# Dossier zur Nutzenbewertung gemäß § 35a SGB V

*Insulin icodec (Awiqli®)*

Novo Nordisk Pharma GmbH

**Modul 4 B – Anhang 4-G**

*Behandlung von Insulin-erfahrenen Erwachsenen mit Typ 2 Diabetes mellitus ohne oder mit kardiovaskulärer Erkrankung*

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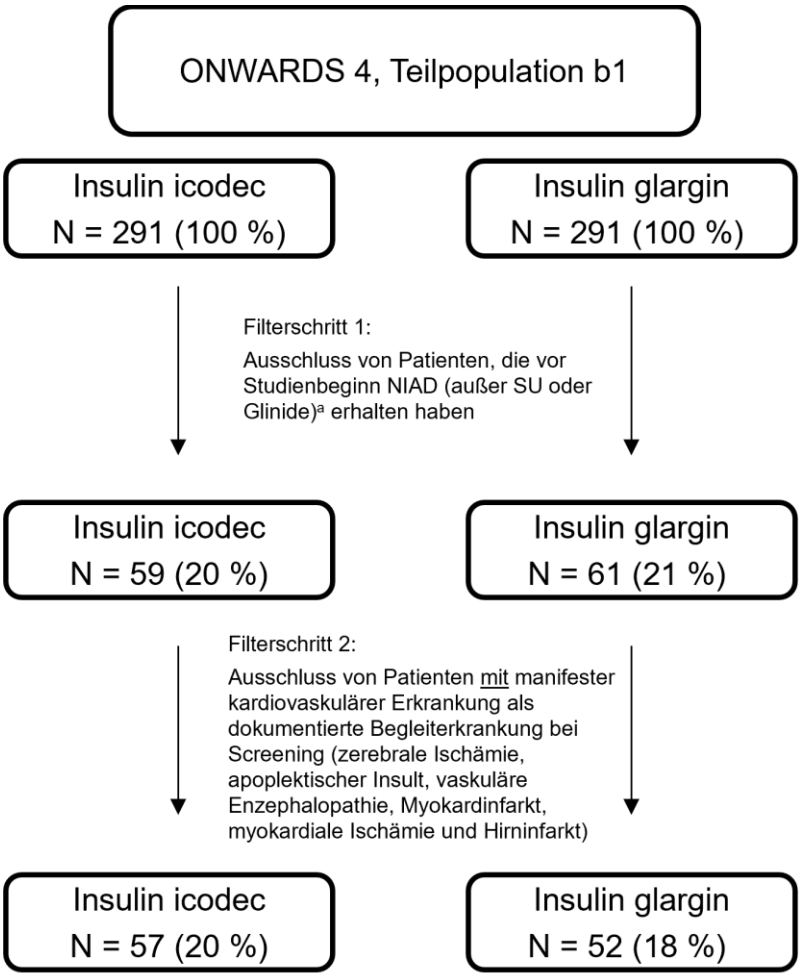
# 1 Auswertungen zur Bewertung der Studie ONWARDS 4 für die Eignung zur Nutzenbewertung von Insulin icodec im vorliegenden Dossier

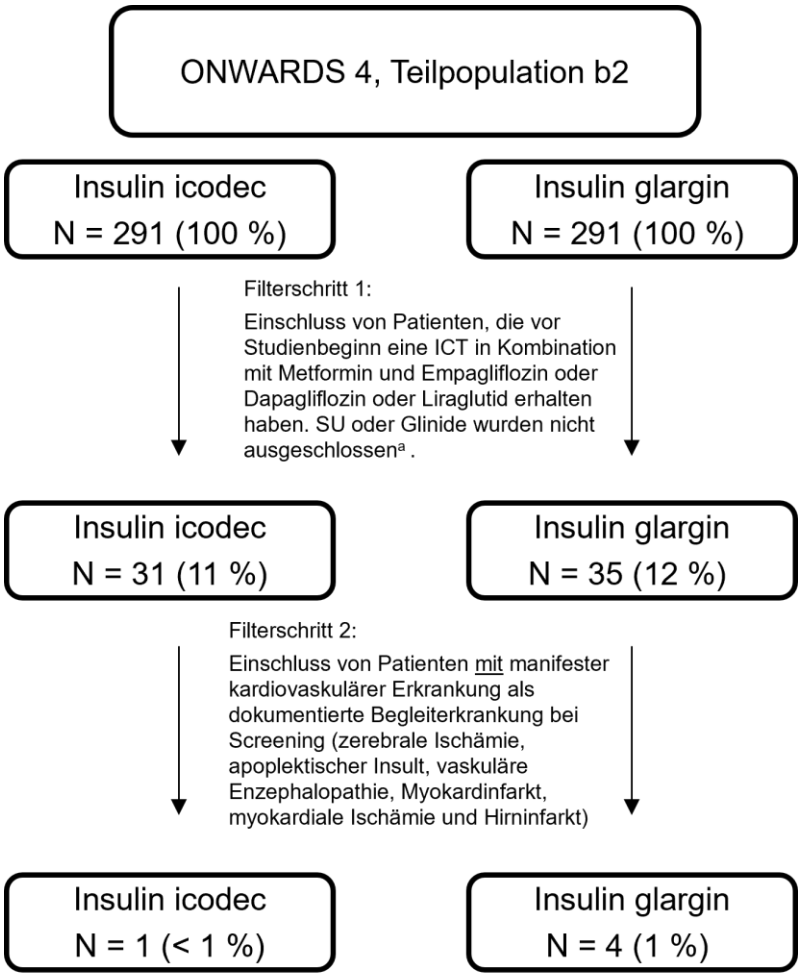
## 1.1 Auswertung der Teilpopulationen aus ONWARDS 4

### 1.1.1 Flow-Chart zur Auswertung der Teilpopulation b1




a: SU und Glinide wurden bei Randomisierung abgesetzt
NIAD: Nicht-Insulin-Antidiabetika (umfasst folgende Wirkstoffe: Metformin, DPP-4-Inhibitoren, SGLT2-Inhibitoren, GLP-1-Rezeptoragonisten, Alpha-Glucosidase-Inhibitoren und Thiazolidindione)

### 1.1.2 Flow-Chart zur Auswertung der Teilpopulation b2




a: SU und Glinide wurden bei Randomisierung abgesetzt
ICT: Intensified Conventional; SU: Sulfonylharnstoff

## 1.2 Summary of label population 1 - Onwards 4 - Full analysis set

| | Ico | | IGlar | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Full analysis set | 291 | (100) | 291 | (100) |
| Remaining subjects without pretreatment of NIADs other than SU or Glinides | 59 | (20) | 61 | (21) |
| Remaining subjects without specific CV disease medical history (population 1) | 57 | (20) | 52 | (18) |

N: number of subjects, NIAD: Non-insulin antidiabetic drugs which included metformin, DPP-4i, SGLT2i, GLP-1, alpha-glucosidase inhibitors, and thiazolidinediones. The medical history terms used to identify specific CV disease are cerebral ischaemia, cerebrovascular accident, vascular encephalopathy, cerebral infarction, myocardial infarction, and myocardial ischaemia.

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## 1.3 Summary of label population 2 - Onwards 4 - Full analysis set

| | Ico | | IGlar | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Full analysis set | 291 | (100) | 291 | (100) |
| Remaining subjects with pretreatment of metformin + dapagliflozin/empagliflozin/liraglutide | 31 | (11) | 35 | (12) |
| Remaining subjects with specific CV disease medical history | 1 | (<1) | 4 | (1) |

N: number of subjects
The medical history terms used to identify specific CV disease are cerebral ischaemia, cerebrovascular accident, vascular encephalopathy, cerebral infarction, myocardial infarction, and myocardial ischaemia.

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# 2 Vollständige Auswertung zu Wirksamkeit und Sicherheit inkl. Subgruppenanalysen zur Teilpopulation b1 aus ONWARDS 4

## 2.1 Change in HbA1c by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico - IGlar | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] | p-value int. |
| HbA1c (%) | | | | | | | | | | | | | |
| All subjects (total) | Week 10 | 57 | 55 | -1.05 (0.73) | | 52 | 47 | -0.88 (0.83) | | | | 0.22 [-0.15; 0.60] | |
| | Week 18 | 57 | 52 | -1.19 (0.79) | | 52 | 46 | -1.07 (1.16) | | | | 0.13 [-0.25; 0.50] | |
| | Week 26 | 57 | 53 | -1.17 (0.75) | -1.05 (0.12) | 52 | 47 | -1.10 (1.00) | -1.03 (0.13) | -0.02 [ -0.36; 0.33] | 0.9209 | 0.07 [-0.30; 0.45] | |
| Gender | | | | | | | | | | | | | |
| Female | Week 10 | 26 | 25 | -1.04 (0.71) | | 28 | 25 | -0.81 (0.86) | | | | 0.29 [-0.25; 0.82] | |
| | Week 18 | 26 | 24 | -1.16 (0.72) | | 28 | 25 | -1.04 (0.93) | | | | 0.14 [-0.39; 0.67] | |
| | Week 26 | 26 | 25 | -1.18 (0.76) | -1.14 (0.18) | 28 | 26 | -1.05 (0.86) | -1.02 (0.18) | -0.12 [ -0.63; 0.38] | 0.6365 | 0.16 [-0.38; 0.69] | 0.6077 |
| Male | Week 10 | 31 | 30 | -1.07 (0.76) | | 24 | 22 | -0.96 (0.82) | | | | 0.14 [-0.40; 0.67] | |
| | Week 18 | 31 | 28 | -1.22 (0.86) | | 24 | 21 | -1.10 (1.41) | | | | 0.11 [-0.43; 0.64] | |
| | Week 26 | 31 | 28 | -1.16 (0.75) | -0.98 (0.17) | 24 | 21 | -1.17 (1.17) | -1.05 (0.19) | 0.07 [ -0.43; 0.56] | 0.7900 | -0.01 [-0.54; 0.52] | |
| Age | | | | | | | | | | | | | |
| <65 years | Week 10 | 37 | 36 | -1.12 (0.78) | | 34 | 31 | -0.94 (0.91) | | | | 0.21 [-0.26; 0.68] | |
| | Week 18 | 37 | 34 | -1.30 (0.84) | | 34 | 30 | -1.15 (1.33) | | | | 0.14 [-0.33; 0.61] | |
| | Week 26 | 37 | 34 | -1.31 (0.82) | -1.16 (0.15) | 34 | 30 | -1.18 (1.10) | -0.97 (0.16) | -0.18 [ -0.61; 0.24] | 0.3963 | 0.13 [-0.33; 0.60] | 0.1929 |
| >=65 years | Week 10 | 20 | 19 | -0.93 (0.62) | | 18 | 16 | -0.76 (0.69) | | | | 0.25 [-0.39; 0.89] | |
| | Week 18 | 20 | 18 | -0.98 (0.67) | | 18 | 16 | -0.92 (0.75) | | | | 0.09 [-0.55; 0.73] | |
| | Week 26 | 20 | 19 | -0.91 (0.52) | -0.85 (0.20) | 18 | 17 | -0.96 (0.81) | -1.15 (0.22) | 0.30 [ -0.28; 0.88] | 0.3175 | -0.07 [-0.71; 0.57] | |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test). The change from baseline in response after 26 weeks is analysed using an analysis of covariance (ANCOVA) model with treatment, region (if applicable), personal CGM device use (and subgroup with interaction between treatment and subgroup, if applicable) as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the last available planned assessments. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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Change in HbA1c by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | IGlar | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] p-value | Hedges' g [95%-CI] p-value int. |
| HbA1c | | | | | | | | | | | |
| <=8,5% | Week 10 | 36 | 36 | -0.95 (0.58) | | 36 | 33 | -0.51 (0.52) | | | 0.80 [ 0.32; 1.28] |
| | Week 18 | 36 | 34 | -1.01 (0.62) | | 36 | 33 | -0.68 (0.51) | | | 0.59 [ 0.12; 1.06] |
| | Week 26 | 36 | 35 | -1.02 (0.60) | -0.95 (0.15) | 36 | 34 | -0.69 (0.64) | -0.69 (0.15) | -0.26 [ -0.67; 0.14] 0.2055 | 0.52 [ 0.05; 0.99] 0.0430 |
| >8,5% | Week 10 | 21 | 19 | -1.25 (0.95) | | 16 | 14 | -1.76 (0.78) | | | -0.56 [-1.22; 0.10] |
| | Week 18 | 21 | 18 | -1.53 (0.98) | | 16 | 13 | -2.05 (1.69) | | | -0.39 [-1.04; 0.27] |
| | Week 26 | 21 | 18 | -1.45 (0.93) | -1.25 (0.20) | 16 | 13 | -2.17 (1.01) | -1.76 (0.24) | 0.51 [ -0.11; 1.13] 0.1083 | -0.73 [-1.40;-0.06] |
| Region | | | | | | | | | | | |
| Europe | Week 10 | 24 | 24 | -1.02 (0.74) | | 24 | 23 | -0.82 (0.82) | | | 0.25 [-0.32; 0.82] |
| | Week 18 | 24 | 24 | -1.19 (0.77) | | 24 | 21 | -1.06 (0.88) | | | 0.15 [-0.41; 0.72] |
| | Week 26 | 24 | 23 | -1.06 (0.79) | -1.01 (0.18) | 24 | 23 | -1.05 (0.96) | -1.12 (0.18) | 0.10 [ -0.40; 0.60] 0.6908 | 0.00 [-0.56; 0.57] 0.8218 |
| North and South America | Week 10 | 24 | 22 | -1.16 (0.75) | | 19 | 16 | -0.94 (0.84) | | | 0.28 [-0.33; 0.88] |
| | Week 18 | 24 | 20 | -1.22 (0.77) | | 19 | 17 | -1.18 (0.93) | | | 0.05 [-0.55; 0.65] |
| | Week 26 | 24 | 21 | -1.33 (0.74) | -1.06 (0.19) | 19 | 17 | -1.06 (0.89) | -0.94 (0.21) | -0.13 [ -0.69; 0.44] 0.6616 | 0.33 [-0.28; 0.93] |
| Asia | Week 10 | 9 | 9 | -0.90 (0.70) | | 9 | 8 | -0.94 (0.98) | | | -0.04 [-0.97; 0.88] |
| | Week 18 | 9 | 8 | -1.12 (1.01) | | 9 | 8 | -0.85 (2.08) | | | 0.16 [-0.77; 1.09] |
| | Week 26 | 9 | 9 | -1.06 (0.66) | -1.10 (0.29) | 9 | 7 | -1.34 (1.46) | -1.01 (0.32) | -0.10 [ -0.94; 0.74] 0.8183 | -0.24 [-1.17; 0.69] |
| Race | | | | | | | | | | | |
| White | Week 10 | 42 | 41 | -1.12 (0.75) | | 39 | 35 | -0.89 (0.85) | | | 0.29 [-0.15; 0.72] |
| | Week 18 | 42 | 39 | -1.24 (0.76) | | 39 | 35 | -1.11 (0.92) | | | 0.15 [-0.29; 0.58] |
| | Week 26 | 42 | 39 | -1.22 (0.78) | -1.16 (0.16) | 39 | 36 | -1.12 (0.94) | -1.15 (0.16) | -0.01 [ -0.41; 0.38] 0.9521 | 0.11 [-0.32; 0.55] 0.9027 |
| Not white | Week 10 | 15 | 14 | -0.86 (0.67) | | 13 | 12 | -0.85 (0.82) | | | 0.02 [-0.72; 0.76] |
| | Week 18 | 15 | 13 | -1.06 (0.91) | | 13 | 11 | -0.93 (1.77) | | | 0.09 [-0.65; 0.84] |
| | Week 26 | 15 | 14 | -1.02 (0.66) | -0.75 (0.30) | 13 | 11 | -1.04 (1.23) | -0.69 (0.32) | -0.06 [ -0.73; 0.61] 0.8598 | -0.02 [-0.76; 0.73] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test). The change from baseline in response after 26 weeks is analysed using an analysis of covariance (ANCOVA) model with treatment, region (if applicable), personal CGM device use (and subgroup with interaction between treatment and subgroup, if applicable) as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the last available planned assessments. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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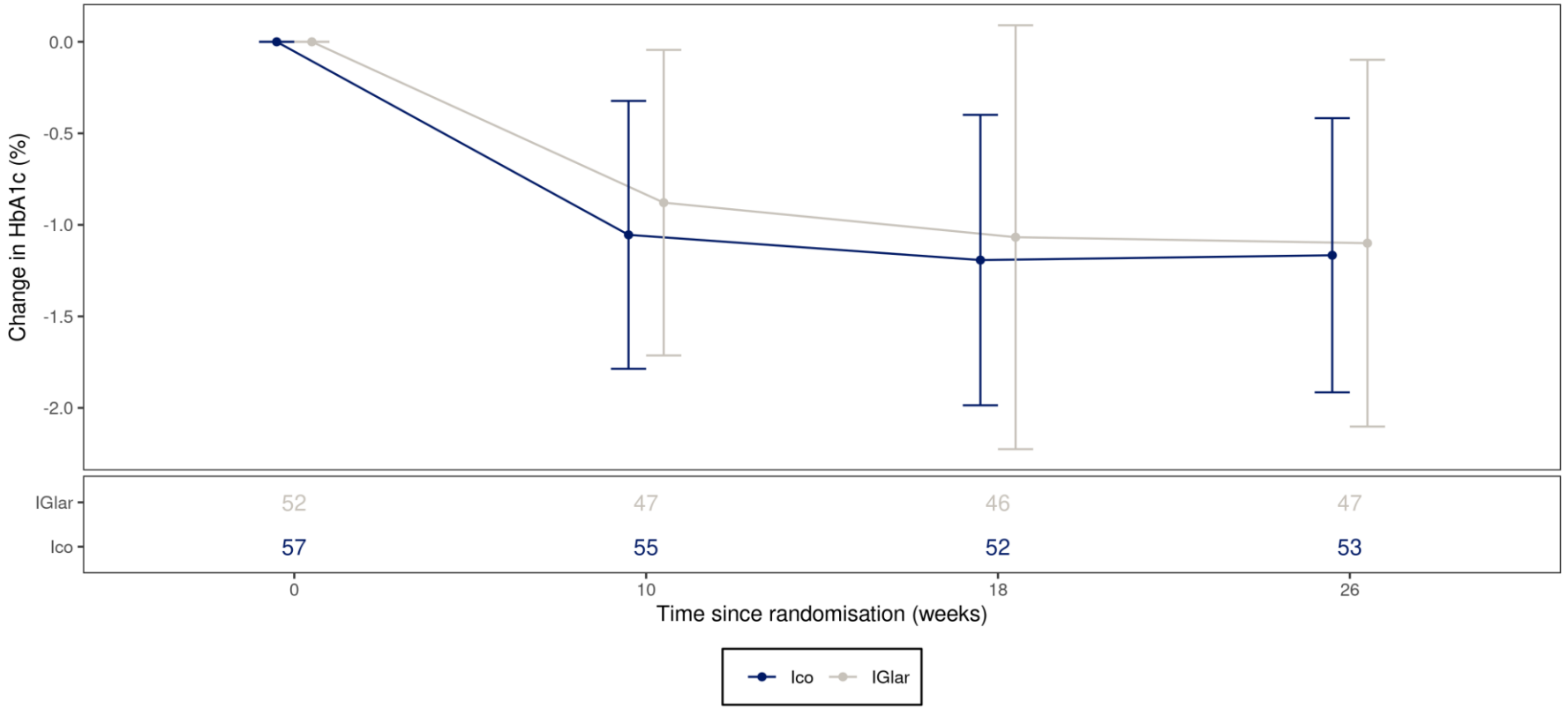
## 2.2 Change in HbA1c by treatment week - Mean plot - Onwards 4 - Population 1 - in-trial - Full analysis set




