# Cover Page for Statistical Analysis Plan

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# Statistical Analysis Plan

# NN1436-4909

# A Study to Evaluate Flash Glucose Monitoring Based Titration of Once-weekly Insulin Icodec in Insulin-naïve Participants with Type 2 Diabetes

## Substance: Insulin icodec

*Redacted statistical analysis plan*
*Includes redaction of personal identifiable information only.*

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**Author**

[redacted]

Insulin & Devices

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# Version History

This Statistical Analysis Plan (SAP) for study NN1436-4909 is based on the protocol version 1.0 dated 09-DEC-2022.

| SAP Version | Date | Change | Rationale |
|---|---|---|---|
| 1.0 | See approval date in the electronic document management system | Not Applicable | Original version |

# List of abbreviations

| | |
|---|---|
| BG | Blood glucose |
| DPS | Data points set |
| FAS | Full analysis set |
| FGM | Flash glucose monitoring |
| $HbA_{1c}$ | Glycated haemoglobin |
| MMRM | Mixed model for repeated measurements |
| SAP | Statistical analysis plan |
| T2D | Type 2 diabetes |
| TAR | Time above range |
| TBR | Time below range |
| TIR | Time in range |

# 1 Introduction

This SAP is based on the protocol: *A Study to Evaluate Flash Glucose Monitoring Based Titration of Once-weekly Insulin Icodec in Insulin-naïve Participants with Type 2 Diabetes*, version 1.0 (dated 09-DEC-2022). Most of the statistical analyses and derivations of endpoints presented in this SAP are identical to those described in the protocol, but some have been updated or added. The changes to the protocol-planned statistical analyses and the reasons for these changes are described in section 4.8. The SAP also contains specifications of additional derivations and analyses in appendix 1, section 6.1.

## 1.1 Objectives, Endpoints, and Estimands

### 1.1.1 Objectives

#### 1.1.1.1 Primary objective

To explore the effect on glycaemic control of FGM-based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve individuals with T2D.

#### 1.1.1.2 Exploratory objective

To explore safety and glycaemic control including FGM-based metrics.

### 1.1.2 Endpoints

#### 1.1.2.1 Primary endpoint

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in $HbA_{1c}$ | From initiation week 0 (V3) to week 26 (V26) | %-point |

#### 1.1.2.2 Exploratory endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) to week 26 (V26) | Number of episodes |
| Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) or severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) to week 26 (V26) | Number of episodes |

| | | |
|---|---|---|
| Mean weekly insulin dose | From week 24 (P24) to week 26 (V26) | U |
| TIR 3.9-10.0 mmol/L (70-180 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings |
| TBR <3.0 mmol/L (54 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings |
| TAR >10.0 mmol/L (180 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings |
| Participant achieved treatment target of $HbA_{1c}$ <7.0% (Yes/No) | Week 26 (V26) | Count of participants |

* using the FreeStyle Libre 2 FGM system

### 1.1.3 Estimands

#### 1.1.3.1 Primary Estimand

The primary clinical question of interest is to explore the glycaemic control in terms of change in glycated haemoglobin ($HbA_{1c}$) 26 weeks after initiation of FGM-based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve T2D patients in need of basal insulin therapy had these patients been able to adhere to both the FGM-based titration and the once-weekly insulin treatment.

The intercurrent event of discontinuing both once-weekly insulin icodec treatment and use of the FGM-based titration will be handled by the hypothetical strategy.

