomized BEGIN trials. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2014;20(4):285-292.

i. Russell-Jones D, Gall MA, Niemeyer M, Diamant M, Del Prato S. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD.* 2015;25(10):898-905.

j. Sorli C, Warren M, Oyer D, Mersebach H, Johansen T, Gough SC. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: A meta-analysis of phase IIIa trials. *Drugs & Aging.* 2013;30(12):1009-1018.
k. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: A meta-analysis of endpoints in phase 3a trials. *Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders.* 2014;5(2):435-446.

These systematic reviews focused on the seven RCTs comparing insulin degludec to insulin glargine U100. They consistently report equivalent glycemic control assessed by HbA1c or fasting plasma glucose and lower rates of hypoglycemic events, particularly nocturnal hypoglycemia. Ratner and colleagues had access to patient-level data from all seven trials.[18] Their results offer the most complete assessment. Among insulin-naive patients with type 2 DM, they found significantly lower rates of overall confirmed (estimated rate ratio (RR) 0.83; 95% CI: 0.70, 0.98), nocturnal confirmed (RR: 0.64; 95% CI: 0.48, 0.86), and severe hypoglycemic episodes (RR 0.14; 95% CI: 0.03, 0.70) with degludec compared with glargine U100. Among patients with type 1 DM, they found the rate of nocturnal confirmed episodes was significantly lower with degludec during maintenance treatment (RR 0.75; 95% CI: 0.60, 0.94). These systematic reviews also note that the findings are similar for patients over the age of 65 years and for patients achieving an HbA1c <7%.

Two of these systematic reviews and meta-analyses focused on quality of life.[60,61] The first summarized the SF-36 results from three of the trials in patients with type 2 DM and found significant improvements with insulin degludec for the domains of Bodily Pain (1.10 points; 95% CI: 0.22, 1.98), Physical Health (0.66 points; 95% CI: 0.04, 1.28), and Vitality (0.81 points; 95% CI: 0.01, 1.59). The SF-36 uses a 100-point scale with a minimally clinically important difference of about 10 points. The same investigators mapped the SF-36 results from six trials to the EuroQoL5D instrument and found that insulin degludec increased the health state quality of life by 0.005 (95% CI: 0.0006, 0.009) on a scale ranging from -0.59 to 1.00.

Appendix E. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Insulin degludec					
A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) **NCT01959529**	RCT	Insulin glargine	N = 7637 Type 2 DM Age ≥ 50 years Known CVD, renal disease or multiple risk factors for CVD	Time to first major adverse cardiovascular event (MACE: CVD death, non-fatal MI, non-fatal stroke)	September 2016

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix F. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study. We excluded trials that evaluated non-standard dosing such as every other day insulin degludec or "flex" dosing that alternates morning and nighttime dosing (alternating 8 and 40 hours between doses) unless the trials also included an arm with usual daily dosing of the basal insulin.

We also included FDA documents related to insulin degludec. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Of note, a combination of insulin degludec and shorter-acting insulin aspart has also been studied and approved by the FDA, but as of this writing there are no public announcements suggesting that this combination will be marketed in the US. These studies were therefore excluded from the assessment.

Our review team extracted information from the accepted studies and developed data summary tables (Appendix Tables F1 though F4).

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[48] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of six months follow-up, clearly defined entry criteria, and use of consecutive samples of patients.