Observed data. Number of subjects contributing to data points appears in the bottom panel. Legend: Mean(symbol) and mean ± standard deviation (error bars).
HbA1c: Haemoglobin A1c.

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## 2.3 Absolute HbA1c by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | IGlar | | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | N | n | Mean (SD) | Hedges' g [95%-CI] |
| HbA1c (%) | | | | | | | | |
| All subjects (total) | Week 0 | 57 | 57 | 8.34 (0.85) | 52 | 52 | 8.13 (0.88) | -0.24 [-0.62; 0.14] |
| | Week 10 | 57 | 55 | 7.25 (0.85) | 52 | 47 | 7.23 (0.63) | -0.03 [-0.40; 0.35] |
| | Week 18 | 57 | 52 | 7.12 (0.83) | 52 | 46 | 7.02 (0.95) | -0.12 [-0.50; 0.26] |
| | Week 26 | 57 | 53 | 7.11 (0.85) | 52 | 47 | 6.98 (0.70) | -0.17 [-0.55; 0.21] |
| Gender | | | | | | | | |
| Female | Week 0 | 26 | 26 | 8.34 (0.85) | 28 | 28 | 8.06 (0.88) | -0.32 [-0.85; 0.22] |
| | Week 10 | 26 | 25 | 7.24 (0.90) | 28 | 25 | 7.20 (0.70) | -0.05 [-0.58; 0.48] |
| | Week 18 | 26 | 24 | 7.09 (0.87) | 28 | 25 | 6.92 (0.62) | -0.22 [-0.76; 0.31] |
| | Week 26 | 26 | 25 | 7.10 (0.95) | 28 | 26 | 6.95 (0.71) | -0.19 [-0.72; 0.35] |
| Male | Week 0 | 31 | 31 | 8.33 (0.86) | 24 | 24 | 8.20 (0.88) | -0.15 [-0.68; 0.39] |
| | Week 10 | 31 | 30 | 7.25 (0.82) | 24 | 22 | 7.25 (0.54) | 0.00 [-0.53; 0.54] |
| | Week 18 | 31 | 28 | 7.16 (0.80) | 24 | 21 | 7.14 (1.24) | -0.02 [-0.55; 0.51] |
| | Week 26 | 31 | 28 | 7.12 (0.76) | 24 | 21 | 7.02 (0.71) | -0.13 [-0.66; 0.40] |
| Age | | | | | | | | |
| <65 years | Week 0 | 37 | 37 | 8.35 (0.88) | 34 | 34 | 8.30 (0.97) | -0.05 [-0.51; 0.42] |
| | Week 10 | 37 | 36 | 7.22 (0.88) | 34 | 31 | 7.33 (0.62) | 0.14 [-0.33; 0.61] |
| | Week 18 | 37 | 34 | 7.04 (0.89) | 34 | 30 | 7.10 (1.10) | 0.06 [-0.40; 0.53] |
| | Week 26 | 37 | 34 | 7.00 (0.91) | 34 | 30 | 7.07 (0.78) | 0.09 [-0.38; 0.55] |
| >=65 years | Week 0 | 20 | 20 | 8.31 (0.80) | 18 | 18 | 7.79 (0.55) | -0.73 [-1.38;-0.07] |
| | Week 10 | 20 | 19 | 7.29 (0.81) | 18 | 16 | 7.03 (0.60) | -0.37 [-1.01; 0.27] |
| | Week 18 | 20 | 18 | 7.29 (0.68) | 18 | 16 | 6.86 (0.57) | -0.67 [-1.32;-0.02] |
| | Week 26 | 20 | 19 | 7.32 (0.69) | 18 | 17 | 6.81 (0.52) | -0.80 [-1.46;-0.14] |
| HbA1c | | | | | | | | |
| <=8,5% | Week 0 | 36 | 36 | 7.78 (0.44) | 36 | 36 | 7.64 (0.41) | -0.34 [-0.80; 0.13] |
| | Week 10 | 36 | 36 | 6.83 (0.56) | 36 | 33 | 7.13 (0.62) | 0.50 [ 0.03; 0.96] |
| | Week 18 | 36 | 34 | 6.78 (0.59) | 36 | 33 | 6.95 (0.63) | 0.27 [-0.19; 0.74] |
| | Week 26 | 36 | 35 | 6.77 (0.66) | 36 | 34 | 6.94 (0.65) | 0.26 [-0.20; 0.72] |
| >8,5% | Week 0 | 21 | 21 | 9.29 (0.41) | 16 | 16 | 9.23 (0.58) | -0.11 [-0.76; 0.54] |
| | Week 10 | 21 | 19 | 8.03 (0.75) | 16 | 14 | 7.46 (0.59) | -0.82 [-1.50;-0.14] |
| | Week 18 | 21 | 18 | 7.77 (0.84) | 16 | 13 | 7.19 (1.51) | -0.48 [-1.14; 0.18] |
| | Week 26 | 21 | 18 | 7.78 (0.77) | 16 | 13 | 7.08 (0.85) | -0.85 [-1.53;-0.17] |
| Region | | | | | | | | |
| Europe | Week 0 | 24 | 24 | 8.27 (0.87) | 24 | 24 | 8.01 (0.74) | -0.31 [-0.88; 0.25] |
| | Week 10 | 24 | 24 | 7.25 (0.93) | 24 | 23 | 7.16 (0.57) | -0.12 [-0.69; 0.44] |
| | Week 18 | 24 | 24 | 7.08 (0.87) | 24 | 21 | 6.89 (0.52) | -0.26 [-0.83; 0.30] |
| | Week 26 | 24 | 23 | 7.13 (0.99) | 24 | 23 | 6.92 (0.62) | -0.25 [-0.82; 0.32] |
| North and South America | Week 0 | 24 | 24 | 8.51 (0.84) | 19 | 19 | 8.22 (1.07) | -0.30 [-0.91; 0.30] |
| | Week 10 | 24 | 22 | 7.28 (0.77) | 19 | 16 | 7.22 (0.77) | -0.07 [-0.67; 0.54] |
| | Week 18 | 24 | 20 | 7.23 (0.64) | 19 | 17 | 6.95 (0.66) | -0.43 [-1.03; 0.18] |
| | Week 26 | 24 | 21 | 7.14 (0.65) | 19 | 17 | 7.06 (0.82) | -0.11 [-0.72; 0.49] |
| Asia | Week 0 | 9 | 9 | 8.04 (0.76) | 9 | 9 | 8.24 (0.82) | 0.24 [-0.69; 1.17] |
| | Week 10 | 9 | 9 | 7.14 (0.92) | 9 | 8 | 7.42 (0.46) | 0.37 [-0.56; 1.30] |
| | Week 18 | 9 | 8 | 7.00 (1.14) | 9 | 8 | 7.51 (1.91) | 0.31 [-0.62; 1.24] |
| | Week 26 | 9 | 9 | 6.99 (0.93) | 9 | 7 | 6.97 (0.75) | -0.02 [-0.94; 0.90] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval.

nn1436/nn1436-amnog/current
23JAN2024:13:35:20 - /HbA1c_4480.txt

Absolute HbA1c by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | IGlar | | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | N | n | Mean (SD) | Hedges' g [95%-CI] |
| Race | | | | | | | | |
| White | Week 0 | 42 | 42 | 8.35 (0.89) | 39 | 39 | 8.12 (0.89) | -0.26 [-0.69; 0.18] |
| | Week 10 | 42 | 41 | 7.20 (0.84) | 39 | 35 | 7.18 (0.62) | -0.02 [-0.46; 0.42] |
| | Week 18 | 42 | 39 | 7.08 (0.78) | 39 | 35 | 6.95 (0.58) | -0.18 [-0.62; 0.25] |
| | Week 26 | 42 | 39 | 7.07 (0.86) | 39 | 36 | 6.93 (0.69) | -0.17 [-0.61; 0.27] |
| Not white | Week 0 | 15 | 15 | 8.29 (0.74) | 13 | 13 | 8.14 (0.86) | -0.18 [-0.92; 0.56] |
| | Week 10 | 15 | 14 | 7.39 (0.89) | 13 | 12 | 7.36 (0.66) | -0.04 [-0.78; 0.70] |
| | Week 18 | 15 | 13 | 7.26 (0.97) | 13 | 11 | 7.23 (1.68) | -0.02 [-0.77; 0.72] |
| | Week 26 | 15 | 14 | 7.24 (0.84) | 13 | 11 | 7.13 (0.77) | -0.13 [-0.87; 0.61] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval.

nn1436/nn1436-amnog/current
23JAN2024:13:35:20 - /HbA1c_4480.txt

## 2.4 Change in fasting plasma glucose (FPG) by treatment week - Onwards 4 - in-trial - Population 1 - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| FPG (mg/dL) | | | | | | | | | | | | |
| All subjects (total) | Week 10 | 57 | 53 | -51.71 (74.74) | | 52 | 42 | -29.99 (86.97) | | | | 0.27 [-0.11; 0.64] |
| | Week 18 | 57 | 51 | -48.41 (62.48) | | 52 | 44 | -43.62 (68.98) | | | | 0.07 [-0.30; 0.45] |
| | Week 26 | 57 | 50 | -41.55 (68.10) | -35.42 (7.63) | 52 | 45 | -33.16 (81.77) | -31.84 (8.05) | -3.58 [-25.45; 18.30] | 0.7486 | 0.11 [-0.26; 0.49] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The change from baseline in response after 26 weeks is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the last available on treatment (LAOT) values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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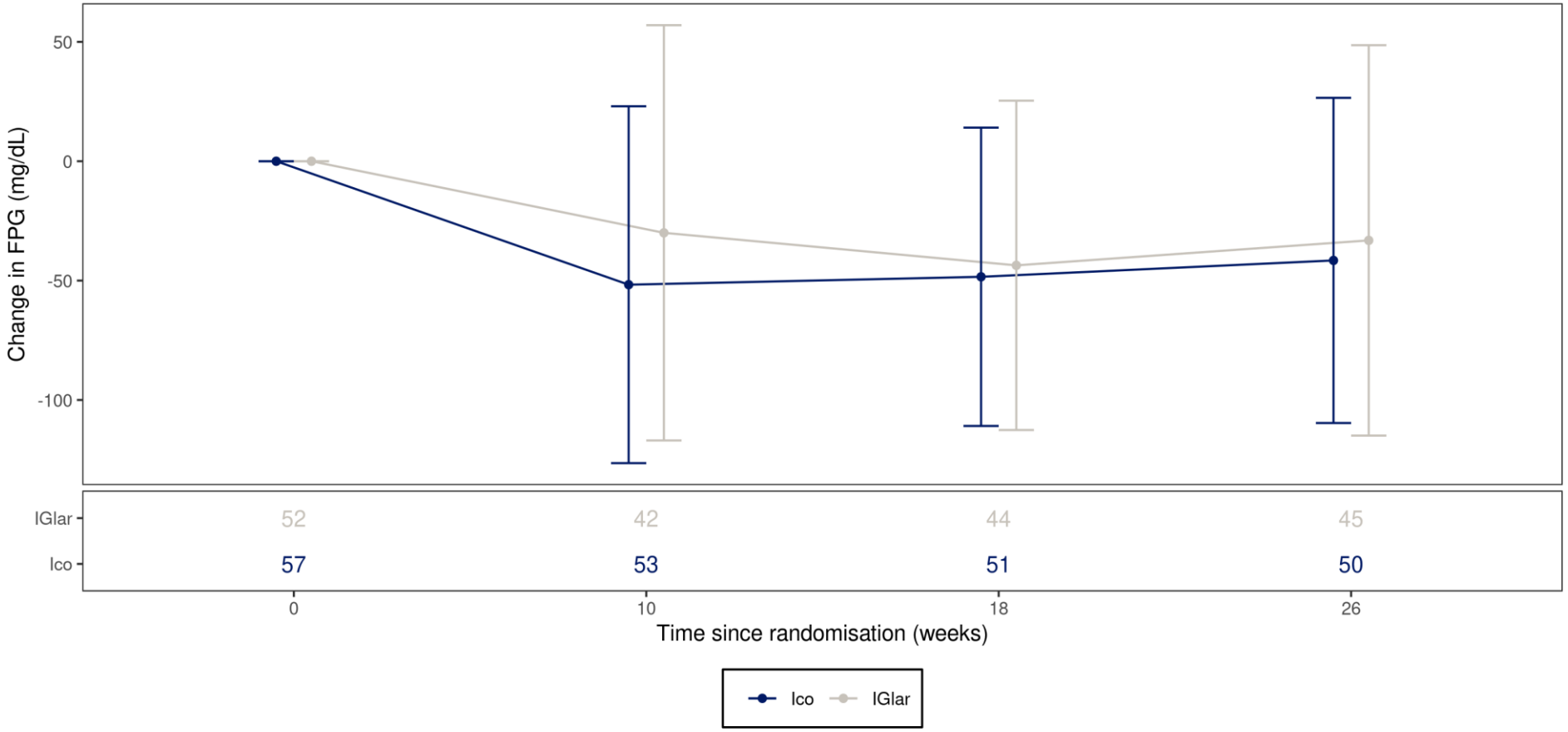
23JAN2024:13:35:22 - /ChangeFPG_4480.txt

## 2.5 Change in fasting plasma glucose (FPG) by treatment week - Mean plot - Onwards 4 - Population 1 - in-trial - Full analysis set