## 1.2 Study Design

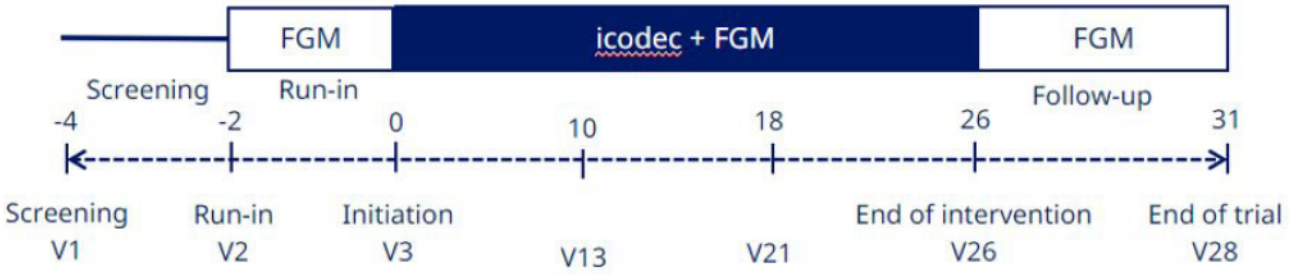
This is an interventional multi-centre, single country, single arm, treat-to-target, and open-label study. The study is designed to explore the initiation and titration of once-weekly insulin icodec using FGM device system in combination with non-insulin antidiabetic drugs in insulin-naïve participants with T2D. The study will include 50 participants who will initiate the trial product.

The study duration is approximately 35 weeks and consists of:

- an up to 2-week screening period
- a 2-week run-in period with FGM
- a 26-week intervention period with FGM
- a 5-week follow-up period with FGM

The overall study design is outlined in Figure 1-1 and the detailed visit schedule can be found in the flowchart (see protocol section 1.2).

**Figure 1-1 Study design**



# 2 Statistical hypotheses

No confirmatory statistical hypotheses are planned to be tested.

## 2.1 Multiplicity Adjustment

Not applicable for this study.

# 3 Analysis Sets

The following participant analysis sets are defined:

| Participant analysis set | Description |
|---|---|
| Full analysis set (FAS) | All participants assigned to insulin icodec. |
| Safety analysis set | All participants who are exposed to insulin icodec. |

The following data points sets are defined:

| Data points set (DPS) | Description |
|---|---|
| DPS1 | For participants who discontinue both FGM titration and icodec treatment, observations from the time of both discontinuations and onwards will not be included. All other data will be included. |
| DPS2 | All observed data will be included in the analysis set irrespective of use FGM based titration or treatment with once-weekly insulin icodec. |

In exceptional cases, participants or observations may be eliminated from the full analysis set. In such case the reasons for their exclusion will be documented before unblinding. The participants and observations excluded from analysis sets, and the reason for this, will be described in the clinical study report.

Baseline assessments are always included in DPS1 and DPS2.

FAS and DPS1 are used to present the efficacy data.

Safety analysis set and DPS2 are used to present safety data.

Hypoglycaemic episodes will also be presented with the safety analysis set and DPS1.

In the output generation, the DPS1 and DPS2 will for simplicity purposes be called ‘baseline to end of treatment visit’ and ‘in-study’, respectively.

# 4 Statistical Analyses

## 4.1 General Considerations

Two-sided 95% confidence interval will be reported for the primary endpoint.

If not otherwise specified, a baseline measurement is defined as the last available measurement prior to exposure to insulin icodec.

## 4.2 Primary endpoint analysis

### 4.2.1 Definition of Endpoint

The primary endpoint is change in $HbA_{1c}$ from initiation week 0 (V3) to week 26 (V26).

### 4.2.2 Main Analytical Approach

The primary endpoint will be analysed by a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model will include visit as fixed factor and baseline $HbA_{1c}$ as a covariate. Interactions between visit and baseline $HbA_{1c}$ will also be included in the model. All post-initiation values obtained at planed visits that are in DPS1 will be included in the analysis.

## 4.3 Secondary endpoint analysis

Not applicable for this study.

## 4.4 Exploratory endpoint analysis

### 4.4.1 Exploratory efficacy endpoints

**Time in range 3.9-10.0 mmol/L (70-180 mg/dL) from week 22 (P23) to week 26 (V26)**

Time in range 3.9-10.0 mmol/L (70-180 mg/dL) measured by FGM during the last 4 weeks of treatment (week 22 to week 26) will be summarised descriptively.