Table F1. Overview of Studies

										Race, %										Diabetes complications, %					
Reference	**Study**	**N**	**FU, Months**	**Treatment**	**Control**	**Population**	**Age, years**	**Sex, %F**	*White*	*Black*	*Asian*	*Other*	**Diabetes duration, years**	**A1c, %**	**BMI, kg/m2**	**Weight, kg**	**SBP, mm Hg**	**DBP, mm Hg**	**LDL, mg/dL**	**HDL, mg/dL**	*Neuropathy*	*Retinopathy*	*Nephropathy*	*Microalbuminuria*	*Hypertension*	*Arteriosclerosis*
Degludec																										
Type 1 DM Basal bolus																										
Heller 2012	BEGIN T1 Long	629	12	Degludec U100	Glargine	Age 18 +, DM2 > 12 months, A1c ≤10, BMI≤35, on basal bolus insulin	43	41	93	2	1	4	19	7.7	26	79	122	74	96	61	NR	NR	NR	NR	NR	NR
Davies 2014	BEGIN Basal Bolus T1	456	6	Degludec U100	Detemir	Age 18 +, DM2 > 12 months, A1c ≤10, BMI≤35, on basal bolus insulin	41	48	45	0.4	54	0.7	14	8	24	67	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mathieu 2013	BEGIN Flex T1	493	6	Degludec U100	Glargine	Age 18 +, DM2 > 12 months, A1c ≤10, BMI≤35, on basal bolus insulin	44	42	98	2	0.4	0.2	19	7.7	NR	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Type 2 DM Basal only																										
Zinman 2012	BEGIN Once Long	1030	12	Degludec U100	Glargine	Age 18 +, DM2 > 6 months, A1c 7-10, BMI≤40, no insulin	59	38	88	7	2	2	9	8.2	31	90	134	80	94	44	7.7	2.7	1.6	1.1	72	1.2
Gough 2013	BEGIN Low	460	6	Degludec U200	Glargine	Age 18 +, DM2 > 6 months, A1c 7-10, BMI≤45, no insulin	58	47	78	14	4	11	8	8.3	32	92	131	79	94	43	NR	NR	NR	NR	NR	NR
Onishi 2013	BEGIN Once Asia	435	6	Degludec U100	Glargine	Age 18 +, DM2 > 6 months, A1c 7-10, BMI≤35, no insulin	59	46	0	0	100	0	12	8.5	25	66	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Meneghini 2013	BEGIN Flex	687	6	Degludec U100	Glargine	Age 18 +, DM2 > 6 months, A1c 7-10, BMI≤40	56	46	67	2	30	1	11	8.4	30	82	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Type 2 DM Basal Bolus treatment																										
Garber 2012	BEGIN Basal Bolus T2	984	12	Degludec U100	Glargine	Age 18 +, DM2 > 6 months, A1c 7-10, BMI≤40, on insulin	59	46	83	9	6	1	14	8.3	32	93	NR	NR	97	47	NR	NR	NR	NR	NR	NR

FU: Follow-Up; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; NR: Not Reported; T1: Type 1; T2: Type 2

Table F2. Quality Metrics

Reference	Study	Adequate randomization	Allocation concealment	Patent blinding	Staff blinding	Outcome adjudication blinding	Completeness of follow-up	Intention to treat analysis	Incomplete data addressed	Selective outcome reporting	Industry funding	Free from other bias	Overall quality
Degludec													
Type 1 DM Basal Bolus													
Heller 2012	BEGIN T1 Long	Yes	Unclear	No	Partial	Partial	86%	Yes	Yes	No	Yes	Yes	Fair
Davies 2014	BEGIN Basal Bolus T1	Yes	Unclear	No	Partial	Partial	92%	Yes	Yes	No	Yes	Yes	Fair
Mathieu 2013	BEGIN Flex T1	Yes	Unclear	No	Partial	Partial	84%*	Yes	Yes	No	Yes	Yes	Fair
Type 2 DM Basal only													
Zinman 2012	BEGIN Once Long	Yes	Unclear	No	Partial	Partial	79%	Yes	Yes	No	Yes	Yes	Fair
Gough 2013	BEGIN Low	Yes	Unclear	No	Partial	Partial	87%	Yes	Yes	No	Yes	Yes	Fair
Onishi 2013	BEGIN Once Asia	Yes	Unclear	No	Partial	Partial	91%	Yes	Yes	No	Yes	Yes	Fair
Meneghini 2013	BEGIN Flex	Yes	Unclear	No	Partial	Partial	89%	Yes	Yes	No	Yes	Yes	Fair
Type 2 DM Basal Bolus treatment													
Garber 2012	BEGIN Basal Bolus T2	Yes	Unclear	No	Partial	Partial	82%	Yes	Yes	No	Yes	Yes	Fair
* More AE-related withdrawals in the degludec arms including hypoglycemia. Overall withdrawals 15.8% in degludec arm; 15.9% in the degludec Flex arm, and 7.3% in the glargine arm.													

