SUPPLEMENTARY MATERIAL FOR:

Long-term Safety and Clinical Outcomes with Insulin Degludec/Insulin Aspart Treatment in Japanese Patients with Diabetes: a Real-world, Prospective, Observational Study

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## Supplementary Table S1. Inclusion, exclusion, and withdrawal criteria

### Inclusion criteria

1. Signed consent obtained before any study-related activities (study-related activities are defined as any procedure related to recording of data according to the protocol)

2. The decision to initiate treatment with commercially available IDegAsp has been made by the patient/legally acceptable representative and the treating physician before and independently from the decision to include the patient in this study

3. Patients with diabetes mellitus requiring insulin therapy for whom the physician has decided to start treatment with IDegAsp

4. Male or female, no age limitation

### Exclusion criteria

1. Patients who are or have previously been treated with IDegAsp

2. Previous participation in this study. Participation is defined as having given informed consent for this study

3. Patients with a history of hypersensitivity to study product components

4. Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation

### Withdrawal criteria

1. The patient may withdraw from this study at will at any time

2. The patient may be withdrawn from this post-marketing surveillance study at the discretion of the physician due to a safety concern

3. Patients enrolment in error (not fulfilling the inclusion and/or fulfilling exclusion criteria)

4. The patient must be withdrawn if IDegAsp treatment is discontinued

IDegAsp, insulin degludec/insulin aspart.
## Supplementary Table S2. AEs by SOC over 1 year of treatment with IDegAsp by age group