**Time spent <3.0 mmol/L (54 mg/dL) and time spent >10.0 mmol/L (180 mg/dL) from week 22 (P23) to week 26 (V26)**

Time spent <3.0 mmol/L (54 mg/dL) and time spent >10.0 mmol/L (180 mg/dL) measured by FGM during the last 4 weeks of treatment (week 22 to week 26) will be summarised descriptively.

**Achievement of $HbA_{1c}$ <7.0% after 26 weeks (yes/no)**

Achievement of $HbA_{1c}$ <7.0% will be summarised descriptively.

### 4.4.2 Exploratory safety endpoints

**Hypoglycaemic episodes**

Hypoglycaemic episodes will be summarised descriptively.

For the definition and classification of hypoglycaemic episodes refer to the protocol appendix 6 (protocol section 10.6).

**Mean weekly insulin dose from week 24 (P24) to week 26 (V26)**

Mean weekly insulin dose from week 24 (P24) to week 26 (V26) will be log-transformed and summarised descriptively.

## 4.5 Other Safety Analysis

The standard safety assessments (adverse events, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest in laboratory parameters.

## 4.6 Other Analysis

### 4.6.1 Other Variables and/or Parameters

For the calculation of derivations please see appendix 1, section 6.1. The derivations will be summarised descriptively.

## 4.7 Interim Analysis

Not applicable for this study.

## 4.8 Changes to Protocol-planned Analysis

In section 3 the analysis sets has been updated with 'insulin icodec' instead of 'study intervention' for clarification.

V24 has been updated to P24 for the 'mean weekly insulin dose' exploratory endpoint as it is a phone visit and not a site visit.

An additional period for hypoglycaemic episodes has been added, including all data from from time of the initiation visit (V3).

# 5 Sample size determination

Please see the protocol section 9.5.

# 6 Supporting Documentation

## 6.1 Appendix 1: Definition and calculation of endpoints, assessments and derivations

| Type | Title | Time frame | Unit | Details |
|---|---|---|---|---|
| Primary endpoint | Change in $HbA_{1c}$ | From initiation week 0 (V3) to week 26 (V26) | %-point | The $HbA_{1c}$ value at initiation week 0 subtracted from the $HbA_{1c}$ value at week 26. |
| Exploratory endpoint | Number of severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) to week 26 (V26) | Number of episodes | The count of all severe hypoglycaemic episodes (level 3) within the time frame. |
| Exploratory endpoint | Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) or severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) to week 26 (V26) | Number of episodes | The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) within the time frame. |
| Exploratory endpoint | Mean weekly insulin dose | From week 24 (P24) to week 26 (V26) | U | The mean of weekly insulin doses during the two weeks. |
| Exploratory endpoint | TIR 3.9-10.0 mmol/L (70-180 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings | Calculated as 100 times the number of recorded measurements in the given glycaemic range, divided by the total number of recorded measurements. |
| Exploratory endpoint | TBR <3.0 mmol/L (54 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings | Calculated as 100 times the number of recorded measurements below 3.0 mmol/L (54 mg/dL) divided by the total number of recorded measurements. |
| Exploratory endpoint | TAR >10.0 mmol/L (180 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings | Calculated as 100 times the number of recorded measurements above 10.0 mmol/L (180 mg/dL) divided by the total number of recorded measurements. |
| Exploratory endpoint | Participant achieved treatment target of $HbA_{1c}$ <7.0% (Yes/No) | Week 26 (V26) | Count of participants | Dichotomous outcome variable:<br>*Yes*: participant achieved $HbA_{1c}$ <7.0%<br><br>*No*: participant did not achieve $HbA_{1c}$ <7.0% |
| Derivation | Change in TIR 3.9-10.0 mmol/L (70-180 mg/dL) | Week -2-0 (V2 to V3) and week 22-26 (P23 to V26) | %-point of readings | The TIR value at week -2 to week 0 subtracted from the TIR value at week 22 to week 26. |
| Derivation | Time spent <3.9 mmol/L (70 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings | Calculated as 100 times the number of recorded measurements below 3.9 mmol/L (70 mg/dL) divided by the total number of recorded measurements. |
| Derivation | Time spent >13.9 mmol/L (250 mg/dL)* | From week 22 (P23) to week 26 (V26) | % of readings | Calculated as 100 times the number of recorded measurements above 13.9 mmol/L (250 mg/dL) divided by the total number of recorded measurements. |