Observed data. Number of subjects contributing to data points appears in the bottom panel. Legend: Mean(symbol) and mean ± standard deviation (error bars).
FPG : Fasting plasma glucose

nn1436/nn1436-amnog/current
23JAN2024:13:35:44 - P:/nn1436/nn1436-amnog/current/stats/program/nonctrprog/meanplot_descriptive.R/FPG2chg4480.png

## 2.6 Change in fasting plasma glucose (FPG) by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | | Ico | | | | IGlar | | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| FPG (mmol/L) | | | | | | | | | | | | |
| All subjects (total) | Week 10 | 57 | 53 | -2.87 (4.15) | | 52 | 42 | -1.66 (4.83) | | | | 0.27 [-0.11; 0.64] |
| | Week 18 | 57 | 51 | -2.69 (3.47) | | 52 | 44 | -2.42 (3.83) | | | | 0.07 [-0.30; 0.45] |
| | Week 26 | 57 | 50 | -2.31 (3.78) | -1.97 (0.42) | 52 | 45 | -1.84 (4.54) | -1.77 (0.45) | -0.20 [-1.41; 1.02] | 0.7486 | 0.11 [-0.26; 0.49] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The change from baseline in response after 26 weeks is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the last available on treatment (LAOT) values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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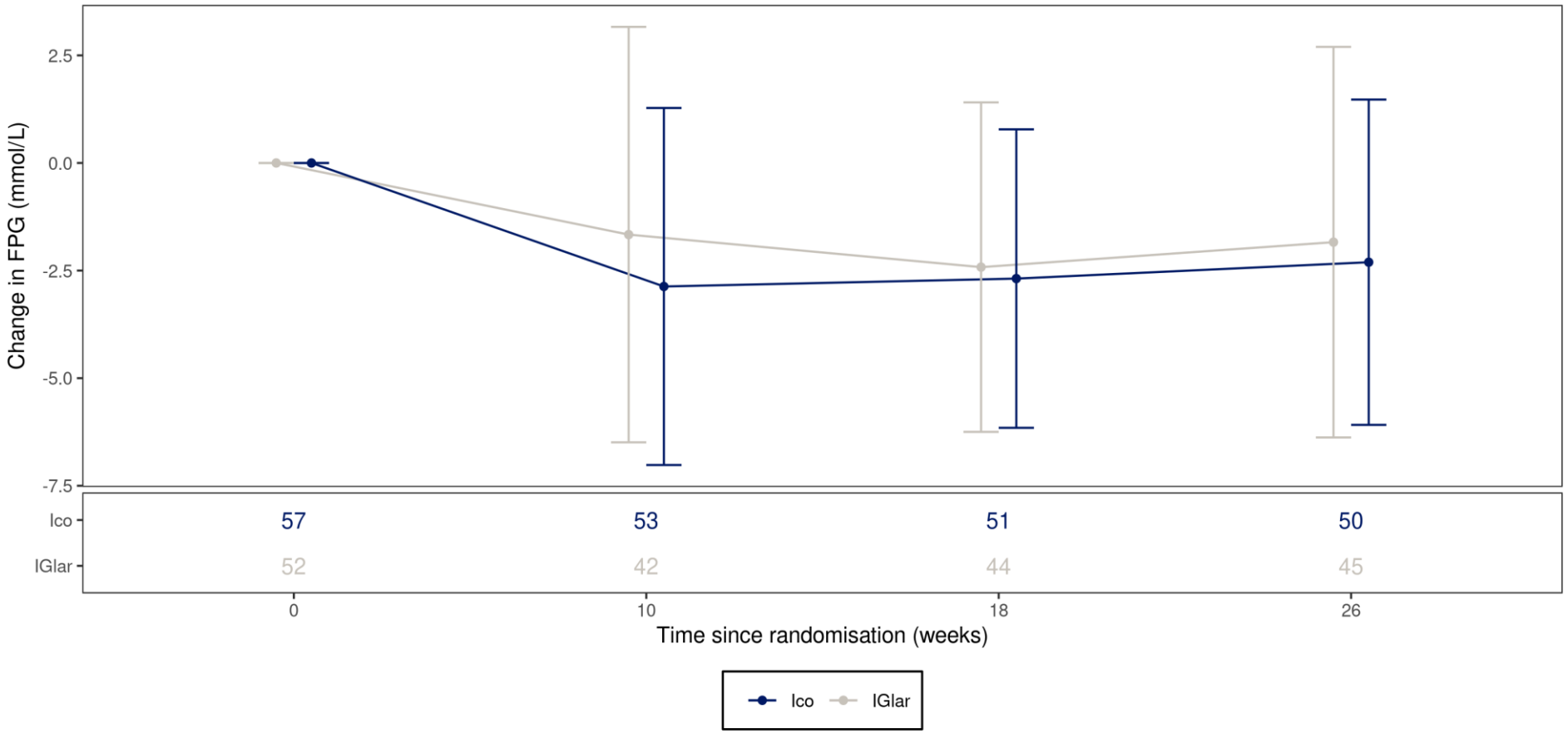
21JUL2023:15:55:57 - /ChangeFPG_4480.txt

## 2.7 Change in fasting plasma glucose (FPG) by treatment week - Mean plot - Onwards 4 - Population 1 - in-trial - Full analysis set




Observed data. Number of subjects contributing to data points appears in the bottom panel. Legend: Mean(symbol) and mean ± standard deviation (error bars).
FPG : Fasting plasma glucose

nn1436/nn1436-amnog/current
21JUL2023:13:54:28 - P:/nn1436/nn1436-amnog/current/stats/program/nonctrprog/meanplot_descriptive.R/FPGchg4480.png

## 2.8 Absolute fasting plasma glucose (FPG) by treatment week - Onwards 4 - in-trial - Population 1 - Full analysis set

| | Week | Ico | | | IGlar | | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | N | n | Mean (SD) | Hedges' g [95%-CI] |
| FPG (mg/dL) | | | | | | | | |
| All subjects (total) | Week 0 | 57 | 56 | 184.09 (63.27) | 52 | 50 | 180.09 (61.89) | -0.06 [-0.44; 0.31] |
| | Week 10 | 57 | 54 | 133.31 (45.23) | 52 | 44 | 149.16 (53.76) | 0.32 [-0.06; 0.70] |
| | Week 18 | 57 | 52 | 137.78 (47.75) | 52 | 45 | 139.68 (46.66) | 0.04 [-0.34; 0.42] |
| | Week 26 | 57 | 51 | 142.43 (51.69) | 52 | 47 | 147.34 (49.49) | 0.10 [-0.28; 0.47] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval.

nn1436/nn1436-amnog/current
23JAN2024:13:35:23 - /FPG_4480.txt

## 2.9 Absolute Fasting plasma glucose (FPG) by treatment week - Onwards 4 - in-trial - Population 1 - Full analysis set

| | | Ico | | | IGlar | | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|
| | Week | N | n | Mean (SD) | N | n | Mean (SD) | Hedges' g [95%-CI] |
| FPG (mmol/L) | | | | | | | | |
| All subjects (total) | Week 0 | 57 | 56 | 10.22 (3.51) | 52 | 50 | 9.99 (3.43) | -0.06 [-0.44; 0.31] |
| | Week 10 | 57 | 54 | 7.40 (2.51) | 52 | 44 | 8.28 (2.98) | 0.32 [-0.06; 0.70] |
| | Week 18 | 57 | 52 | 7.65 (2.65) | 52 | 45 | 7.75 (2.59) | 0.04 [-0.34; 0.42] |
| | Week 26 | 57 | 51 | 7.90 (2.87) | 52 | 47 | 8.18 (2.75) | 0.10 [-0.28; 0.47] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval.

nn1436/nn1436-amnog/current
21JUL2023:15:55:59 - /FPG_4480.txt

## 2.10 Change in body weight by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | | Ico | | | IGlar | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week | N n Mean (SD) | LS Mean (SE) | | N n Mean (SD) | LS Mean (SE) | | ETD [95%-CI] p-value | Hedges' g [95%-CI] p-value | int. |
| All subjects (total) | Week 14 | 57 51 1.74 (2.75) | | | 52 49 0.88 (4.08) | | | | -0.25 [-0.62; 0.13] | |
| | Week 26 | 57 54 2.95 (3.74) | 2.69 (0.54) | | 52 47 2.60 (4.58) | 2.46 (0.58) | | 0.24 [-1.32; 1.79] 0.7656 | -0.08 [-0.46; 0.29] | |
| Gender | | | | | | | | | | |
| Female | Week 14 | 26 23 1.43 (2.98) | | | 28 26 0.64 (1.72) | | | | -0.33 [-0.86; 0.21] | |
| | Week 26 | 26 25 2.87 (3.66) | 3.17 (0.86) | | 28 26 2.16 (2.59) | 2.10 (0.80) | | 1.07 [-1.24; 3.37] 0.3651 | -0.22 [-0.76; 0.32] | 0.3426 |
| Male | Week 14 | 31 28 2.00 (2.58) | | | 24 23 1.17 (5.73) | | | | -0.19 [-0.73; 0.34] | |
| | Week 26 | 31 29 3.02 (3.86) | 2.32 (0.78) | | 24 21 3.14 (6.26) | 2.85 (0.87) | | -0.54 [-2.79; 1.72] 0.6416 | 0.02 [-0.51; 0.56] | |
| Age | | | | | | | | | | |
| <65 years | Week 14 | 37 33 2.02 (3.22) | | | 34 32 1.59 (3.82) | | | | -0.12 [-0.59; 0.34] | |
| | Week 26 | 37 35 3.53 (4.25) | 2.90 (0.70) | | 34 30 3.32 (5.29) | 2.87 (0.74) | | 0.03 [-1.93; 1.99] 0.9774 | -0.04 [-0.51; 0.42] | 0.7154 |
| >=65 years | Week 14 | 20 18 1.22 (1.51) | | | 18 17 -0.43 (4.35) | | | | -0.51 [-1.16; 0.14] | |
| | Week 26 | 20 19 1.88 (2.27) | 2.31 (0.95) | | 18 17 1.32 (2.61) | 1.67 (1.00) | | 0.64 [-1.99; 3.28] 0.6325 | -0.22 [-0.86; 0.41] | |
| HbA1c | | | | | | | | | | |
| <=8,5% | Week 14 | 36 34 1.49 (2.37) | | | 36 34 0.19 (3.39) | | | | -0.44 [-0.91; 0.03] | |
| | Week 26 | 36 35 2.35 (3.18) | 2.26 (0.66) | | 36 34 1.52 (2.49) | 1.74 (0.68) | | 0.51 [-1.35; 2.38] 0.5897 | -0.29 [-0.75; 0.18] | 0.5343 |
| >8,5% | Week 14 | 21 17 2.23 (3.42) | | | 16 15 2.46 (5.12) | | | | 0.05 [-0.60; 0.70] | |
| | Week 26 | 21 19 4.06 (4.47) | 3.46 (0.91) | | 16 13 5.43 (7.15) | 4.03 (1.09) | | -0.56 [-3.37; 2.24] 0.6929 | 0.23 [-0.42; 0.88] | |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test). The change from baseline in response after 26 weeks is analysed using an analysis of covariance (ANCOVA) model with treatment, region (if applicable), personal CGM device use (and subgroup with interaction between treatment and subgroup, if applicable) as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the last available planned assessments. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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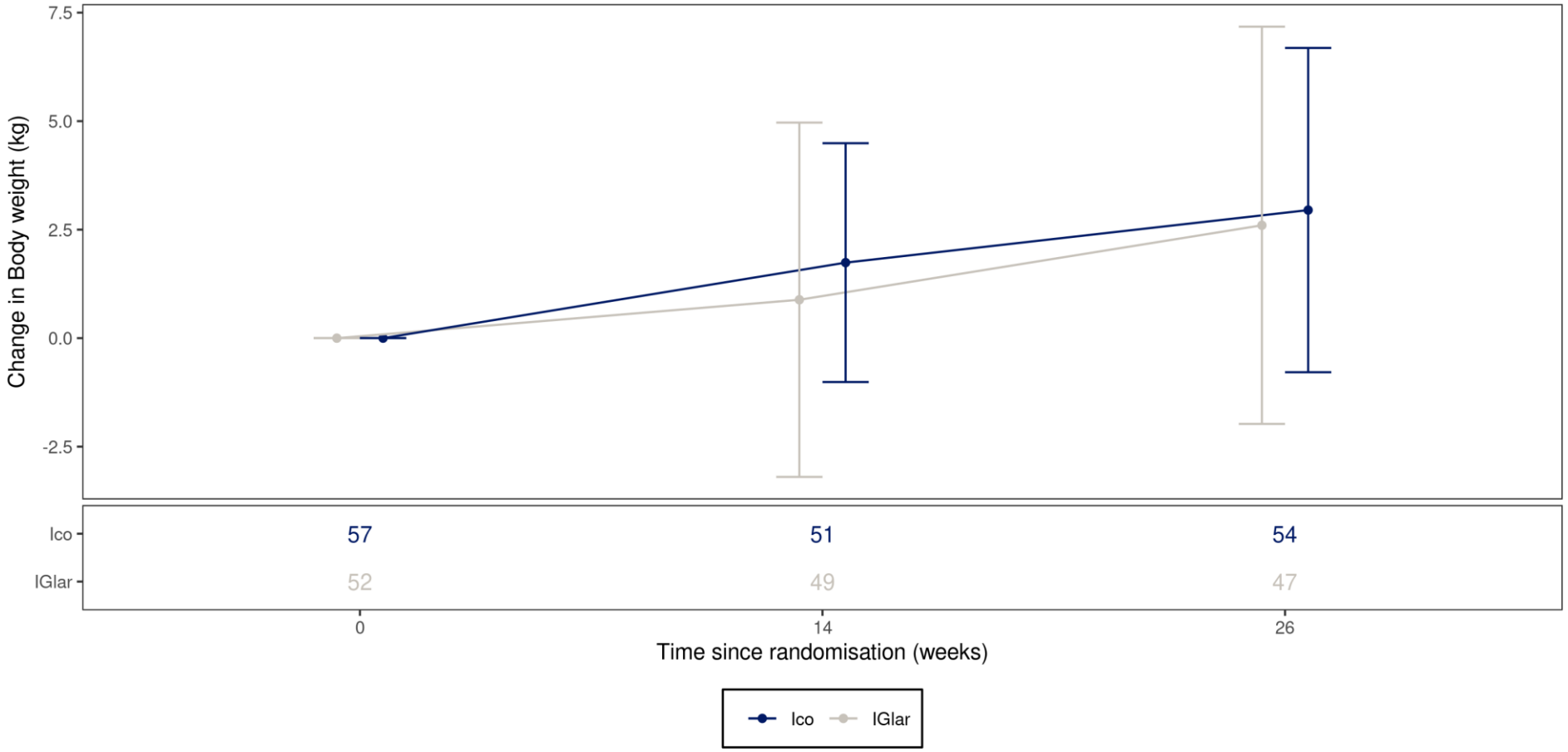
Change in body weight by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | | Ico | | | | IGlar | | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] p-value int. |
| Region | | | | | | | | | | | | |
| Europe | Week 14 | 24 | 24 | 1.32 (2.58) | | 24 | 24 | 0.81 (1.89) | | | | -0.23 [-0.79; 0.34] |
| | Week 26 | 24 | 24 | 2.05 (3.47) | 2.13 (0.84) | 24 | 23 | 1.86 (2.39) | 1.95 (0.85) | 0.18 [-2.15; 2.51] | 0.8790 | -0.06 [-0.63; 0.50] 0.9655 |
| North and South America | Week 14 | 24 | 18 | 2.49 (3.17) | | 19 | 17 | 1.23 (6.45) | | | | -0.25 [-0.86; 0.35] |
| | Week 26 | 24 | 21 | 4.40 (3.95) | 3.51 (0.89) | 19 | 17 | 4.05 (6.67) | 3.21 (1.00) | 0.30 [-2.29; 2.89] | 0.8218 | -0.06 [-0.67; 0.54] |
| Asia | Week 14 | 9 | 9 | 1.34 (2.22) | | 9 | 8 | 0.38 (2.64) | | | | -0.38 [-1.31; 0.55] |
| | Week 26 | 9 | 9 | 1.98 (3.14) | 2.50 (1.41) | 9 | 7 | 1.53 (3.40) | 1.71 (1.53) | 0.80 [-3.15; 4.75] | 0.6928 | -0.13 [-1.06; 0.79] |
| Race | | | | | | | | | | | | |
| White | Week 14 | 42 | 39 | 1.85 (2.95) | | 39 | 37 | 1.09 (4.48) | | | | -0.20 [-0.64; 0.24] |
| | Week 26 | 42 | 40 | 3.17 (3.89) | 3.07 (0.70) | 39 | 36 | 3.15 (4.83) | 3.25 (0.73) | -0.18 [-1.96; 1.61] | 0.8454 | 0.00 [-0.44; 0.43] 0.3387 |
| Not white | Week 14 | 15 | 12 | 1.38 (2.05) | | 13 | 12 | 0.24 (2.53) | | | | -0.49 [-1.24; 0.27] |
| | Week 26 | 15 | 14 | 2.33 (3.31) | 1.63 (1.38) | 13 | 11 | 0.79 (3.18) | 0.08 (1.48) | 1.55 [-1.52; 4.63] | 0.3219 | -0.46 [-1.21; 0.29] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test). The change from baseline in response after 26 weeks is analysed using an analysis of covariance (ANCOVA) model with treatment, region (if applicable), personal CGM device use (and subgroup with interaction between treatment and subgroup, if applicable) as fixed factors, and baseline response as covariate. Missing values at week 26 are imputed by the baseline value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the last available planned assessments. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

nn1436/nn1436-amnog/current
21JUL2023:15:56:00 - /ChangeWeight_4480.txt

## 2.11 Change in body weight by treatment week - Mean plot - Onwards 4 - Population 1 - in-trial - Full analysis set




Observed data. Number of subjects contributing to data points appears in the bottom panel. Legend: Mean(symbol) and mean ± standard deviation (error bars).