| AEs by SOC                                 | <65 years old |                                       | ≥65--<75 years old |                                       | ≥75 years old |
|--------------------------------------------|---------------|----------------------------------------|--------------------|----------------------------------------|---------------|
|                                            | N = 446       | N = 446                                | N = 428            |                                       |               |
| n                           | E          | %       | R       | 95% CI  | n                           | E          | %       | R       | 95% CI  | n                           | E          | %       | R       | 95% CI  |
| All AEs                                  | 37           | 56      | 8.3     | 13.2    | 9.7;16.6 | 38           | 49         | 8.5     | 11.3    | 8.1;14.5 | 57           | 99         | 13.3    | 24.8                | 19.9;29.7 |
| Infections and infestations               | 8            | 8       | 1.8     | 1.9     | 0.6;3.2  | 5            | 5          | 1.1     | 1.2     | 0.1;2.2  | 8            | 10         | 1.9     | 2.5              | 1.0;4.1   |
| Neoplasms benign, malignant, and unspecified* | 2           | 2       | 0.4     | 0.5     | 0.0;1.1  | -           | -          | -       | -       | -       | 11           | 11         | 2.6     | 2.8              | 1.1;4.4   |
| Blood and lymphatic system disorders      | -            | -       | -       | -       | -        | -           | -          | -       | -       | -        | 1            | 1          | 0.2     | 0.3              | 0.0;0.7   |
| Immune system disorders                   | -            | -       | -       | -       | -        | 1           | 1          | 0.2     | 0.2     | 0.0;0.7  | -            | -          | -       | -                | -         |
| Endocrine disorders                       | 1            | 1       | 0.2     | 0.2     | 0.0;0.7  | 1           | 1          | 0.2     | 0.2     | 0.0;0.7  | -            | -          | -       | -                | -         |
| Metabolism and nutrition disorders        | 10           | 11      | 2.2     | 2.6     | 1.1;4.1  | 14           | 15         | 3.1     | 3.5     | 1.7;5.2  | 18           | 34         | 4.2     | 8.5              | 5.7;11.4  |
| Psychiatric disorders                     | 2            | 2       | 0.4     | 0.5     | 0.0;1.1  | -           | -          | -       | -       | -        | -            | -          | -       | -                | -         |
| Nervous system disorders                  | 1            | 1       | 0.2     | 0.2     | 0.0;0.7  | 4           | 4          | 0.9     | 0.9     | 0.0;1.8  | 6            | 6          | 1.4     | 1.5              | 0.3;2.7   |
| Eye disorders                             | -            | -       | -       | -       | -        | 2           | 2          | 0.4     | 0.5     | 0.0;1.1  | -            | -          | -       | -                | -         |
| Cardiac disorders                         | 2            | 2       | 0.4     | 0.5     | 0.0;1.1  | 4           | 4          | 0.9     | 0.9     | 0.0;1.8  | 6            | 6          | 1.4     | 1.5              | 0.3;2.7   |
| Vascular disorders                        | 8            | 8       | 1.8     | 1.9     | 0.6;3.2  | 4           | 4          | 0.9     | 0.9     | 0.0;1.8  | 3            | 3          | 0.7     | 0.8              | 0.0;1.6   |
| Respiratory, thoracic, and mediastinal disorders | 2           | 2       | 0.4     | 0.5     | 0.0;1.1  | 3           | 4          | 0.7     | 0.9     | 0.0;1.8  | 3            | 3          | 0.7     | 0.8              | 0.0;1.6   |
| System Organ Class                        | E | N | n | pro. | CI | R  | pro. | CI  |
|------------------------------------------|---|---|---|------|----|-----|------|-----|
| Gastrointestinal disorders               | 4 | 5 | 0.9 | 1.2  | 0.1;2.2 | 2 | 2 | 0.4 | 0.5 | 0.0;1.1 | 3 | 3 | 0.7 | 0.8 | 0.0;1.6 |
| Hepatobiliary disorders                  | 2 | 2 | 0.4 | 0.5  | 0.0;1.1 | - | - | - | - | - | 1 | 1 | 0.2 | 0.3 | 0.0;0.7 |
| Skin and subcutaneous tissue disorders   | - | - | - | - | - | - | - | - | - | - | 3 | 3 | 0.7 | 0.8 | 0.0;1.6 |
| Musculoskeletal and connective tissue disorders | 2 | 2 | 0.4 | 0.5  | 0.0;1.1 | 1 | 1 | 0.2 | 0.2 | 0.0;0.7 | 2 | 2 | 0.5 | 0.5 | 0.0;1.2 |
| Renal and urinary disorders              | 1 | 1 | 0.2 | 0.2  | 0.0;0.7 | - | - | - | - | - | 1 | 1 | 0.2 | 0.3 | 0.0;0.7 |
| Reproductive system and breast disorders | 1 | 1 | 0.2 | 0.2  | 0.0;0.7 | - | - | - | - | - | - | - | - | - | - |
| General disorders and administration-site conditions | 1 | 1 | 0.2 | 0.2  | 0.0;0.7 | 2 | 2 | 0.4 | 0.5 | 0.0;1.1 | 4 | 4 | 0.9 | 1.0 | 0.0;2.0 |
| Investigations                           | 4 | 4 | 0.9 | 0.9  | 0.0;1.9 | - | - | - | - | - | 5 | 5 | 1.2 | 1.3 | 0.2;2.3 |
| Injury, poisoning, and procedural complications | 3 | 3 | 0.7 | 0.7  | 0.0;1.5 | 4 | 4 | 0.9 | 0.9 | 0.0;1.8 | 4 | 6 | 0.9 | 1.5 | 0.3;2.7 |

Safety analysis set.

%, proportion of patients with at least one event; AE, adverse events; CI, confidence interval; E, number of events; N, number of patients; n, number of patients with at least one event; R, rate of events per 100 person-years of exposure; SOC, system organ class.
| ADRs by SOC                                      | <65 years old (N = 446) | ≥65−<75 years old (N = 446) | ≥75 years old (N = 428) |
|------------------------------------------------|-------------------------|-----------------------------|------------------------|
|                                                |  n  | E  | %  | R  | 95% CI |  n  | E  | %  | R  | 95% CI |  n  | E  | %  | R  | 95% CI |
| All ADRs                                       | 12  | 13 | 2.7 | 3.1 | 1.4;4.7 | 13  | 14 | 2.9 | 3.2 | 1.5;4.9 | 16  | 31 | 3.7 | 7.8 | 5.0;10.5 |
| Infections and infestations                    | 1   | 1  | 0.2 | -   | -       | -   | -  | -   | -   | -       | -   | -  | -   | -   | -       |
| Metabolism and nutrition disorders             | 9   | 10 | 2.0 | 11  | 2.2     | 10  | 11 | 2.2 | -   | -       | 16  | 30 | 3.7 | -   | -       |
| Eye disorders                                  | -   | -  | -   | -   | -       | 1   | 1  | 0.2 | -   | -       | 1   | 1  | 0.2 | -   | -       |
| Cardiac disorders                              | -   | -  | -   | -   | -       | 1   | 1  | 0.2 | -   | -       | 1   | 1  | 0.2 | -   | -       |
| Vascular disorders                             | 1   | 1  | 0.2 | -   | -       | -   | -  | -   | -   | -       | -   | -  | -   | -   | -       |
| General disorders and administration-site      | 1   | 1  | 0.2 | 1   | 1       | 1   | 1  | 0.2 | -   | -       | 1   | 1  | 0.2 | -   | -       |
| conditions                                     | -   | -  | -   | -   | -       | -   | -  | -   | -   | -       | -   | -  | -   | -   | -       |
| Investigations                                 | -   | -  | -   | -   | -       | 1   | 1  | 0.2 | -   | -       |