| Type | Title | Time frame | Unit | Details |
|---|---|---|---|---|
| Derivation | Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) | From initiation week 0 (V3) | Number of participants | The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) within the time frame. |
| Derivation | Number of severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) | Number of participants | The count of all severe hypoglycaemic episodes (level 3) within the time frame. |
| Derivation | Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by BG meter) or severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) | Number of participants | The count of all clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) within the time frame. |
| Derivation | Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) | From initiation week 0 (V3) | Number of participants | Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive. |
| Derivation | Number of nocturnal severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) | Number of participants | Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive. |
| Derivation | Number of nocturnal clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) | From initiation week 0 (V3) | Number of participants | Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive. |
| Derivation | Achievement of $HbA_{1c}$<7.0% after 26 weeks without severe (level 3) or clinically significant | Week 26 (V26) | Count of participants | Dichotomous outcome variable:<br>*Yes*: participant achieved $HbA_{1c}$ < 7.0% after 26 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks |

| Type | Title | Time frame | Unit | Details |
|---|---|---|---|---|
| | hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no) | | | *No*: participant did not achieve $HbA_{1c}$ < 7.0% after 26 weeks **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant discontinued treatment prematurely |
| Derivation | Achievement of $HbA_{1c}$ <7.0% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no) | Week 26 (V26) | Count of participants | Dichotomous outcome variable:<br>*Yes*: participant achieved $HbA_{1c}$ <7.0% after 26 weeks without severe hypoglycaemic episodes during the prior 12 weeks<br><br>*No*: participant did not achieve $HbA_{1c}$ <7.0% after 26 weeks **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant discontinued treatment prematurely |
| Derivation | Achievement of $HbA_{1c}$≤6.5% after 26 weeks (yes/no) | Week 26 (V26) | Count of participants | Dichotomous outcome variable:<br>*Yes*: participant achieved $HbA_{1c}$ ≤6.5% after 26 weeks<br><br>*No*: participant did not achieve $HbA_{1c}$ ≤6.5% after 26 weeks |
| Derivation | Achievement of $HbA_{1c}$≤6.5% after 26 weeks without severe (level 3) or clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) during the prior 12 weeks (yes/no) | Week 26 (V26) | Count of participants | Dichotomous outcome variable:<br>*Yes*: participant achieved $HbA_{1c}$ ≤6.5% after 26 weeks without severe or clinically significant hypoglycaemic episodes during the prior 12 weeks<br><br>*No*: participant did not achieve $HbA_{1c}$ ≤6.5% after 26 weeks **or** participant had a severe or clinically significant hypoglycaemic episode during the prior 12 weeks **or** participant discontinued treatment prematurely |
| Derivation | Achievement of $HbA_{1c}$≤6.5% after 26 weeks without severe hypoglycaemic episodes (level 3) during the prior 12 weeks (yes/no) | Week 26 (V26) | Count of participants | Dichotomous outcome variable:<br>*Yes*: participant achieved $HbA_{1c}$ ≤6.5% after 26 weeks without severe hypoglycaemic episodes during the prior 12 weeks<br><br>*No*: participant did not achieve $HbA_{1c}$ ≤6.5% after 26 weeks **or** participant had a severe hypoglycaemic episode during the prior 12 weeks **or** participant discontinued treatment prematurely |

* using the FreeStyle Libre 2 FGM system