nn1436/nn1436-amnog/current
21JUL2023:13:54:29 - P:/nn1436/nn1436-amnog/current/stats/program/nonctrprog/meanplot_descriptive.R/WEIGHTchg4480.png

## 2.12 Absolute body weight by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | IGlar | | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | N | n | Mean (SD) | Hedges' g [95%-CI] |
| Body weight (kg) | | | | | | | | |
| All subjects (total) | Week 0 | 57 | 57 | 84.58 (16.53) | 52 | 52 | 82.17 (16.46) | -0.14 [-0.52; 0.23] |
| | Week 14 | 57 | 51 | 85.53 (17.99) | 52 | 49 | 83.86 (18.16) | -0.09 [-0.47; 0.28] |
| | Week 26 | 57 | 54 | 86.69 (17.22) | 52 | 47 | 86.07 (18.60) | -0.03 [-0.41; 0.34] |
| Gender | | | | | | | | |
| Female | Week 0 | 26 | 26 | 78.65 (13.39) | 28 | 28 | 80.27 (15.20) | 0.11 [-0.42; 0.65] |
| | Week 14 | 26 | 23 | 79.61 (14.59) | 28 | 26 | 81.45 (15.78) | 0.12 [-0.42; 0.65] |
| | Week 26 | 26 | 25 | 81.56 (14.33) | 28 | 26 | 82.98 (16.59) | 0.09 [-0.44; 0.62] |
| Male | Week 0 | 31 | 31 | 89.55 (17.45) | 24 | 24 | 84.38 (17.89) | -0.29 [-0.82; 0.25] |
| | Week 14 | 31 | 28 | 90.39 (19.28) | 24 | 23 | 86.58 (20.54) | -0.19 [-0.72; 0.34] |
| | Week 26 | 31 | 29 | 91.11 (18.48) | 24 | 21 | 89.90 (20.58) | -0.06 [-0.59; 0.47] |
| Age | | | | | | | | |
| <65 years | Week 0 | 37 | 37 | 88.43 (15.74) | 34 | 34 | 83.75 (17.67) | -0.28 [-0.75; 0.19] |
| | Week 14 | 37 | 33 | 90.25 (18.08) | 34 | 32 | 86.51 (19.36) | -0.20 [-0.66; 0.27] |
| | Week 26 | 37 | 35 | 90.68 (16.47) | 34 | 30 | 89.17 (20.32) | -0.08 [-0.55; 0.38] |
| >=65 years | Week 0 | 20 | 20 | 77.45 (15.92) | 18 | 18 | 79.19 (13.87) | 0.11 [-0.52; 0.75] |
| | Week 14 | 20 | 18 | 76.88 (14.63) | 18 | 17 | 78.85 (14.91) | 0.13 [-0.51; 0.77] |
| | Week 26 | 20 | 19 | 79.32 (16.50) | 18 | 17 | 80.61 (14.02) | 0.08 [-0.56; 0.72] |
| HbA1c | | | | | | | | |
| <=8,5% | Week 0 | 36 | 36 | 84.14 (18.22) | 36 | 36 | 80.38 (14.37) | -0.23 [-0.69; 0.24] |
| | Week 14 | 36 | 34 | 84.57 (19.17) | 36 | 34 | 81.23 (15.08) | -0.19 [-0.65; 0.27] |
| | Week 26 | 36 | 35 | 85.26 (17.92) | 36 | 34 | 82.56 (14.93) | -0.16 [-0.62; 0.30] |
| >8,5% | Week 0 | 21 | 21 | 85.33 (13.52) | 16 | 16 | 86.21 (20.35) | 0.05 [-0.60; 0.70] |
| | Week 14 | 21 | 17 | 87.44 (15.74) | 16 | 15 | 89.81 (23.24) | 0.12 [-0.53; 0.77] |
| | Week 26 | 21 | 19 | 89.32 (15.97) | 16 | 13 | 95.26 (24.22) | 0.29 [-0.36; 0.95] |
| Region | | | | | | | | |
| Europe | Week 0 | 24 | 24 | 83.52 (13.64) | 24 | 24 | 81.08 (15.07) | -0.17 [-0.73; 0.40] |
| | Week 14 | 24 | 24 | 84.85 (14.98) | 24 | 24 | 81.88 (15.02) | -0.19 [-0.76; 0.37] |
| | Week 26 | 24 | 24 | 85.57 (14.57) | 24 | 23 | 83.10 (15.59) | -0.16 [-0.73; 0.41] |
| North and South America | Week 0 | 24 | 24 | 90.63 (17.36) | 19 | 19 | 88.79 (17.63) | -0.10 [-0.71; 0.50] |
| | Week 14 | 24 | 18 | 92.89 (19.95) | 19 | 17 | 91.86 (21.65) | -0.05 [-0.65; 0.55] |
| | Week 26 | 24 | 21 | 93.72 (17.52) | 19 | 17 | 94.67 (21.32) | 0.05 [-0.55; 0.65] |
| Asia | Week 0 | 9 | 9 | 71.28 (14.10) | 9 | 9 | 71.11 (11.37) | -0.01 [-0.94; 0.91] |
| | Week 14 | 9 | 9 | 72.62 (14.86) | 9 | 8 | 72.78 (11.82) | 0.01 [-0.91; 0.93] |
| | Week 26 | 9 | 9 | 73.26 (15.84) | 9 | 7 | 74.94 (12.65) | 0.11 [-0.81; 1.04] |
| Race | | | | | | | | |
| White | Week 0 | 42 | 42 | 85.94 (16.35) | 39 | 39 | 83.44 (16.18) | -0.15 [-0.59; 0.28] |
| | Week 14 | 42 | 39 | 88.07 (18.12) | 39 | 37 | 85.08 (18.38) | -0.16 [-0.60; 0.27] |
| | Week 26 | 42 | 40 | 88.27 (16.69) | 39 | 36 | 87.33 (18.94) | -0.05 [-0.49; 0.38] |
| Not white | Week 0 | 15 | 15 | 80.78 (16.99) | 13 | 13 | 78.37 (17.37) | -0.14 [-0.88; 0.61] |
| | Week 14 | 15 | 12 | 77.27 (15.46) | 13 | 12 | 80.07 (17.69) | 0.16 [-0.58; 0.91] |
| | Week 26 | 15 | 14 | 82.15 (18.54) | 13 | 11 | 81.94 (17.65) | -0.01 [-0.75; 0.73] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval.

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## 2.13 Total weekly insulin dose by treatment week (U) - Onwards 4 - Population 1 - on-treatment - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico / IGlar | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETR [95%-CI] p-value | Hedges' g [95%-CI] |
| Total Weekly Actual Insulin Dose (U) | | | | | | | | | | | |
| All subjects (total) | Week 1 | 57 | 56 | 536.88 (371.50) | | 52 | 52 | 478.97 (258.30) | | | -0.18 [-0.55; 0.20] |
| | Week 2 | 57 | 54 | 451.40 (321.44) | | 52 | 52 | 462.68 (254.68) | | | 0.04 [-0.34; 0.41] |
| | Week 3 | 57 | 54 | 444.72 (316.11) | | 52 | 51 | 464.21 (253.62) | | | 0.07 [-0.31; 0.44] |
| | Week 4 | 57 | 54 | 463.55 (309.92) | | 52 | 51 | 475.33 (256.06) | | | 0.04 [-0.33; 0.42] |
| | Week 5 | 57 | 54 | 465.65 (316.79) | | 52 | 51 | 485.17 (257.99) | | | 0.07 [-0.31; 0.44] |
| | Week 6 | 57 | 54 | 454.03 (277.38) | | 52 | 51 | 498.09 (266.40) | | | 0.16 [-0.22; 0.54] |
| | Week 7 | 57 | 54 | 450.56 (282.57) | | 52 | 50 | 489.40 (261.46) | | | 0.14 [-0.23; 0.52] |
| | Week 8 | 57 | 54 | 482.03 (314.90) | | 52 | 50 | 497.04 (272.25) | | | 0.05 [-0.33; 0.43] |
| | Week 9 | 57 | 54 | 483.11 (298.69) | | 52 | 49 | 504.01 (276.30) | | | 0.07 [-0.30; 0.45] |
| | Week 10 | 57 | 54 | 480.61 (303.15) | | 52 | 49 | 516.13 (283.17) | | | 0.12 [-0.26; 0.50] |
| | Week 11 | 57 | 54 | 480.54 (304.16) | | 52 | 48 | 521.35 (290.42) | | | 0.14 [-0.24; 0.51] |
| | Week 12 | 57 | 54 | 489.49 (299.10) | | 52 | 48 | 535.00 (297.87) | | | 0.15 [-0.23; 0.53] |
| | Week 13 | 57 | 54 | 480.51 (311.68) | | 52 | 48 | 542.38 (304.48) | | | 0.20 [-0.18; 0.58] |
| | Week 14 | 57 | 54 | 506.60 (313.83) | | 52 | 49 | 546.31 (302.48) | | | 0.13 [-0.25; 0.50] |
| | Week 15 | 57 | 53 | 517.51 (325.83) | | 52 | 49 | 542.57 (267.14) | | | 0.08 [-0.29; 0.46] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test).The log-transformed response at week 26 is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate. Missing mean values at week 26 are imputed by the log-transformed screening value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the log-transformed LAOT values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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Total weekly insulin dose by treatment week (U) - Onwards 4 - Population 1 - on-treatment - Full analysis set

| Week | Ico | | | | IGlar | | | | Ico / IGlar | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETR [95%-CI] | p-value | Hedges' g [95%-CI] |
| Week 16 | 57 | 53 | 515.56 (329.33) | | 52 | 49 | 552.14 (276.22) | | | | 0.12 [-0.26; 0.50] |
| Week 17 | 57 | 53 | 522.28 (336.72) | | 52 | 49 | 563.02 (284.41) | | | | 0.13 [-0.25; 0.51] |
| Week 18 | 57 | 53 | 522.27 (346.38) | | 52 | 48 | 565.53 (291.36) | | | | 0.13 [-0.24; 0.51] |
| Week 19 | 57 | 52 | 513.50 (359.93) | | 52 | 47 | 574.00 (299.87) | | | | 0.18 [-0.20; 0.56] |
| Week 20 | 57 | 52 | 527.21 (360.17) | | 52 | 46 | 567.43 (308.33) | | | | 0.12 [-0.26; 0.49] |
| Week 21 | 57 | 52 | 530.94 (365.28) | | 52 | 46 | 566.91 (303.19) | | | | 0.11 [-0.27; 0.48] |
| Week 22 | 57 | 52 | 518.49 (371.30) | | 52 | 46 | 578.62 (321.66) | | | | 0.17 [-0.21; 0.55] |
| Week 23 | 57 | 52 | 524.75 (375.51) | | 52 | 46 | 583.98 (329.29) | | | | 0.17 [-0.21; 0.54] |
| Week 24 | 57 | 52 | 522.55 (382.31) | | 52 | 46 | 594.89 (331.35) | | | | 0.20 [-0.18; 0.58] |
| Week 25 | 57 | 52 | 526.98 (392.24) | | 52 | 46 | 590.20 (341.34) | | | | 0.17 [-0.21; 0.55] |
| Week 26 | 57 | 52 | 518.54 (390.63) | 412.48 (0.08) | 52 | 46 | 599.55 (366.40) | 516.69 (0.08) | 0.80 [0.64;1.00] | 0.0453 | 0.21 [-0.16; 0.59] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test).The log-transformed response at week 26 is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate. Missing mean values at week 26 are imputed by the log-transformed screening value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the log-transformed LAOT values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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## 2.14 Total weekly basal insulin dose by treatment week (U) - Onwards 4 - Population 1 - on-treatment - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico / IGlar | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETR [95%-CI] p-value | Hedges' g [95%-CI] |
| Weekly insulin dose (U) | | | | | | | | | | | |
| All subjects (total) | Week 1 | 57 | 55 | 333.36 (220.40) | | 52 | 52 | 232.34 (139.75) | | | -0.54 [-0.92;-0.16] |
| | Week 2 | 57 | 54 | 239.72 (179.14) | | 52 | 52 | 234.15 (141.03) | | | -0.03 [-0.41; 0.34] |
| | Week 3 | 57 | 54 | 238.70 (181.12) | | 52 | 51 | 243.43 (152.30) | | | 0.03 [-0.35; 0.40] |
| | Week 4 | 57 | 53 | 261.98 (184.97) | | 52 | 51 | 253.55 (154.58) | | | -0.05 [-0.42; 0.33] |
| | Week 5 | 57 | 52 | 270.77 (191.76) | | 52 | 51 | 261.44 (154.70) | | | -0.05 [-0.43; 0.32] |
| | Week 6 | 57 | 54 | 250.26 (159.29) | | 52 | 51 | 270.23 (160.87) | | | 0.12 [-0.25; 0.50] |
| | Week 7 | 57 | 54 | 260.37 (163.29) | | 52 | 50 | 270.30 (155.21) | | | 0.06 [-0.31; 0.44] |
| | Week 8 | 57 | 53 | 287.36 (198.08) | | 52 | 50 | 278.12 (168.51) | | | -0.05 [-0.43; 0.33] |
| | Week 9 | 57 | 54 | 290.93 (188.76) | | 52 | 49 | 278.88 (170.02) | | | -0.07 [-0.44; 0.31] |
| | Week 10 | 57 | 53 | 293.68 (191.89) | | 52 | 49 | 285.61 (177.46) | | | -0.04 [-0.42; 0.33] |
| | Week 11 | 57 | 52 | 297.12 (180.11) | | 52 | 48 | 286.73 (179.90) | | | -0.06 [-0.43; 0.32] |
| | Week 12 | 57 | 54 | 289.63 (176.53) | | 52 | 48 | 290.00 (184.88) | | | 0.00 [-0.37; 0.38] |
| | Week 13 | 57 | 51 | 296.67 (183.41) | | 52 | 48 | 289.65 (184.04) | | | -0.04 [-0.41; 0.34] |
| | Week 14 | 57 | 54 | 301.57 (183.18) | | 52 | 49 | 293.12 (183.63) | | | -0.05 [-0.42; 0.33] |
| | Week 15 | 57 | 52 | 309.90 (189.97) | | 52 | 49 | 294.72 (178.69) | | | -0.08 [-0.46; 0.29] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test).The log-transformed response at week 26 is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate. Missing mean values at week 26 are imputed by the log-transformed screening value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the log-transformed LAOT values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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Total weekly basal insulin dose by treatment week (U) - Onwards 4 - Population 1 - on-treatment - Full analysis set