T1: Type 1; T2: Type 2

Table F3. Outcomes

Reference	Study	Intervention	N	A1c	Annual Rate Hypoglycemia	Annual Rate Severe Hypoglycemia	Annual Rate Nocturnal Hypoglycemia	Change in weight	Final basal insulin dose, units/kg	SF36 other domains
Degludec										
Type 1 DM Basal bolus										
Heller 2012	BEGIN T1 Long	Degludec U100 basal bolus	472	-0.4%	42.5	0.21	4.4	1.8	0.35	
		Glargine basal bolus	154	-0.4%	40.2	0.16	5.9	1.6	0.39	
		Rate ratio or difference		-0.01% (-0.14 to 0.12)	1.07 (0.89-1.28)	1.38 (0.72-2.64)	0.75 (0.59-0.96)	0.2 (p=0.62)	p<0.001	0/10 significant
Davies 2014	BEGIN Basal Bolus T1	Degludec U100 basal bolus	302	-0.73%	45.8	0.31	4.14	1.5	0.54	
		Detemir basal bolus	153	-0.65	45.7	0.39	5.93	0.4	0.63	
		Rate ratio or difference		-0.09% (-0.23 to 0.05)	0.98 (0.80-1.20)	0.92 (0.46-1.81)	0.66 (0.49-0.88)	1.1 (0.6-1.6)		NR
Mathieu 2013	BEGIN Flex T1	Degludec U100 daily	165	-0.4%	88.3%	0.4%	9.6%	NR	0.33	
		Glargine	164	-0.6%	79.7%	0.5%	10.0%	NR	0.42	
		Rate ratio or difference		0.17% (0.04-0.30)	NR	NR	NR	NR	NR	NR
		Degludec U100 Flex	164	-0.4%	82.4%	0.3%	6.2%	NR	0.35	
Type 2 DM Basal only										
Zinman 2012	BEGIN Once Long	Degludec U100 daily	773	-1.1%	1.5	0.003	0.25	2.4 kg	0.59	
		Glargine	257	-1.2%	1.9	0.023	0.39	2.1 kg	0.60	
		Rate ratio or difference		0.09% (-0.04 to 0.22)	0.82 (0.64-1.04)	0.14 (0.03-0.70)	0.64 (0.42-0.98)	0.3 NS		2/10 significant: Physical functioning and Overall Physical favors degludec
Gough 2013	BEGIN Low	Degludec U200 daily	228	-1.3%	1.2	0	0.18	1.9 kg	0.53	
		Glargine	229	-1.3%	1.4	0	0.28	1.5 kg	0.60	
		Rate ratio or difference		0.04% (-0.11 to 0.19)	0.86 (0.58-1.28)		0.64 (0.30-1.37)	0.44 (-0.20 to 1.08)	p<0.05	2/10 significant: Bodily Pain and Vitality favors degludec
Onishi 2013	BEGIN Once Asia	Degludec U100 daily	289	-1.2%	3.0	0.00	0.8	1.3 kg	0.28	
		Glargine	146	-1.3%	3.7	0.01	1.2	1.4 kg	0.35	
		Rate ratio or difference		0.11% (-0.03 to 0.24)	0.82 (0.60-1.11)		0.62 (0.38-1.04)	-0.17 kg (-0.59 to 0.26)	p<0.05	0/10 significant
Meneghini 2013	BEGIN Flex	Degludec U100 daily	226	-1.1%	3.6	0.02	0.6	1.6	0.5	
		Glargine	229	-1.3%	3.5	0.02	0.8	1.3	0.5	
		Rate ratio or difference		NR	NR	NS	NR	0.3 (NR)	NS	NR
		Degludec U100 Flex	230	-1.3%	3.6	0.02	0.6	1.5	0.5	
Type 2 DM Basal Bolus treatment										
Garber 2012	BEGIN Basal Bolus T2	Degludec U100 basal bolus	744	-1.1%	11.1	0.06	1.4	3.6	0.75	
		Glargine basal bolus	248	-1.2%	13.6	0.05	1.8	4	0.69	
		Rate ratio or difference		0.08% (-0.05 to 0.21)	0.82 (0.69-0.99)	NR	0.75 (0.58-0.99)	-0.4 (NS)	p<0.05	1/10 significant: Bodily Pain favors degludec