Safety analysis set.

%, proportion of patients with at least one reaction; ADR, adverse drug reaction; CI, confidence interval; E, number of reactions; N, number of patients; n, number of patients with at least one event; R, rate of reactions per 100 person-years of exposure.
Supplementary Table S4. Hypoglycaemic and severe hypoglycaemic episodes over 1 year after the initiation of IDegAsp, overall and by diabetes type or age group

|                          | Hypoglycaemic episodes |                          | Severe hypoglycaemic episodes |                          |
|--------------------------|------------------------|--------------------------|-----------------------------|--------------------------|
|                          | n          | %            | E              | R              | 95% CI   | n          | %            | E              | R              | 95% CI   |
| Overall, N = 1321        |            |              |                |                |          |            |              |                |                |          |
| T1D, N = 55              | 3          | 5.5          | 4              | 7.6            | 0.2;15.0 | 0          | 0.4          | 6              | 0.5            | 0.1;0.9  |
| T2D, N = 1257            | 29         | 2.3          | 42             | 3.5            | 2.4;4.6  | 5          | 0.4          | 6              | 0.5            | 0.1;0.9  |
| Age group                |            |              |                |                |          |            |              |                |                |          |
| <65 years old, N = 446   | 8          | 1.8;2.2      | 9              | 2.1            | 0.7;3.5  | 0          | 0            | 0              | 0              | -        |
| ≥65–<75 years old, N = 446| 10         | 3.3          | 11             | 2.5            | 1.0;4.0  | 1          | 0.2          | 1              | 0.2            | 0.0;0.7  |
| ≥75 years old, N = 428   | 14         | 3.3          | 26             | 6.5            | 4.0;9.0  | 4          | 0.9          | 5              | 1.3            | 0.2;2.3  |

Safety analysis set.

%, proportion of patients with at least one episode; CI, confidence interval; E, number of events; N, number of patients; n, number of patients with at least one event; R, rate of episodes per 100 person-years of exposure; T1D, type 1 diabetes; T2D, type 2 diabetes.
Supplementary Fig. S1. Study design

EAS, effectiveness analysis set; IDegAsp, insulin degludec/insulin aspart; SAS, safety analysis set.
Supplementary Fig. S2. Change from baseline in FPG, overall and by diabetes type, (a) after 1 year and (b) over 1 year after initiation of IDegAsp

Effectiveness analysis set. Data are observed means (± SEM in Fig. 3b). Data were included for patients with an available FPG measurement at a given time point; missing data were not imputed.

FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; N, number of patients; n, number of patients with an FPG measurement at time point; T1D, type 1 diabetes; T2D, type 2 diabetes; SEM, standard error of the mean.
Supplementary Fig. S3. Responders for (a) HbA$_1c$ <6%, <7% and <8%, and (b) for HbA1c <6%, <7%, and <8% without severe hypoglycaemia, after 1 year of treatment with IDegAsp, overall and by diabetes type.

Effectiveness analysis set. Data are observed proportions. Missing data were not imputed.

HbA$_1c$, glycated haemoglobin; IDegAsp, insulin degludec/insulin aspart; T1D, type 1 diabetes; T2D, type 2 diabetes.