| Week | Ico | | | | IGlar | | | | Ico / IGlar | | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETR [95%-CI] | p-value | Hedges' g [95%-CI] |
| Week 16 | 57 | 52 | 310.19 (191.13) | | 52 | 49 | 298.43 (183.62) | | | | -0.06 [-0.44; 0.31] |
| Week 17 | 57 | 53 | 313.58 (193.37) | | 52 | 49 | 303.69 (189.18) | | | | -0.05 [-0.43; 0.32] |
| Week 18 | 57 | 52 | 314.71 (198.86) | | 52 | 48 | 308.17 (192.60) | | | | -0.03 [-0.41; 0.34] |
| Week 19 | 57 | 49 | 321.12 (207.99) | | 52 | 47 | 311.32 (196.62) | | | | -0.05 [-0.42; 0.33] |
| Week 20 | 57 | 50 | 324.63 (203.76) | | 52 | 46 | 305.83 (197.25) | | | | -0.09 [-0.47; 0.28] |
| Week 21 | 57 | 50 | 327.40 (208.21) | | 52 | 46 | 306.63 (203.33) | | | | -0.10 [-0.48; 0.28] |
| Week 22 | 57 | 48 | 332.71 (213.87) | | 52 | 46 | 312.74 (206.90) | | | | -0.09 [-0.47; 0.28] |
| Week 23 | 57 | 49 | 328.27 (219.29) | | 52 | 46 | 310.42 (205.95) | | | | -0.08 [-0.46; 0.29] |
| Week 24 | 57 | 48 | 333.75 (211.11) | | 52 | 46 | 315.93 (206.36) | | | | -0.08 [-0.46; 0.29] |
| Week 25 | 57 | 49 | 336.12 (220.54) | | 52 | 46 | 316.74 (218.44) | | | | -0.09 [-0.46; 0.29] |
| Week 26 | 57 | 47 | 336.60 (214.80) | 300.11 (0.03) | 52 | 46 | 313.96 (220.32) | 279.42 (0.03) | 1.07 [0.99;1.17] | 0.0854 | -0.10 [-0.48; 0.27] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test).The log-transformed response at week 26 is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate. Missing mean values at week 26 are imputed by the log-transformed screening value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the log-transformed LAOT values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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## 2.15 Total weekly bolus insulin dose by treatment week (U) - Onwards 4 - Population 1 - on-treatment - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico / IGlar | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETR [95%-CI] p-value | Hedges' g [95%-CI] |
| Weekly Actual Bolus Dose (U) | | | | | | | | | | | |
| All subjects (total) | Week 1 | 57 | 56 | 209.47 (179.28) | | 52 | 51 | 251.46 (170.06) | | | 0.24 [-0.14; 0.62] |
| | Week 2 | 57 | 54 | 211.68 (169.27) | | 52 | 52 | 228.52 (163.20) | | | 0.10 [-0.28; 0.48] |
| | Week 3 | 57 | 54 | 206.01 (159.06) | | 52 | 51 | 220.78 (149.02) | | | 0.09 [-0.28; 0.47] |
| | Week 4 | 57 | 54 | 206.42 (153.12) | | 52 | 51 | 221.78 (146.16) | | | 0.10 [-0.27; 0.48] |
| | Week 5 | 57 | 54 | 204.91 (153.55) | | 52 | 51 | 223.74 (150.33) | | | 0.12 [-0.25; 0.50] |
| | Week 6 | 57 | 54 | 203.77 (153.25) | | 52 | 51 | 227.86 (153.34) | | | 0.16 [-0.22; 0.53] |
| | Week 7 | 57 | 53 | 193.78 (145.97) | | 52 | 50 | 219.10 (146.10) | | | 0.17 [-0.20; 0.55] |
| | Week 8 | 57 | 54 | 199.99 (154.19) | | 52 | 50 | 218.92 (145.13) | | | 0.13 [-0.25; 0.50] |
| | Week 9 | 57 | 54 | 192.19 (141.92) | | 52 | 49 | 225.12 (147.24) | | | 0.23 [-0.15; 0.60] |
| | Week 10 | 57 | 54 | 192.37 (145.77) | | 52 | 49 | 230.51 (150.07) | | | 0.26 [-0.12; 0.63] |
| | Week 11 | 57 | 54 | 194.43 (150.38) | | 52 | 48 | 234.62 (150.69) | | | 0.27 [-0.11; 0.64] |
| | Week 12 | 57 | 54 | 199.86 (155.58) | | 52 | 48 | 245.00 (156.16) | | | 0.29 [-0.09; 0.67] |
| | Week 13 | 57 | 54 | 200.32 (153.52) | | 52 | 48 | 252.73 (163.43) | | | 0.33 [-0.05; 0.71] |
| | Week 14 | 57 | 54 | 205.03 (161.46) | | 52 | 49 | 253.19 (156.83) | | | 0.30 [-0.08; 0.68] |
| | Week 15 | 57 | 53 | 213.45 (164.64) | | 52 | 49 | 247.86 (133.93) | | | 0.23 [-0.15; 0.60] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test).The log-transformed response at week 26 is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate. Missing mean values at week 26 are imputed by the log-transformed screening value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the log-transformed LAOT values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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Total weekly bolus insulin dose by treatment week (U) - Onwards 4 - Population 1 - on-treatment - Full analysis set

| Week | Ico | | | | IGlar | | | | Ico / IGlar | Ico - IGlar |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETR [95%-CI] p-value | Hedges' g [95%-CI] |
| Week 16 | 57 | 53 | 211.22 (170.72) | | 52 | 49 | 253.71 (138.77) | | | 0.27 [-0.11; 0.65] |
| Week 17 | 57 | 53 | 208.69 (175.90) | | 52 | 49 | 259.33 (146.32) | | | 0.31 [-0.07; 0.69] |
| Week 18 | 57 | 53 | 213.50 (180.39) | | 52 | 48 | 257.36 (147.21) | | | 0.26 [-0.11; 0.64] |
| Week 19 | 57 | 52 | 210.90 (183.02) | | 52 | 47 | 262.68 (153.33) | | | 0.30 [-0.07; 0.68] |
| Week 20 | 57 | 52 | 215.06 (189.75) | | 52 | 46 | 261.60 (161.40) | | | 0.26 [-0.12; 0.64] |
| Week 21 | 57 | 52 | 216.13 (189.83) | | 52 | 46 | 260.28 (151.89) | | | 0.25 [-0.12; 0.63] |
| Week 22 | 57 | 52 | 211.37 (185.33) | | 52 | 46 | 265.88 (161.14) | | | 0.31 [-0.07; 0.69] |
| Week 23 | 57 | 52 | 215.43 (188.90) | | 52 | 46 | 273.57 (170.99) | | | 0.32 [-0.06; 0.70] |
| Week 24 | 57 | 52 | 214.47 (201.33) | | 52 | 46 | 278.96 (169.68) | | | 0.34 [-0.04; 0.72] |
| Week 25 | 57 | 52 | 210.25 (204.92) | | 52 | 46 | 273.46 (162.22) | | | 0.34 [-0.04; 0.72] |
| Week 26 | 57 | 52 | 214.31 (204.94) | 199.88 (0.04) | 52 | 46 | 285.59 (193.90) | 257.50 (0.04) | 0.78 [0.70;0.86] <0.0001 | 0.35 [-0.02; 0.73] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test).The log-transformed response at week 26 is analysed using an analysis of covariance (ANCOVA) model with treatment, region and personal CGM device use as fixed factors, and log-transformed screening response as covariate. Missing mean values at week 26 are imputed by the log-transformed screening value and a random term, using multiple imputation. The random term is normally distributed with mean 0 and standard deviation equal to the estimated residual standard deviation from the ANCOVA model fitted to the log-transformed LAOT values. The model includes the same factors and covariates as the model used for analysis. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

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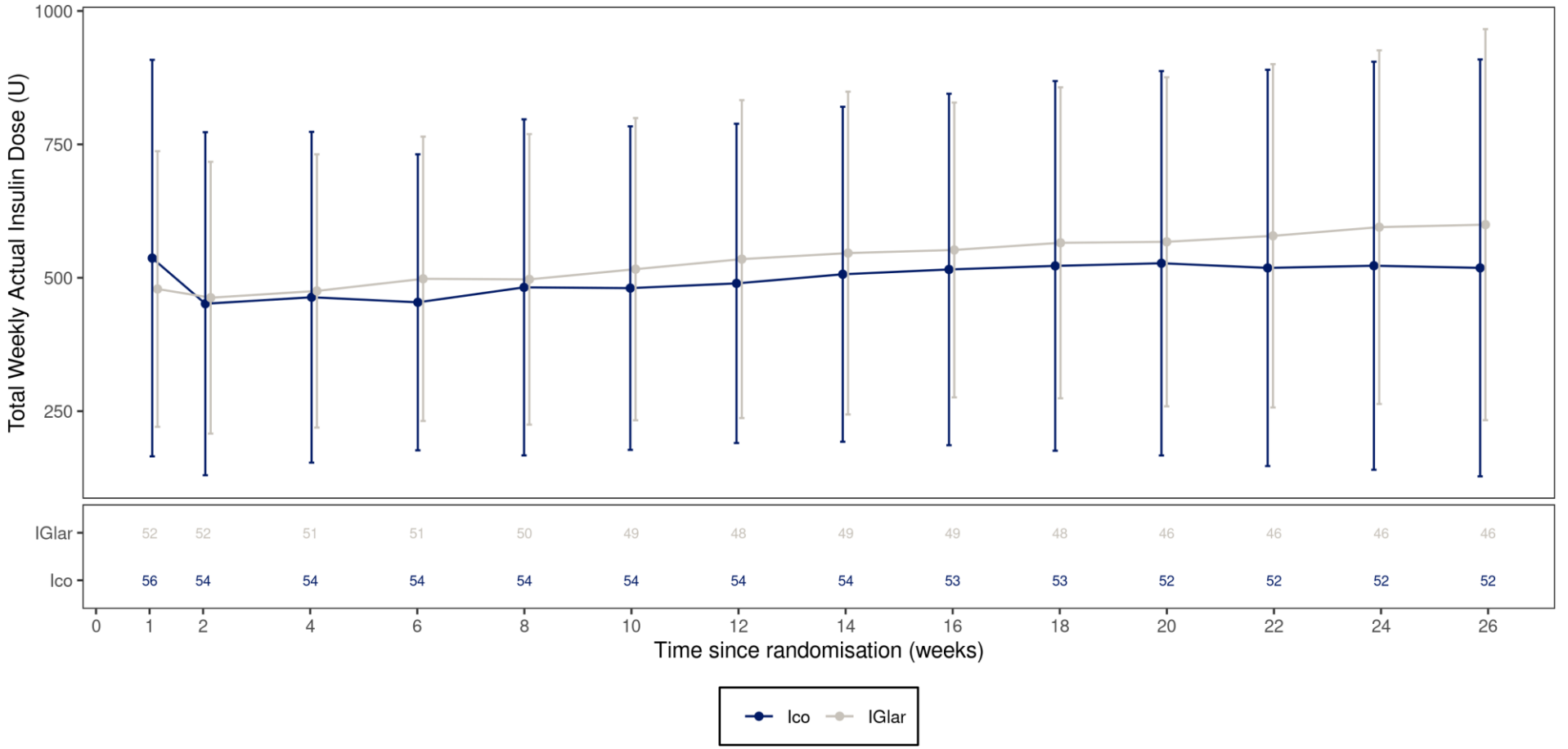
## 2.16 Total weekly insulin dose by treatment week (U) - Mean plot - Onwards 4 - Population 1 - on-treatment - Full analysis set




Observed data. Number of subjects contributing to data points appears in the bottom panel. Legend: Mean(symbol) and mean ± standard deviation (error bars).

nn1436/nn1436-amnog/current
23JAN2024:13:35:41 - P:/nn1436/nn1436-amnog/current/stats/program/nonctrprog/meanplot_descriptive.R/TOTDWACtotal4480.png

## 2.17 Time spent below range < 3.0 mmol/L (54 mg/dL) by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| Time spent < 3.0 mmol/L (54 mg/dL) (%) | | | | | | | | | | | | |
| All subjects (total) | Week 0-4 | 57 | 48 | 0.77 (1.69) | | 52 | 48 | 0.60 (0.85) | | | | -0.12 [-0.50; 0.25] |
| | Week 22-26 | 57 | 45 | 1.04 (1.30) | 0.96 (0.14) | 52 | 45 | 0.64 (0.75) | 0.64 (0.15) | 0.31 [ -0.09; 0.72] | 0.1285 | -0.37 [-0.75; 0.01] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The response from week 22 to week 26 is analysed using an analysis of variance (ANOVA) model with treatment, region and personal CGM device use as fixed factors. Missing values are imputed using multiple imputation based on values for subjects from the comparator group who completed randomised treatment. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

nn1436/nn1436-amnog/current
23JAN2024:13:35:34 - /TBR_4480.txt

## 2.18 Time in range 3.0-3.9 mmol/L (54-70 mg/dL) by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | | IGlar | | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) | LS Mean (SE) | N | n | Mean (SD) | LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| Time Spent in Range 3.0-3.9 mmol/L (54-70 mg/dL) (%) | | | | | | | | | | | | |
| All subjects (total) | Week 0-4 | 57 | 48 | 1.62 (2.21) | | 52 | 48 | 1.64 (2.10) | | | | 0.01 [-0.36; 0.39] |
| | Week 22-26 | 57 | 45 | 2.65 (2.54) | 2.54 (0.33) | 52 | 45 | 2.09 (2.10) | 2.07 (0.34) | 0.47 [ -0.47; 1.40] | 0.3267 | -0.24 [-0.61; 0.14] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The response from week 22 to week 26 is analysed using an analysis of variance (ANOVA) model with treatment, region and personal CGM device use as fixed factors. Missing values are imputed using multiple imputation based on values for subjects from the comparator group who completed randomised treatment. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

nn1436/nn1436-amnog/current
23JAN2024:13:35:35 - /TIRL_4480.txt

## 2.19 Time in range 3.9-10.0 mmol/L (70-180mg/dL) by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| | Week | Ico | | | IGlar | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | n | Mean (SD) LS Mean (SE) | N | n | Mean (SD) LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (%) | | | | | | | | | | |
| All subjects (total) | Week 0-4 | 57 | 48 | 55.97 (19.69) | 52 | 48 | 54.54 (19.14) | | | -0.07 [-0.45; 0.30] |
| | Week 22-26 | 57 | 45 | 62.36 (14.89) 63.17 (2.44) | 52 | 45 | 64.93 (17.83) 64.57 (2.47) | -1.40 [ -8.24; 5.43] | 0.6874 | 0.16 [-0.22; 0.53] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The response from week 22 to week 26 is analysed using an analysis of variance (ANOVA) model with treatment, region and personal CGM device use as fixed factors. Missing values are imputed using multiple imputation based on values for subjects from the comparator group who completed randomised treatment. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

nn1436/nn1436-amnog/current
23JAN2024:13:35:36 - /TIR_4480.txt

## 2.20 Time in range 10.0-13.9 mmol/L (180-250.2 mg/dL) by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| Week | Ico | | | IGlar | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | Mean (SD) LS Mean (SE) | N | n | Mean (SD) LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| Time Spent in Range 10.0-13.9 mmol/L (180-250.2 mg/dL) (%) | | | | | | | | | |
| All subjects (total) Week 0-4 | 57 | 48 | 27.95 (10.40) | 52 | 48 | 28.54 (10.12) | | | 0.06 [-0.32; 0.43] |
| Week 22-26 | 57 | 45 | 23.37 (7.85) 22.92 (1.25) | 52 | 45 | 22.23 (9.00) 22.44 (1.27) | 0.48 [ -3.04; 4.00] | 0.7892 | -0.13 [-0.51; 0.24] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The response from week 22 to week 26 is analysed using an analysis of variance (ANOVA) model with treatment, region and personal CGM device use as fixed factors. Missing values are imputed using multiple imputation based on values for subjects from the comparator group who completed randomised treatment. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