Table F4. Harms

Reference	Study	Intervention	N	Any AE	SAE	Death	Possibly Drug related	Discontinue due to AE	Injection reaction	MACE		
										N	*%*	*Rate per 100 person-years*
Degludec												
Type 1 DM Basal bolus												
Heller 2012	BEGIN T1 Long	Degludec U100 basal bolus	472	84%	10%	NR	6%	3%	3%	3	NR	NR
		Glargine basal bolus	154	83%	11%	NR	5%	1%	5%	1	NR	NR
Davies 2014	BEGIN Basal Bolus T1	Degludec U100 basal bolus	301	73%	7%	0%	22%	1%	4%	0	0%	0
		Detemir basal bolus	152	74%	5%	0%	21%	1%	2%	0	0%	0
Mathieu 2013	BEGIN Flex T1	Degludec U100 basal bolus	165	76%	4.2%	0.6%	19%	2.4%	1.8%	3*	NR	NR
		Glargine basal bolus	161	72%	5.0%	0.0%	16%	0.6%	2.5%		NR	NR
		Degludec U100 Flex	164	68%	5.5%	0.0%	21%	3.0%	4.9%		NR	NR
Type 2 DM Basal only												
Zinman 2012	BEGIN Once Long	Degludec U100	773	75%	8%	0.1%	12%	3%	6%	12	1.6	13
		Glargine	257	71%	10%	0.4%	14%	2%	7%	2	0.8	2
Gough 2013	BEGIN Low	Degludec U200	228	65%	7%	0.0%	NR	1.8%	2%	NR	NR	NR
		Glargine	228	68%	4%	0.9%	NR	2.2%	0%	NR	NR	NR
Onishi 2013	BEGIN Once Asia	Degludec U100	289	59%	3%	0%	8%	0.7%	1.8%	NR	NR	NR
		Glargine	146	65%	6%	0%	5%	2.1%	2.1%	NR	NR	NR
Meneghini 2013	BEGIN Flex	Degludec U100 daily	226	57%	4%	0.4%	9%	0.4%	3.5%	NR	NR	NR
		Glargine	229	56%	2%	0.4%	8%	0.9%	1.7%	NR	NR	NR
		Degludec U100 Flex	230	53%	3%	0%	11%	0.9%	1.3%	NR	NR	NR
Type 2 DM Basal Bolus treatment												
Garber 2012	BEGIN Basal Bolus T2	Degludec U100 basal bolus	753	81%	15%	1.1%	20%	4%	4%	NR	NR	3
		Glargine basal bolus	251	79%	16%	0.8%	16%	4%	3%	NR	NR	2
* 3 adjudicated major adverse cardiovascular events (MACE) reported, but not reported by treatment group												

AE: Adverse Event; SAE: Serious Adverse Event; NR: Not Reported

Appendix G. Comparative Value Supplemental Information

Table G1. Model Parameters: Complication Costs (2014 $)

Input	Fatal	Non-Fatal	Subsequent Annual	Source
No complications	--	--	1,024	Assumption
Severe hypoglycemia	--	1,883	0	Leese 2003[69]
Mild/moderate hypoglycemia (both daytime and nocturnal)	--	0	0	Assumption
Ischemic heart disease	--	8,830	2,295	Zhuo 2013[72]
Myocardial infarction	25,615	44,761	2,474	Zhuo 2013[72]
Heart failure	--	11,768	4,029	Heidenreich 2013[73]
Stroke	61,644	61,644	20,566	Zhuo 2013[72]
Amputation	80,364	58,401	10,240	Zhuo 2013,[72] assumption (annual)
Blindness	--	1,894	6,247	Zhuo 2013[72]
Renal failure	82,673	82,673	82,673	Zhuo 2013[72]
Ulcer	--	16,271	1,024	Rice 2013[74]

Table G2. Model Parameters: Utility Decrements

Input	Time of Event	Subsequent Years	Source
Ischemic heart disease	0	0	Alva 2014 (UKPDS OM2 default value[78]
Myocardial infarction	-0.065	0	Alva 2014 (UKPDS OM2 default value[78]
Heart failure	-0.101	-0.101	Alva 2014 (UKPDS OM2 default value)[78]
Stroke	-0.165	-0.165	Alva 2014 (UKPDS OM2 default value)[78]
Amputation	-0.172	-0.172	Alva 2014 (UKPDS OM2 default value)[78]
Blindness	0	0	Alva 2014 (UKPDS OM2 default value)[78]
Renal failure	-0.330	-0.330	Lung 2011 (UKPDS OM2 default value)[86]
Ulcer	-0.210	-0.210	Lung 2011 (UKPDS OM2 default value)[86]

Table G3. Scenario Analysis Using Point Estimates for Hypoglycemia Events, HbA1c, and Weight Change (Regardless of Statistical Significance)*

