

Trial	Participants	Duration	Comparative Treatment	Primary Outcome	Key Findings	Level 2 or 3 Hypoglycemia (events per patient-year)
<a href="#">ONWARDS 1</a>	984 insulin-naïve individuals with type 2 diabetes.	78 weeks	Once-daily insulin glargine U100	Reduction in HbA1c.	Icodec: - 1.55% Glargine: -1.35%	0.30 (icodec) vs. 0.16 (glargine) (estimated rate ratio, 1.64; 95% CI, 0.98 to 2.75)
<a href="#">ONWARDS 2</a>	526 individuals with type 2 diabetes switching from once-daily insulin.	26 weeks	Once-daily insulin degludec	Reduction in HbA1c	Icodec: -1.17% Degludec: -1.10%	0.73 (icodec) vs. 0.27 (degludec) (estimated rate ratio 1.93; 95% CI 0.93 to 4.02)
<a href="#">ONWARDS 3</a>	588 insulin-naïve individuals with type 2 diabetes.	26 weeks	Once-daily insulin degludec.	Reduction in HbA1c.	Icodec: -1.57% Degludec: -1.29%	0.31 (icodec) vs. 0.15 (degludec) (estimated rate ratio, 1.82; 95% CI, 0.87-3.80)
<a href="#">ONWARDS 4</a>	582 individuals with type 2 diabetes treated with basal and bolus insulin.	26 weeks	Once-daily insulin glargine U100, both combined with mealtime insulin (insulin aspart).	Reduction in HbA1c	Icodec: -1.16% Glargine: -1.18%	5.64 (icodec) vs. 5.62 (glargine) (estimated risk ratio, 0.99; 95% CI 0.73-1.33)
<a href="#">ONWARDS 5</a>	1,085 insulin-naïve individuals with type 2 diabetes in a real-world setting	52 weeks	Once-daily insulin glargine or degludec	Reduction in HbA1c.	Icodec: -1.68% Basal insulin: -1.31%	0.19 (icodec) vs. 0.14 (basal insulin) (estimated rate ratio, 1.17; 95% CI, 0.73 to 1.86)
<a href="#">ONWARDS 6</a>	583 individuals with type 1 diabetes	52 weeks	Once-daily insulin degludec, both combined with mealtime insulin (insulin aspart)	Reduction in HbA1c	Icodec: -0.47% Degludec: -0.51%	19.9 (icodec) vs. 10.4 (degludec) (estimated risk ratio, 1.9, 95% CI 1.5-2.3)

**Note:** Starting dose of insulin icodec was 70 U per week. Trials were treat-to-target, with insulin doses adjusted to breakfast BG of 4.4-7.2 mmol/L. See titration schedule below.

## KEY FINDINGS

The ONWARDS clinical trials are a series of six phase 3a global trials evaluating the efficacy and safety of once-weekly insulin icodec in individuals with type 1 or type 2 diabetes.

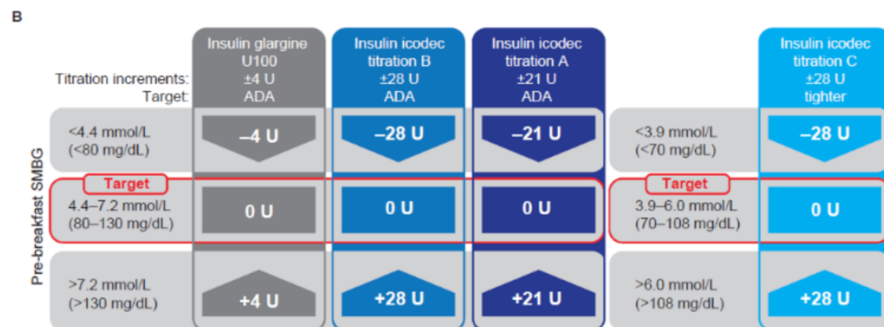
### Severe Hypoglycemia:

Type 2 Diabetes (T2DM): In trials involving T2DM, the rate of severe hypoglycemia was generally low and comparable between insulin icodec and daily basal insulins. The confidence intervals for these rates suggest a consistent safety profile across different patient populations and study durations.

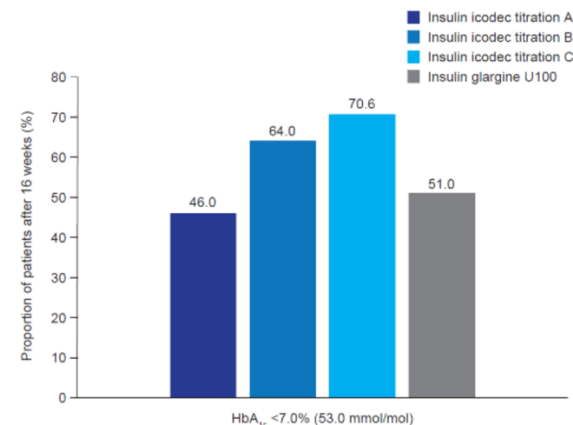
Type 1 Diabetes (T1DM): In ONWARDS 6, which involved individuals with T1DM, the rate of severe hypoglycemia was significantly higher for insulin icodec compared to insulin degludec. This higher rate in T1DM highlights a potential area of concern for this patient group.

### Dosing:

Insulin icodec was administered once weekly at a dose of 70 units. See example titration schedule: [Weekly Insulin Titration Suggestion](#)



**Supplemental Figure S3—Proportion of patients achieving HbA<sub>1c</sub> <7.0% (53.0 mmol/mol) after 16 weeks**



**Conclusion:** The results for icodec titration A (80–130 mg/dL; ±21 units/week) displayed the best balance between glycemic control and risk of hypoglycemia. Level 2 hypoglycemia was low in all groups (0.05, 0.15, 0.38, 0.00 events per patient-year of exposure for icodec titrations A, B, and C and IGlir U100, respectively), with no episodes of severe hypoglycemia.

## CADTH Draft Reimbursement Recommendation

- Reviews pricing justification and answers common questions from drug plans
- Summary: using the sponsor submitted price for insulin icodec and publicly listed price for all other long-acting basal insulin comparators, insulin icodec was more costly than the lowest cost comparator. Insufficient evidence was provided to demonstrate improved treatment efficacy with insulin Icodec versus other long-acting basal insulin analogues. To ensure cost-effectiveness, the total drug cost of insulin icodec should not exceed the total drug cost of the least costly long-acting basal insulin analogue.

### **Bottom Line:**

- While insulin icodec initial results do look promising statistically, the clinical significance is limited.
- Looking at the results from ONWARDS 1, although the reduction in A1C of -0.19% is statistically significant, this likely does not correspond to much difference clinically. Moreover, the incidence of severe hypoglycemia is nearly double in patients treated with insulin icodec vs. insulin glargine, albeit not statistically significant.
- Looking at the results from ONWARDS 6, although insulin icodec achieved non-inferiority compared to insulin degludec in patients with type 1 diabetes, the overall rate of combined clinically significant or severe hypoglycemia (baseline to week 26) was statistically significantly higher with icodec than degludec (19.9 vs. 10.4 events per patient-year of exposure; estimated rate ratio 1.9 [95% CI 1.5 to 2.3];  $p < 0.0001$ ).
- Insulin icodec may be considered if patient compliance is of concern, however this must be balanced with the risk of severe hypoglycemia.