nn1436/nn1436-amnog/current
23JAN2024:13:35:37 - /TIRH_4480.txt

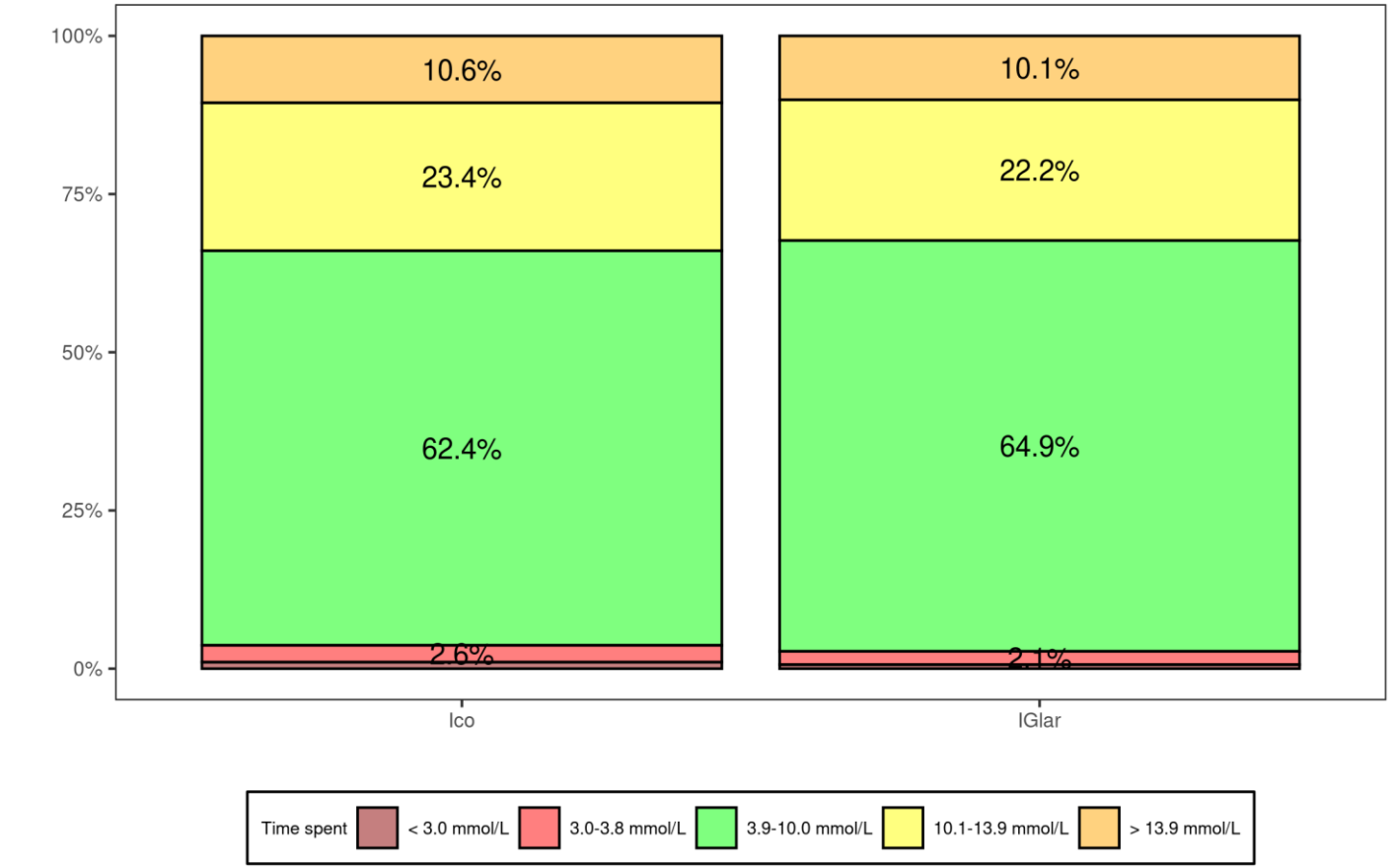
## 2.21 Time spent above range > 13.9 mmol/L (250 mg/dL) by treatment week - Onwards 4 - Population 1 - in-trial - Full analysis set

| Week | Ico | | | IGlar | | | Ico - IGlar | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | Mean (SD) LS Mean (SE) | N | n | Mean (SD) LS Mean (SE) | ETD [95%-CI] | p-value | Hedges' g [95%-CI] |
| Time spent > 13.9 mmol/L (250 mg/dL) (%) | | | | | | | | | |
| All subjects (total) Week 0-4 | 57 | 48 | 13.70 (15.11) | 52 | 48 | 14.68 (13.89) | | | 0.07 [-0.31; 0.44] |
| Week 22-26 | 57 | 45 | 10.58 (9.27) 10.36 (1.58) | 52 | 45 | 10.10 (11.72) 10.20 (1.59) | 0.16 [ -4.26; 4.58] | 0.9437 | -0.05 [-0.42; 0.33] |

N: number of subjects in the analysis set, n: number of subjects with an observation, SD: Standard deviation, SE: Standard error, CI: confidence interval, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test). The response from week 22 to week 26 is analysed using an analysis of variance (ANOVA) model with treatment, region and personal CGM device use as fixed factors. Missing values are imputed using multiple imputation based on values for subjects from the comparator group who completed randomised treatment. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

nn1436/nn1436-amnog/current
23JAN2024:13:35:38 - /TAR_4480.txt

## 2.22 CGM ranges from week 22-26 - Onwards 4 - Population 1 - in-trial - Full analysis set




Observed data including data obtained after premature treatment discontinuation. Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements. Values <2% are shown on the plot but the numbers are not displayed.

nn1436/nn1436-amnog/current
23JAN2024:13:36:07 - P:/nn1436/nn1436-amnog/current/stats/program/nonctrprog/fcgmrangebar.R/fcgmrangesintfasow4.png

## 2.23 All-cause mortality - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 0 ( 0.0) | 52 | 1 ( 1.9) | 0.30 (0.01, 7.49) | 0.30 (0.01, 7.32) | -1.92 (-5.66, 1.81) | 0.3593 | |
| Gender | | | | | | | | | NA |
| Female | 26 | 0 ( 0.0) | 28 | 0 ( 0.0) | 1.08 (0.02, 56.16) | 1.07 (0.02, 52.26) | 0.00 (0.00, 0.00) | NA | |
| Male | 31 | 0 ( 0.0) | 24 | 1 ( 4.2) | 0.25 (0.01, 6.38) | 0.26 (0.01, 6.12) | -4.17 (-12.16, 3.83) | 0.3406 | |
| Age | | | | | | | | | NA |
| <65 years | 37 | 0 ( 0.0) | 34 | 1 ( 2.9) | 0.30 (0.01, 7.56) | 0.31 (0.01, 7.29) | -2.94 (-8.62, 2.74) | 0.3590 | |
| >=65 years | 20 | 0 ( 0.0) | 18 | 0 ( 0.0) | 0.90 (0.02, 47.82) | 0.90 (0.02, 43.40) | 0.00 (0.00, 0.00) | NA | |
| HbA1c | | | | | | | | | NA |
| <=8,5% | 36 | 0 ( 0.0) | 36 | 0 ( 0.0) | 1.00 (0.02, 51.76) | 1.00 (0.02, 49.08) | 0.00 (0.00, 0.00) | NA | |
| >8,5% | 21 | 0 ( 0.0) | 16 | 1 ( 6.2) | 0.24 (0.01, 6.30) | 0.26 (0.01, 5.94) | -6.25 (-18.11, 5.61) | 0.3367 | |
| Region | | | | | | | | | NA |
| Europe | 24 | 0 ( 0.0) | 24 | 1 ( 4.2) | 0.32 (0.01, 8.25) | 0.33 (0.01, 7.80) | -4.17 (-12.16, 3.83) | 0.5265 | |
| North and South America | 24 | 0 ( 0.0) | 19 | 0 ( 0.0) | 0.80 (0.02, 41.95) | 0.80 (0.02, 38.57) | 0.00 (0.00, 0.00) | NA | |
| Asia | 9 | 0 ( 0.0) | 9 | 0 ( 0.0) | 1.00 (0.02, 55.80) | 1.00 (0.02, 45.63) | 0.00 (0.00, 0.00) | NA | |
| Race | | | | | | | | | NA |
| White | 42 | 0 ( 0.0) | 39 | 1 ( 2.6) | 0.30 (0.01, 7.63) | 0.31 (0.01, 7.39) | -2.56 (-7.52, 2.40) | 0.3604 | |
| Not white | 15 | 0 ( 0.0) | 13 | 0 ( 0.0) | 0.87 (0.02, 46.95) | 0.88 (0.02, 41.27) | 0.00 (0.00, 0.00) | NA | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:39 - /ACM_4480.txt

## 2.24 Adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 33 (57.9) | 52 | 31 (59.6) | 0.93 (0.43, 2.00) | 0.97 (0.71, 1.33) | -1.72 (-20.22, 16.78) | 0.8881 | |
| Gender | | | | | | | | | 0.1562 |
| Female | 26 | 17 (65.4) | 28 | 15 (53.6) | 1.64 (0.55, 4.91) | 1.22 (0.78, 1.90) | 11.81 (-14.18, 37.81) | 0.5284 | |
| Male | 31 | 16 (51.6) | 24 | 16 (66.7) | 0.53 (0.18, 1.61) | 0.77 (0.50, 1.21) | -15.05 (-40.84, 10.74) | 0.3406 | |
| Age | | | | | | | | | 0.4037 |
| <65 years | 37 | 19 (51.4) | 34 | 20 (58.8) | 0.74 (0.29, 1.89) | 0.87 (0.57, 1.33) | -7.47 (-30.56, 15.62) | 0.5955 | |
| >=65 years | 20 | 14 (70.0) | 18 | 11 (61.1) | 1.48 (0.39, 5.71) | 1.15 (0.72, 1.83) | 8.89 (-21.29, 39.06) | 0.6248 | |
| HbA1c | | | | | | | | | 0.1428 |
| <=8,5% | 36 | 23 (63.9) | 36 | 20 (55.6) | 1.42 (0.55, 3.64) | 1.15 (0.79, 1.68) | 8.33 (-14.24, 30.91) | 0.5303 | |
| >8,5% | 21 | 10 (47.6) | 16 | 11 (68.8) | 0.41 (0.11, 1.61) | 0.69 (0.40, 1.21) | -21.13 (-52.31, 10.05) | 0.2183 | |
| Region | | | | | | | | | 0.9220 |
| Europe | 24 | 12 (50.0) | 24 | 12 (50.0) | 1.00 (0.32, 3.10) | 1.00 (0.57, 1.76) | 0.00 (-28.29, 28.29) | 1.0000 | |
| North and South America | 24 | 17 (70.8) | 19 | 14 (73.7) | 0.87 (0.23, 3.34) | 0.96 (0.66, 1.39) | -2.85 (-29.73, 24.03) | 0.8521 | |
| Asia | 9 | 4 (44.4) | 9 | 5 (55.6) | 0.64 (0.10, 4.11) | 0.80 (0.31, 2.04) | -11.11 (-57.02, 34.80) | 0.8145 | |
| Race | | | | | | | | | 0.6345 |
| White | 42 | 24 (57.1) | 39 | 22 (56.4) | 1.03 (0.43, 2.48) | 1.01 (0.69, 1.48) | 0.73 (-20.86, 22.32) | 0.9994 | |
| Not white | 15 | 9 (60.0) | 13 | 9 (69.2) | 0.67 (0.14, 3.19) | 0.87 (0.50, 1.50) | -9.23 (-44.50, 26.04) | 0.6615 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:40 - /AE_4480.txt

## 2.25 Severe adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 4 ( 7.0) | 52 | 3 ( 5.8) | 1.23 (0.26, 5.79) | 1.22 (0.29, 5.18) | 1.25 (-7.92, 10.42) | 0.8132 | |
| Gender | | | | | | | | | 0.5000 |
| Female | 26 | 2 ( 7.7) | 28 | 1 ( 3.6) | 2.25 (0.19, 26.41) | 2.15 (0.21, 22.37) | 4.12 (-8.21, 16.46) | 0.5945 | |
| Male | 31 | 2 ( 6.5) | 24 | 2 ( 8.3) | 0.76 (0.10, 5.82) | 0.77 (0.12, 5.10) | -1.88 (-15.92, 12.16) | 0.8399 | |
| Age | | | | | | | | | 0.1394 |
| <65 years | 37 | 2 ( 5.4) | 34 | 3 ( 8.8) | 0.59 (0.09, 3.77) | 0.61 (0.11, 3.45) | -3.42 (-15.42, 8.58) | 0.6177 | |
| >=65 years | 20 | 2 (10.0) | 18 | 0 ( 0.0) | 5.00 (0.22, 111.43) | 4.52 (0.23, 88.38) | 10.00 (-3.15, 23.15) | 0.2158 | |
| HbA1c | | | | | | | | | 0.1843 |
| <=8,5% | 36 | 3 ( 8.3) | 36 | 1 ( 2.8) | 3.18 (0.32, 32.14) | 3.00 (0.33, 27.50) | 5.56 (-4.95, 16.06) | 0.3648 | |
| >8,5% | 21 | 1 ( 4.8) | 16 | 2 (12.5) | 0.35 (0.03, 4.25) | 0.38 (0.04, 3.84) | -7.74 (-26.33, 10.85) | 0.5617 | |
| Region | | | | | | | | | 0.9556 |
| Europe | 24 | 1 ( 4.2) | 24 | 1 ( 4.2) | 1.00 (0.06, 16.97) | 1.00 (0.07, 15.08) | 0.00 (-11.31, 11.31) | 1.0000 | |
| North and South America | 24 | 2 ( 8.3) | 19 | 1 ( 5.3) | 1.64 (0.14, 19.54) | 1.58 (0.16, 16.17) | 3.07 (-11.87, 18.01) | 0.7236 | |
| Asia | 9 | 1 (11.1) | 9 | 1 (11.1) | 1.00 (0.05, 18.91) | 1.00 (0.07, 13.64) | 0.00 (-29.04, 29.04) | 1.0000 | |
| Race | | | | | | | | | 0.7705 |
| White | 42 | 3 ( 7.1) | 39 | 2 ( 5.1) | 1.42 (0.22, 9.00) | 1.39 (0.25, 7.90) | 2.01 (-8.41, 12.44) | 0.7714 | |
| Not white | 15 | 1 ( 6.7) | 13 | 1 ( 7.7) | 0.86 (0.05, 15.22) | 0.87 (0.06, 12.52) | -1.03 (-20.24, 18.19) | 0.9950 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:41 - /SevAE_4480.txt

## 2.26 Serious adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 4 ( 7.0) | 52 | 4 ( 7.7) | 0.91 (0.21, 3.82) | 0.91 (0.24, 3.46) | -0.67 (-10.49, 9.15) | 0.9468 | |
| Gender | | | | | | | | | 0.3181 |
| Female | 26 | 2 ( 7.7) | 28 | 1 ( 3.6) | 2.25 (0.19, 26.41) | 2.15 (0.21, 22.37) | 4.12 (-8.21, 16.46) | 0.5945 | |
| Male | 31 | 2 ( 6.5) | 24 | 3 (12.5) | 0.48 (0.07, 3.15) | 0.52 (0.09, 2.85) | -6.05 (-21.86, 9.76) | 0.6018 | |
| Age | | | | | | | | | 0.4567 |
| <65 years | 37 | 2 ( 5.4) | 34 | 3 ( 8.8) | 0.59 (0.09, 3.77) | 0.61 (0.11, 3.45) | -3.42 (-15.42, 8.58) | 0.6177 | |
| >=65 years | 20 | 2 (10.0) | 18 | 1 ( 5.6) | 1.89 (0.16, 22.79) | 1.80 (0.18, 18.21) | 4.44 (-12.43, 21.32) | 0.7118 | |
| HbA1c | | | | | | | | | 0.3384 |
| <=8,5% | 36 | 3 ( 8.3) | 36 | 2 ( 5.6) | 1.55 (0.24, 9.85) | 1.50 (0.27, 8.45) | 2.78 (-8.95, 14.50) | 0.7502 | |
| >8,5% | 21 | 1 ( 4.8) | 16 | 2 (12.5) | 0.35 (0.03, 4.25) | 0.38 (0.04, 3.84) | -7.74 (-26.33, 10.85) | 0.5617 | |
| Region | | | | | | | | | 0.7819 |
| Europe | 24 | 1 ( 4.2) | 24 | 2 ( 8.3) | 0.48 (0.04, 5.66) | 0.50 (0.05, 5.15) | -4.17 (-17.81, 9.48) | 0.6791 | |
| North and South America | 24 | 2 ( 8.3) | 19 | 1 ( 5.3) | 1.64 (0.14, 19.54) | 1.58 (0.16, 16.17) | 3.07 (-11.87, 18.01) | 0.7236 | |
| Asia | 9 | 1 (11.1) | 9 | 1 (11.1) | 1.00 (0.05, 18.91) | 1.00 (0.07, 13.64) | 0.00 (-29.04, 29.04) | 1.0000 | |
| Race | | | | | | | | | 0.9651 |
| White | 42 | 3 ( 7.1) | 39 | 3 ( 7.7) | 0.92 (0.17, 4.87) | 0.93 (0.20, 4.33) | -0.55 (-11.98, 10.88) | 0.9955 | |
| Not white | 15 | 1 ( 6.7) | 13 | 1 ( 7.7) | 0.86 (0.05, 15.22) | 0.87 (0.06, 12.52) | -1.03 (-20.24, 18.19) | 0.9950 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:42 - /SerAE_4480.txt