		Type 1 DM		Type 2 DM Basal-only		Type 2 DM Basal-bolus	
		QALY	Total Costs	QALY	Total Costs	QALY	Total Costs
Insulin glargine U100	UKPDS	16.819	$95,748	11.972	$108,679	11.617	$214,130
	Hypoglycemia	-4.050	$9,037	-0.193	$1,086	-1.290	$2,684
	Total	12.769	$104,785	11.779	$109,765	10.327	$216,814
Insulin degludec	UKPDS	16.820	$99,386	11.950	$120,858	11.602	$253,638
	Hypoglycemia	-4.187	$11,862	-0.157	$543	-1.056	$3,221
	Total	12.632	$111,248	11.793	$121,401	10.546	$256,859
Increment (insulin degludec - insulin glargine U100)		-0.136	$6,463	0.014	$11,636	0.220	$40,045
Cost/QALY			Dominated		$807,942		$182,298

NOTE: UKPDS refers to projected clinical outcomes and costs regardless of insulin treatment, according to calculations in the UKPDS outcomes model.

* Future costs and QALYs are discounted 3% a year.

Table G4. Budget Impact Threshold Price Calculations

Population	(A) Average Person-Years	(B) Budget Impact/Year	(C) Difference from Threshold $904m – (B)	(D) Difference per Person-Year (C)÷(A)	(E) Base-case Price per Year	(F) Budget Impact Threshold Price (D)+(E)
Type 1 DM (n=54,889)	32,934	$5,903,440	$898,096,560	$27,270	$2,873	$30,142
Type 2 DM Basal-only (n=350,183)	210,111	$165,608,238	$738,391,762	$3,514	$5,486	$9,001
Type 2 DM Basal-bolus (n=155,202)	93,120	$246,769,352	$657,230,648	$7,058	$14,765	$21,823
Total (n=560,274)	336,165	$418,281,030	$2,293,718,970*	$6,823	$7,800	$14,624

*Sum of type 1 DM, type 2 basal-only, and type 2 basal-bolus differences.

Appendix H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the February 12, 2016 public meeting of the California Technology Assessment Forum.

Table H1. ICER Staff and Consultant Conflict of Interest Disclosures

Name	Organization	COI
Rick Chapman, PhD, MS	ICER	None
Sonya Khan, MPH	ICER	None
Daniel Ollendorf, PhD	ICER	None
Steven Pearson, MD, MSc	ICER	None
Matt Seidner, BS	ICER	None
Jeff Tice, MD	UCSF	None
Jed Weissberg, MD	ICER	None

Table H2. CTAF Panel Member COI Disclosures

Name	Organization	COI
Ralph Brindis, MD, MPH, MACC, FSCAI, FAHA	UCSF	*
Christine Castano, MD	HealthCare Partners Medical Group	*
Robert Collyar	Patient Advocates in Research	*
Meg Durbin, MD	Sutter Health/PAMF	*
Rena Fox, MD	UCSF	*
Marjorie E. Ginsberg, BSN, MPH	Center for Healthcare Decisions	*
Luanda Grazette, MD, MPH, FACC	USC	*
Kimberly Gregory, MD, MPH	Cedars-Sinai Medical Center	*
Paul Heidenreich, MD, MS (Vice-Chair)	Stanford University	*
Jeff Klingman, MD	The Permanente Medical Group	*
Joy Melnikow, MD, MPH	UC Davis	*
Robert E. Rentschler, MD	Beaver Medical Group	*
Rita F. Redberg, MD, MSc, FACC	UCSF	*
Michael Steinberg, MD	UCLA	*
Daniel J. Ullyot, MD (Chair)	Retired, UCSF	*

* No conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from relevant health care manufacturers or insurers

Table H3. Policy Roundtable Participant Disclosures

Name	Position and Organization	Conflict of Interest
Neal Kohatsu, MD, MPH	Medical Director, California Department of Health Care Services	No personal conflict. Full-time employee of California Department of Health Care Services
Elizabeth Murphy, MD, DPhil	Chief, Endocrinology and Metabolism Division and Director of Diabetes Center for High Risk Populations, San Francisco General Hospital; Professor of Clinical Medicine, UCSF	None declared.
Manuel Quiñones, MD	Internal Medicine and Diabetology, Healthcare Partners - Anaheim	Receipt of payments >$5,000 as part of service on advisory panels for Janssen Pharmaceuticals, AstraZeneca, Merck, and Novo Nordisk; speakers bureau for Janssen Pharmaceuticals, AstraZeneca, Novo Nordisk, and GlaxoSmithKline.
Tony Van Goor, MD, MMM, CPE, FACP	Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California	Full-time employee of Blue Shield of California with equity interest > $10,000

No conflicts of interest were declared by ICER staff. No relevant conflicts of interest were declared by the CTAF Panel.