Insulin icodec-abae is approved by the US FDA for the treatment of T2D. It is not currently approved for the treatment of T1D, and its safety and efficacy have not been established for the treatment of T1D. There is no guarantee that insulin icodec-abae will be commercially available for the use(s) under investigation.

ONWARDS 4

Switch from Previous Basal-Bolus Insulin Therapy

Insulin Icodec-abae 700 units/mL injection vs **Insulin glargine injection, U-100**

Study Design

ONWARDS 4 was a Phase 3a, randomized, treat-to-target, open-label trial comparing the safety and efficacy of once-weekly insulin icodec-abae to insulin glargine injection, U-100, Sanofi-Aventis U.S. LLC in adult patients (≥ 18 years old) with type 2 diabetes as part of a basal-bolus regimen with or without non-insulin glucose-lowering drugs.[1]

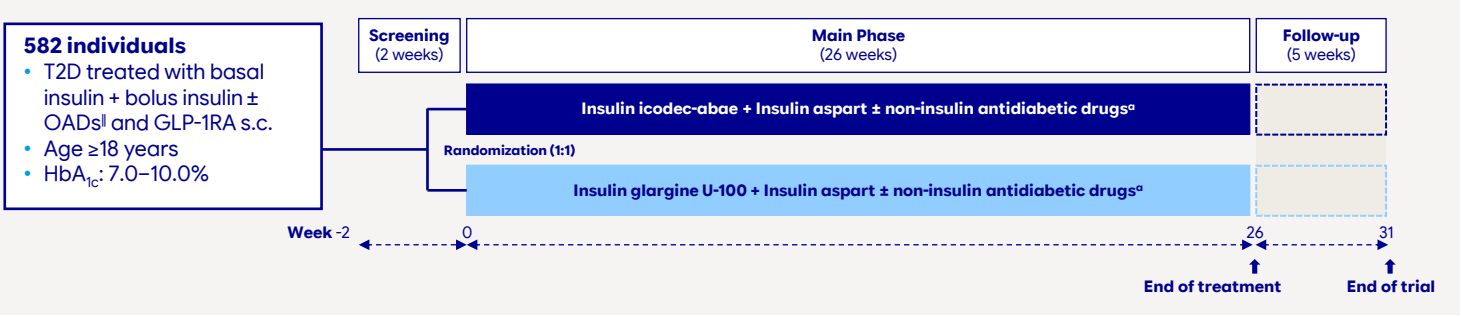
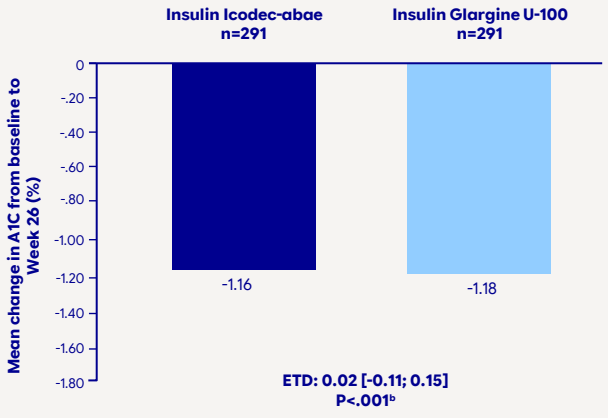


Figure 1. ONWARDS 4 Trial Design[1]

Primary Efficacy Endpoint

The primary endpoint was change in glycosylated hemoglobin (A1C) from baseline to Week 26.[1]



ETD: 0.02 [-0.11; 0.15]
P<.001[b]

Secondary Efficacy Endpoints

Mean change in FPG from baseline to Week 26 (mg/dL)

- 32 Insulin Icodec-abae | **- 29** Insulin Glargine U-100

ETD: -2.48 mg/dL [-10.59; 5.63]
P=.55

Proportion of Time in Range (TIR) (%) from Week 22 to 26[c]

66.90% Insulin Icodec-abae | **66.40%** Insulin Glargine U-100

ETD: 0.29 [-2.52; 3.09]
P=.84

Patients achieving A1C <7% at Week 26 (%)

41% Insulin Icodec-abae | **45%** Insulin Glargine U-100

EOR: 0.82 [0.58; 1.17]
P=.27

Patients achieving A1C <7% at Week 26 without level 2 or 3 hypoglycemia (%)

26% Insulin Icodec-abae | **25%** Insulin Glargine U-100

EOR: 1.07 [0.73; 1.55]
P=.74*

Safety

Combined level 2 or level 3 hypoglycemia from baseline to Week 26

	n (%)	E (rate per PYE)
Insulin Icodec-abae	**150 (51)**	**944 (5.64)**
Insulin Glargine U-100	162 (56)	938 (5.62)

ERR: 0.99 [0.73; 1.33]
P=0.93

Proportion of Time Below Range (TBR) (%) from Week 22 to 26[c,‡]

0.70% Insulin Icodec-abae | **0.60%** Insulin Glargine U-100

ETR: 1.20 [0.91; 1.58]
P=0.20

a. Most common background non-insulin glucose-lowering drugs at screening included metformin, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors.
b. Primary endpoint assessed for non-inferiority.
c. Measurements were conducted via double-blinded continuous glucose monitoring (CGM) using the Dexcom G6 system during Weeks 0 to 4 (after randomization) and from Weeks 22 to 26.
‖Pre-trial all OADs including oral GLP-1RAs are allowed but sulfonylureas and glinides are to be discontinued at randomization. * Patients achieving A1C <7% at Week 26 without level 2 or 3 hypoglycemia during the prior 12 weeks. ‡ The percentage of time spent with glucose levels in the very low range (<54 mg/dL).
Abbreviations: A1C: glycosylated hemoglobin; E: episodes; EOR: estimated odds ratio; ERR: estimated rate ratio; ETD: estimated treatment difference; FPG: fasting plasma glucose; n: number of patients; PYE: Patient Year of Exposure.

Mathieu C, et al. Lancet. 2023;401(10392):1929-1940.