## 2.27 Adverse events leading to permanent trial product discontinuation - Onwards 4 - Population 1 - in- trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 1 ( 1.8) | 52 | 1 ( 1.9) | 0.91 (0.06, 14.94) | 0.91 (0.06, 14.22) | -0.17 (-5.22, 4.89) | 0.9994 | |
| Gender | | | | | | | | | NA |
| Female | 26 | 0 ( 0.0) | 28 | 0 ( 0.0) | 1.08 (0.02, 56.16) | 1.07 (0.02, 52.26) | 0.00 (0.00, 0.00) | NA | |
| Male | 31 | 1 ( 3.2) | 24 | 1 ( 4.2) | 0.77 (0.05, 12.92) | 0.77 (0.05, 11.75) | -0.94 (-11.07, 9.19) | 0.9127 | |
| Age | | | | | | | | | 0.1553 |
| <65 years | 37 | 0 ( 0.0) | 34 | 1 ( 2.9) | 0.30 (0.01, 7.56) | 0.31 (0.01, 7.29) | -2.94 (-8.62, 2.74) | 0.3590 | |
| >=65 years | 20 | 1 ( 5.0) | 18 | 0 ( 0.0) | 2.85 (0.11, 74.38) | 2.71 (0.12, 62.70) | 5.00 (-4.55, 14.55) | 0.5135 | |
| HbA1c | | | | | | | | | NA |
| <=8,5% | 36 | 1 ( 2.8) | 36 | 1 ( 2.8) | 1.00 (0.06, 16.63) | 1.00 (0.07, 15.38) | 0.00 (-7.59, 7.59) | 1.0000 | |
| >8,5% | 21 | 0 ( 0.0) | 16 | 0 ( 0.0) | 0.77 (0.01, 40.75) | 0.77 (0.02, 36.99) | 0.00 (0.00, 0.00) | NA | |
| Region | | | | | | | | | NA |
| Europe | 24 | 0 ( 0.0) | 24 | 0 ( 0.0) | 1.00 (0.02, 52.44) | 1.00 (0.02, 48.45) | 0.00 (0.00, 0.00) | NA | |
| North and South America | 24 | 0 ( 0.0) | 19 | 0 ( 0.0) | 0.80 (0.02, 41.95) | 0.80 (0.02, 38.57) | 0.00 (0.00, 0.00) | NA | |
| Asia | 9 | 1 (11.1) | 9 | 1 (11.1) | 1.00 (0.05, 18.91) | 1.00 (0.07, 13.64) | 0.00 (-29.04, 29.04) | 1.0000 | |
| Race | | | | | | | | | NA |
| White | 42 | 0 ( 0.0) | 39 | 0 ( 0.0) | 0.93 (0.02, 47.97) | 0.93 (0.02, 45.78) | 0.00 (0.00, 0.00) | NA | |
| Not white | 15 | 1 ( 6.7) | 13 | 1 ( 7.7) | 0.86 (0.05, 15.22) | 0.87 (0.06, 12.52) | -1.03 (-20.24, 18.19) | 0.9950 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:45 - /AEdisc_4480.txt

## 2.28 Adverse events leading to study withdrawal - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:46 - /AEwith_4480.txt

## 2.29 Adverse events excluding disease-associated events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 33 (57.9) | 52 | 31 (59.6) | 0.93 (0.43, 2.00) | 0.97 (0.71, 1.33) | -1.72 (-20.22, 16.78) | 0.8881 | |
| Gender | | | | | | | | | 0.1562 |
| Female | 26 | 17 (65.4) | 28 | 15 (53.6) | 1.64 (0.55, 4.91) | 1.22 (0.78, 1.90) | 11.81 (-14.18, 37.81) | 0.5284 | |
| Male | 31 | 16 (51.6) | 24 | 16 (66.7) | 0.53 (0.18, 1.61) | 0.77 (0.50, 1.21) | -15.05 (-40.84, 10.74) | 0.3406 | |
| Age | | | | | | | | | 0.4037 |
| <65 years | 37 | 19 (51.4) | 34 | 20 (58.8) | 0.74 (0.29, 1.89) | 0.87 (0.57, 1.33) | -7.47 (-30.56, 15.62) | 0.5955 | |
| >=65 years | 20 | 14 (70.0) | 18 | 11 (61.1) | 1.48 (0.39, 5.71) | 1.15 (0.72, 1.83) | 8.89 (-21.29, 39.06) | 0.6248 | |
| HbA1c | | | | | | | | | 0.1428 |
| <=8,5% | 36 | 23 (63.9) | 36 | 20 (55.6) | 1.42 (0.55, 3.64) | 1.15 (0.79, 1.68) | 8.33 (-14.24, 30.91) | 0.5303 | |
| >8,5% | 21 | 10 (47.6) | 16 | 11 (68.8) | 0.41 (0.11, 1.61) | 0.69 (0.40, 1.21) | -21.13 (-52.31, 10.05) | 0.2183 | |
| Region | | | | | | | | | 0.9220 |
| Europe | 24 | 12 (50.0) | 24 | 12 (50.0) | 1.00 (0.32, 3.10) | 1.00 (0.57, 1.76) | 0.00 (-28.29, 28.29) | 1.0000 | |
| North and South America | 24 | 17 (70.8) | 19 | 14 (73.7) | 0.87 (0.23, 3.34) | 0.96 (0.66, 1.39) | -2.85 (-29.73, 24.03) | 0.8521 | |
| Asia | 9 | 4 (44.4) | 9 | 5 (55.6) | 0.64 (0.10, 4.11) | 0.80 (0.31, 2.04) | -11.11 (-57.02, 34.80) | 0.8145 | |
| Race | | | | | | | | | 0.6345 |
| White | 42 | 24 (57.1) | 39 | 22 (56.4) | 1.03 (0.43, 2.48) | 1.01 (0.69, 1.48) | 0.73 (-20.86, 22.32) | 0.9994 | |
| Not white | 15 | 9 (60.0) | 13 | 9 (69.2) | 0.67 (0.14, 3.19) | 0.87 (0.50, 1.50) | -9.23 (-44.50, 26.04) | 0.6615 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:47 - /AEexcl_4480.txt

## 2.30 Severe adverse events excluding disease-associated events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 3 ( 5.3) | 52 | 3 ( 5.8) | 0.91 (0.17, 4.71) | 0.91 (0.19, 4.32) | -0.51 (-9.09, 8.08) | 0.9831 | |
| Gender | | | | | | | | | 0.8422 |
| Female | 26 | 1 ( 3.8) | 28 | 1 ( 3.6) | 1.08 (0.06, 18.20) | 1.08 (0.07, 16.35) | 0.27 (-9.82, 10.37) | 1.0000 | |
| Male | 31 | 2 ( 6.5) | 24 | 2 ( 8.3) | 0.76 (0.10, 5.82) | 0.77 (0.12, 5.10) | -1.88 (-15.92, 12.16) | 0.8399 | |
| Age | | | | | | | | | 0.0769 |
| <65 years | 37 | 1 ( 2.7) | 34 | 3 ( 8.8) | 0.29 (0.03, 2.90) | 0.31 (0.03, 2.81) | -6.12 (-16.99, 4.75) | 0.2947 | |
| >=65 years | 20 | 2 (10.0) | 18 | 0 ( 0.0) | 5.00 (0.22, 111.43) | 4.52 (0.23, 88.38) | 10.00 (-3.15, 23.15) | 0.2158 | |
| HbA1c | | | | | | | | | 0.3072 |
| <=8,5% | 36 | 2 ( 5.6) | 36 | 1 ( 2.8) | 2.06 (0.18, 23.77) | 2.00 (0.19, 21.09) | 2.78 (-6.43, 11.99) | 0.6805 | |
| >8,5% | 21 | 1 ( 4.8) | 16 | 2 (12.5) | 0.35 (0.03, 4.25) | 0.38 (0.04, 3.84) | -7.74 (-26.33, 10.85) | 0.5617 | |
| Region | | | | | | | | | 0.9906 |
| Europe | 24 | 1 ( 4.2) | 24 | 1 ( 4.2) | 1.00 (0.06, 16.97) | 1.00 (0.07, 15.08) | 0.00 (-11.31, 11.31) | 1.0000 | |
| North and South America | 24 | 1 ( 4.2) | 19 | 1 ( 5.3) | 0.78 (0.05, 13.39) | 0.79 (0.05, 11.85) | -1.10 (-13.93, 11.74) | 0.9633 | |
| Asia | 9 | 1 (11.1) | 9 | 1 (11.1) | 1.00 (0.05, 18.91) | 1.00 (0.07, 13.64) | 0.00 (-29.04, 29.04) | 1.0000 | |
| Race | | | | | | | | | 0.9661 |
| White | 42 | 2 ( 4.8) | 39 | 2 ( 5.1) | 0.92 (0.12, 6.91) | 0.93 (0.14, 6.28) | -0.37 (-9.82, 9.09) | 0.9994 | |
| Not white | 15 | 1 ( 6.7) | 13 | 1 ( 7.7) | 0.86 (0.05, 15.22) | 0.87 (0.06, 12.52) | -1.03 (-20.24, 18.19) | 0.9950 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:47 - /SevAEexcl_4480.txt

## 2.31 Serious adverse events excluding disease-associated events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 3 ( 5.3) | 52 | 4 ( 7.7) | 0.67 (0.14, 3.13) | 0.68 (0.16, 2.91) | -2.43 (-11.71, 6.85) | 0.6431 | |
| Gender | | | | | | | | | 0.6387 |
| Female | 26 | 1 ( 3.8) | 28 | 1 ( 3.6) | 1.08 (0.06, 18.20) | 1.08 (0.07, 16.35) | 0.27 (-9.82, 10.37) | 1.0000 | |
| Male | 31 | 2 ( 6.5) | 24 | 3 (12.5) | 0.48 (0.07, 3.15) | 0.52 (0.09, 2.85) | -6.05 (-21.86, 9.76) | 0.6018 | |
| Age | | | | | | | | | 0.2621 |
| <65 years | 37 | 1 ( 2.7) | 34 | 3 ( 8.8) | 0.29 (0.03, 2.90) | 0.31 (0.03, 2.81) | -6.12 (-16.99, 4.75) | 0.2947 | |
| >=65 years | 20 | 2 (10.0) | 18 | 1 ( 5.6) | 1.89 (0.16, 22.79) | 1.80 (0.18, 18.21) | 4.44 (-12.43, 21.32) | 0.7118 | |
| HbA1c | | | | | | | | | 0.5170 |
| <=8,5% | 36 | 2 ( 5.6) | 36 | 2 ( 5.6) | 1.00 (0.13, 7.51) | 1.00 (0.15, 6.72) | 0.00 (-10.58, 10.58) | 1.0000 | |
| >8,5% | 21 | 1 ( 4.8) | 16 | 2 (12.5) | 0.35 (0.03, 4.25) | 0.38 (0.04, 3.84) | -7.74 (-26.33, 10.85) | 0.5617 | |
| Region | | | | | | | | | 0.9256 |
| Europe | 24 | 1 ( 4.2) | 24 | 2 ( 8.3) | 0.48 (0.04, 5.66) | 0.50 (0.05, 5.15) | -4.17 (-17.81, 9.48) | 0.6791 | |
| North and South America | 24 | 1 ( 4.2) | 19 | 1 ( 5.3) | 0.78 (0.05, 13.39) | 0.79 (0.05, 11.85) | -1.10 (-13.93, 11.74) | 0.9633 | |
| Asia | 9 | 1 (11.1) | 9 | 1 (11.1) | 1.00 (0.05, 18.91) | 1.00 (0.07, 13.64) | 0.00 (-29.04, 29.04) | 1.0000 | |
| Race | | | | | | | | | 0.8377 |
| White | 42 | 2 ( 4.8) | 39 | 3 ( 7.7) | 0.60 (0.09, 3.80) | 0.62 (0.11, 3.51) | -2.93 (-13.49, 7.63) | 0.6194 | |
| Not white | 15 | 1 ( 6.7) | 13 | 1 ( 7.7) | 0.86 (0.05, 15.22) | 0.87 (0.06, 12.52) | -1.03 (-20.24, 18.19) | 0.9950 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:48 - /SerAEexcl_4480.txt

## 2.32 Non-severe hypoglycaemic episodes (G-BA definition) - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 1 ( 1.8) | 52 | 0 ( 0.0) | 2.79 (0.11, 69.95) | 2.74 (0.11, 65.85) | 1.75 (-1.65, 5.16) | 0.5144 | |
| Gender | | | | | | | | | NA |
| Female | 26 | 1 ( 3.8) | 28 | 0 ( 0.0) | 3.35 (0.13, 86.03) | 3.22 (0.14, 75.75) | 3.85 (-3.55, 11.24) | 0.3578 | |
| Male | 31 | 0 ( 0.0) | 24 | 0 ( 0.0) | 0.78 (0.01, 40.61) | 0.78 (0.02, 38.02) | 0.00 (0.00, 0.00) | NA | |
| Age | | | | | | | | | NA |
| <65 years | 37 | 1 ( 2.7) | 34 | 0 ( 0.0) | 2.84 (0.11, 71.99) | 2.76 (0.12, 65.62) | 2.70 (-2.52, 7.93) | 0.5140 | |
| >=65 years | 20 | 0 ( 0.0) | 18 | 0 ( 0.0) | 0.90 (0.02, 47.82) | 0.90 (0.02, 43.40) | 0.00 (0.00, 0.00) | NA | |
| HbA1c | | | | | | | | | NA |
| <=8,5% | 36 | 0 ( 0.0) | 36 | 0 ( 0.0) | 1.00 (0.02, 51.76) | 1.00 (0.02, 49.08) | 0.00 (0.00, 0.00) | NA | |
| >8,5% | 21 | 1 ( 4.8) | 16 | 0 ( 0.0) | 2.41 (0.09, 63.25) | 2.32 (0.10, 53.42) | 4.76 (-4.35, 13.87) | 0.5157 | |
| Region | | | | | | | | | NA |
| Europe | 24 | 0 ( 0.0) | 24 | 0 ( 0.0) | 1.00 (0.02, 52.44) | 1.00 (0.02, 48.45) | 0.00 (0.00, 0.00) | NA | |
| North and South America | 24 | 1 ( 4.2) | 19 | 0 ( 0.0) | 2.49 (0.10, 64.62) | 2.40 (0.10, 55.79) | 4.17 (-3.83, 12.16) | 0.5153 | |
| Asia | 9 | 0 ( 0.0) | 9 | 0 ( 0.0) | 1.00 (0.02, 55.80) | 1.00 (0.02, 45.63) | 0.00 (0.00, 0.00) | NA | |
| Race | | | | | | | | | NA |
| White | 42 | 1 ( 2.4) | 39 | 0 ( 0.0) | 2.86 (0.11, 72.19) | 2.79 (0.12, 66.54) | 2.38 (-2.23, 6.99) | 0.5141 | |
| Not white | 15 | 0 ( 0.0) | 13 | 0 ( 0.0) | 0.87 (0.02, 46.95) | 0.88 (0.02, 41.27) | 0.00 (0.00, 0.00) | NA | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand. Non-severe hypoglycaemic episodes are defined as being blood-glucose confirmed (< 3.0 mmol/L) with symptoms and not requiring medical assistance. Medical assistance is defined as an event either requiring administration of i.v. glucose or glucagon, is life threatening, leads to hospitalisation, calling of an emergency doctor, or is associated with the subject entering a coma or unconscious.

nn1436/nn1436-amnog/current
21FEB2024:13:15:49 - /nonsevhypo_4480.txt

## 2.33 Severe hypoglycaemic episodes (G-BA definition) - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 2 ( 3.5) | 52 | 0 ( 0.0) | 4.73 (0.22, 100.85) | 4.57 (0.22, 93.01) | 3.51 (-1.27, 8.29) | 0.2214 | |
| Gender | | | | | | | | | NA |
| Female | 26 | 2 ( 7.7) | 28 | 0 ( 0.0) | 5.82 (0.27, 127.06) | 5.37 (0.27, 106.88) | 7.69 (-2.55, 17.93) | 0.1653 | |
| Male | 31 | 0 ( 0.0) | 24 | 0 ( 0.0) | 0.78 (0.01, 40.61) | 0.78 (0.02, 38.02) | 0.00 (0.00, 0.00) | NA | |
| Age | | | | | | | | | NA |
| <65 years | 37 | 2 ( 5.4) | 34 | 0 ( 0.0) | 4.86 (0.23, 104.92) | 4.61 (0.23, 92.63) | 5.41 (-1.88, 12.69) | 0.2198 | |
| >=65 years | 20 | 0 ( 0.0) | 18 | 0 ( 0.0) | 0.90 (0.02, 47.82) | 0.90 (0.02, 43.40) | 0.00 (0.00, 0.00) | NA | |
| HbA1c | | | | | | | | | NA |
| <=8,5% | 36 | 1 ( 2.8) | 36 | 0 ( 0.0) | 3.08 (0.12, 78.27) | 3.00 (0.13, 71.28) | 2.78 (-2.59, 8.15) | 0.5277 | |
| >8,5% | 21 | 1 ( 4.8) | 16 | 0 ( 0.0) | 2.41 (0.09, 63.25) | 2.32 (0.10, 53.42) | 4.76 (-4.35, 13.87) | 0.5157 | |
| Region | | | | | | | | | NA |
| Europe | 24 | 0 ( 0.0) | 24 | 0 ( 0.0) | 1.00 (0.02, 52.44) | 1.00 (0.02, 48.45) | 0.00 (0.00, 0.00) | NA | |
| North and South America | 24 | 2 ( 8.3) | 19 | 0 ( 0.0) | 4.33 (0.20, 95.84) | 4.00 (0.20, 78.66) | 8.33 (-2.72, 19.39) | 0.2538 | |
| Asia | 9 | 0 ( 0.0) | 9 | 0 ( 0.0) | 1.00 (0.02, 55.80) | 1.00 (0.02, 45.63) | 0.00 (0.00, 0.00) | NA | |
| Race | | | | | | | | | NA |
| White | 42 | 2 ( 4.8) | 39 | 0 ( 0.0) | 4.88 (0.23, 104.82) | 4.65 (0.23, 93.95) | 4.76 (-1.68, 11.20) | 0.2206 | |
| Not white | 15 | 0 ( 0.0) | 13 | 0 ( 0.0) | 0.87 (0.02, 46.95) | 0.88 (0.02, 41.27) | 0.00 (0.00, 0.00) | NA | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand. Severe hypoglycaemic episodes are defined as events requiring medical assistance. Medical assistance is defined as an event either requiring administration of i.v. glucose or glucagon, is life threatening, leads to hospitalisation, calling of an emergency doctor, or is associated with the subject entering a coma or unconscious.

nn1436/nn1436-amnog/current
21FEB2024:13:15:51 - /sevhypo_4480.txt

## 2.34 Serious adverse events - hypoglycaemia - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 1 ( 1.8) | 52 | 0 ( 0.0) | 2.79 (0.11, 69.95) | 2.74 (0.11, 65.85) | 1.75 (-1.65, 5.16) | 0.5144 | |
| Gender | | | | | | | | | NA |
| Female | 26 | 1 ( 3.8) | 28 | 0 ( 0.0) | 3.35 (0.13, 86.03) | 3.22 (0.14, 75.75) | 3.85 (-3.55, 11.24) | 0.3578 | |
| Male | 31 | 0 ( 0.0) | 24 | 0 ( 0.0) | 0.78 (0.01, 40.61) | 0.78 (0.02, 38.02) | 0.00 (0.00, 0.00) | NA | |
| Age | | | | | | | | | NA |
| <65 years | 37 | 1 ( 2.7) | 34 | 0 ( 0.0) | 2.84 (0.11, 71.99) | 2.76 (0.12, 65.62) | 2.70 (-2.52, 7.93) | 0.5140 | |
| >=65 years | 20 | 0 ( 0.0) | 18 | 0 ( 0.0) | 0.90 (0.02, 47.82) | 0.90 (0.02, 43.40) | 0.00 (0.00, 0.00) | NA | |
| HbA1c | | | | | | | | | NA |
| <=8,5% | 36 | 1 ( 2.8) | 36 | 0 ( 0.0) | 3.08 (0.12, 78.27) | 3.00 (0.13, 71.28) | 2.78 (-2.59, 8.15) | 0.5277 | |
| >8,5% | 21 | 0 ( 0.0) | 16 | 0 ( 0.0) | 0.77 (0.01, 40.75) | 0.77 (0.02, 36.99) | 0.00 (0.00, 0.00) | NA | |
| Region | | | | | | | | | NA |
| Europe | 24 | 0 ( 0.0) | 24 | 0 ( 0.0) | 1.00 (0.02, 52.44) | 1.00 (0.02, 48.45) | 0.00 (0.00, 0.00) | NA | |
| North and South America | 24 | 1 ( 4.2) | 19 | 0 ( 0.0) | 2.49 (0.10, 64.62) | 2.40 (0.10, 55.79) | 4.17 (-3.83, 12.16) | 0.5153 | |
| Asia | 9 | 0 ( 0.0) | 9 | 0 ( 0.0) | 1.00 (0.02, 55.80) | 1.00 (0.02, 45.63) | 0.00 (0.00, 0.00) | NA | |
| Race | | | | | | | | | NA |
| White | 42 | 1 ( 2.4) | 39 | 0 ( 0.0) | 2.86 (0.11, 72.19) | 2.79 (0.12, 66.54) | 2.38 (-2.23, 6.99) | 0.5141 | |
| Not white | 15 | 0 ( 0.0) | 13 | 0 ( 0.0) | 0.87 (0.02, 46.95) | 0.88 (0.02, 41.27) | 0.00 (0.00, 0.00) | NA | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:15:44 - /SerAEhyp_4480.txt

## 2.35 EAC evaluated cardiovascular events - Onwards 4 - Population 1 -in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:52 - /allEAC_4480.txt

## 2.36 EAC evaluated cardiovascular events - Acute coronary syndrome - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:52 - /allEACacs_4480.txt

## 2.37 EAC evaluated cardiovascular events - Cerebrovascular event - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:53 - /allEACce_4480.txt

## 2.38 EAC evaluated cardiovascular events - Heart failure - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:54 - /allEAChf_4480.txt

## 2.39 EAC evaluated cardiovascular events - Death - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:54 - /allEACd_4480.txt

## 2.40 Severe EAC evaluated cardiovascular events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:55 - /SevEAC_4480.txt

## 2.41 Severe EAC evaluated cardiovascular events - Acute coronary syndrome - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:56 - /SevEACacs_4480.txt

## 2.42 Severe EAC evaluated cardiovascular events - Cerebrovascular event - Onwards 4 - Population 1 - in- trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:56 - /SevEACce_4480.txt

## 2.43 Severe EAC evaluated cardiovascular events - Heart failure - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:57 - /SevEAChf_4480.txt

## 2.44 Severe EAC evaluated cardiovascular events - Death - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:15:58 - /SevEACd_4480.txt

## 2.45 Serious EAC evaluated cardiovascular events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:02 - /SerEAC_4480.txt

## 2.46 Serious EAC evaluated cardiovascular events - Acute coronary syndrome - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:02 - /SerEACacs_4480.txt

## 2.47 Serious EAC evaluated cardiovascular events - Cerebrovascular event - Onwards 4 - Population 1 - in- trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:03 - /SerEACce_4480.txt

## 2.48 Serious EAC evaluated cardiovascular events - Heart failure - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:03 - /SerEAChf_4480.txt

## 2.49 Serious EAC evaluated cardiovascular events - Death - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:04 - /SerEACd_4480.txt

## 2.50 Hypersensitivity adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value | p-value int. |
| All subjects (total) | 57 | 1 ( 1.8) | 52 | 1 ( 1.9) | 0.91 (0.06, 14.94) | 0.91 (0.06, 14.22) | -0.17 (-5.22, 4.89) | 0.9994 | |
| Gender | | | | | | | | | 0.1887 |
| Female | 26 | 0 ( 0.0) | 28 | 1 ( 3.6) | 0.35 (0.01, 8.87) | 0.36 (0.02, 8.42) | -3.57 (-10.45, 3.30) | 0.5136 | |
| Male | 31 | 1 ( 3.2) | 24 | 0 ( 0.0) | 2.41 (0.09, 61.81) | 2.34 (0.10, 55.11) | 3.23 (-2.99, 9.45) | 0.5161 | |
| Age | | | | | | | | | 0.1553 |
| <65 years | 37 | 0 ( 0.0) | 34 | 1 ( 2.9) | 0.30 (0.01, 7.56) | 0.31 (0.01, 7.29) | -2.94 (-8.62, 2.74) | 0.3590 | |
| >=65 years | 20 | 1 ( 5.0) | 18 | 0 ( 0.0) | 2.85 (0.11, 74.38) | 2.71 (0.12, 62.70) | 5.00 (-4.55, 14.55) | 0.5135 | |
| HbA1c | | | | | | | | | NA |
| <=8,5% | 36 | 1 ( 2.8) | 36 | 1 ( 2.8) | 1.00 (0.06, 16.63) | 1.00 (0.07, 15.38) | 0.00 (-7.59, 7.59) | 1.0000 | |
| >8,5% | 21 | 0 ( 0.0) | 16 | 0 ( 0.0) | 0.77 (0.01, 40.75) | 0.77 (0.02, 36.99) | 0.00 (0.00, 0.00) | NA | |
| Region | | | | | | | | | NA |
| Europe | 24 | 0 ( 0.0) | 24 | 0 ( 0.0) | 1.00 (0.02, 52.44) | 1.00 (0.02, 48.45) | 0.00 (0.00, 0.00) | NA | |
| North and South America | 24 | 1 ( 4.2) | 19 | 0 ( 0.0) | 2.49 (0.10, 64.62) | 2.40 (0.10, 55.79) | 4.17 (-3.83, 12.16) | 0.5153 | |
| Asia | 9 | 0 ( 0.0) | 9 | 1 (11.1) | 0.30 (0.01, 8.35) | 0.33 (0.02, 7.24) | -11.11 (-31.64, 9.42) | 0.5213 | |
| Race | | | | | | | | | NA |
| White | 42 | 0 ( 0.0) | 39 | 0 ( 0.0) | 0.93 (0.02, 47.97) | 0.93 (0.02, 45.78) | 0.00 (0.00, 0.00) | NA | |
| Not white | 15 | 1 ( 6.7) | 13 | 1 ( 7.7) | 0.86 (0.05, 15.22) | 0.87 (0.06, 12.52) | -1.03 (-20.24, 18.19) | 0.9950 | |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:16:05 - /allCQ01_4480.txt

## 2.51 Severe hypersensitivity adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:06 - /SevCQ01_4480.txt

## 2.52 Serious hypersensitivity adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:07 - /SerCQ01_4480.txt

## 2.53 Injection site reactions adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:08 - /allCQ02_4480.txt

## 2.54 Severe injection site reactions adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:08 - /SevCQ02_4480.txt

## 2.55 Serious injection site reactions adverse events - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:16:10 - /SerCQ02_4480.txt

## 2.56 Adverse events by preferred term - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | |
|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value |
| COVID-19 | | | | | | | | |
| All subjects (total) | 57 | 6 (10.5) | 52 | 8 (15.4) | 0.65 (0.21, 2.01) | 0.68 (0.25, 1.84) | -4.86 (-17.49, 7.78) | 0.5302 |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval. The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand. Preferred terms are ordered by total number of events in descending sequence.

nn1436/nn1436-amnog/current
21FEB2024:13:57:54 - /AEbyPT_4480.txt

## 2.57 Adverse events by system organ class - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | | Ico vs. IGlar | | | |
|---|---|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | OR (95% CI) | RR (95% CI) | RD (95% CI) | p-value |
| Infections and infestations | | | | | | | | |
| All subjects (total) | 57 | 13 (22.8) | 52 | 19 (36.5) | 0.51 (0.22, 1.19) | 0.62 (0.34, 1.13) | -13.73 (-30.76, 3.30) | 0.1240 |
| Gastrointestinal disorders | | | | | | | | |
| All subjects (total) | 57 | 11 (19.3) | 52 | 9 (17.3) | 1.14 (0.43, 3.03) | 1.12 (0.50, 2.47) | 1.99 (-12.52, 16.51) | 0.8132 |
| Eye disorders | | | | | | | | |
| All subjects (total) | 57 | 6 (10.5) | 52 | 6 (11.5) | 0.90 (0.27, 2.99) | 0.91 (0.31, 2.65) | -1.01 (-12.80, 10.77) | 0.8968 |
| Musculoskeletal and connective tissue disorders | | | | | | | | |
| All subjects (total) | 57 | 5 ( 8.8) | 52 | 6 (11.5) | 0.74 (0.21, 2.58) | 0.76 (0.25, 2.34) | -2.77 (-14.14, 8.61) | 0.7185 |

N: number of subjects, n: number of subjects with at least one event, OR: Odds Ratio, RR: Relative Risk, RD: Risk Difference, CI: Confidence Interval.
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table. P-values (two-sided) are based on Barnard's unconditional exact test if the minimum of the four cell counts in the 2x2 contingency table is <= 5 or the sum of the four cell counts is <= 200. Otherwise, Fisher's exact test is applied. P-value (two-sided) for the interaction of subgroups is calculated using the Breslow-Day test for homogeneity across 2x2xk contingency tables for k levels of each subgroup. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand. System organ classes are ordered by total number of events in descending sequence.

nn1436/nn1436-amnog/current
21FEB2024:13:57:55 - /AEbySOC_4480.txt

## 2.58 Serious adverse events by preferred term - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:57:56 - /SAEbyPT_4480.txt

## 2.59 Serious adverse events by system organ class - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:57:57 - /SAEbySOC_4480.txt

## 2.60 Severe adverse events by preferred term - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:57:57 - /SevAEbyPT_4480.txt

## 2.61 Severe adverse events by system organ class - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:57:58 - /SevAEbySOC_4480.txt

## 2.62 Adverse events leading to permanent trial product discontinuation by preferred term - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | |
|---|---|---|---|---|
| | N | n (%) | N | n (%) |
| Pneumonia | | | | |
| All subjects (total) | 57 | 1 ( 1.8) | 52 | 0 ( 0.0) |
| Upper gastrointestinal haemorrhage | | | | |
| All subjects (total) | 57 | 0 ( 0.0) | 52 | 1 ( 1.9) |

N: number of subjects, n: number of subjects with at least one event. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:58:01 - /AEDiscbyPT_4480.txt

## 2.63 Adverse events leading to permanent trial product discontinuation by system organ class - Onwards 4 - Population 1 - in-trial - Safety analysis set

| | Ico | | IGlar | |
|---|---|---|---|---|
| | N | n (%) | N | n (%) |
| Gastrointestinal disorders | | | | |
| All subjects (total) | 57 | 0 ( 0.0) | 52 | 1 ( 1.9) |
| Infections and infestations | | | | |
| All subjects (total) | 57 | 1 ( 1.8) | 52 | 0 ( 0.0) |

N: number of subjects, n: number of subjects with at least one event. In-trial onset is captured on or after the day of randomisation and no later than week 31 (or week 26 for treatment discontinuation) or withdrawal/death date for subjects that withdraws/dies beforehand.

nn1436/nn1436-amnog/current
21FEB2024:13:58:01 - /AEDiscbySOC_4480.txt

## 2.64 Adverse events leading to study withdrawal by preferred term - Onwards 4 - Population 1 - in-trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:58:02 - /AEWithbyPT_4480.txt

## 2.65 Adverse events leading to study withdrawal by system organ class - Onwards 4 - Population 1 - in- trial - Safety analysis set

There is no data for this output

nn1436/nn1436-amnog/current
21FEB2024:13:58:03 - /AEWithbySOC_4480.txt

# 3 Auswertung zum Anteil von Patienten, die in deutschen Studienzentren rekrutiert wurden

## 3.1 Summary of subjects from Germany in the insulin icodec RCT pool

| Study | N | n DE | % DE |
|---|---|---|---|
| ONWARDS 1 | 984 | 0 | 0 |
| ONWARDS 2 | 526 | 45 | 8,6 |
| ONWARDS 3 | 588 | 0 | 0 |
| ONWARDS 4 | 582 | 0 | 0 |
| ONWARDS 5 | 1085 | 101 | 9,3 |
| ONWARDS 6 | 582 | 46 | 7,9 |
| NN1436-4466 | 154 | 32 | 20,8 |
| NN1436-4465 | 205 | 38 | 18,5 |
| NN1436-4462 | 43 | 0 | 0 |
| NN1436-4422 | 24 | 0 | 0 |
| NN1436-4383 | 247 | 0 | 0 |
| NN1436-4314 (I287) | 48 | 48 | 100 |
| NN1436-4225 | 66 | 66 | 100 |
| NN1436-4057 | 49 | 49 | 100 |
| NN1436-3955 (part 1 and 2 combined) | 69 | 69 | 100 |
| **Sum** | **5252** | **494** | **9,4** |

N is given as all subjects in the study, independent of having insulin icodec or comparative investigational medicinal product.
DE: Deutschland (Germany); N: number of subjects; n: number of subjects from Germany;
RCT: randomized controlled trial