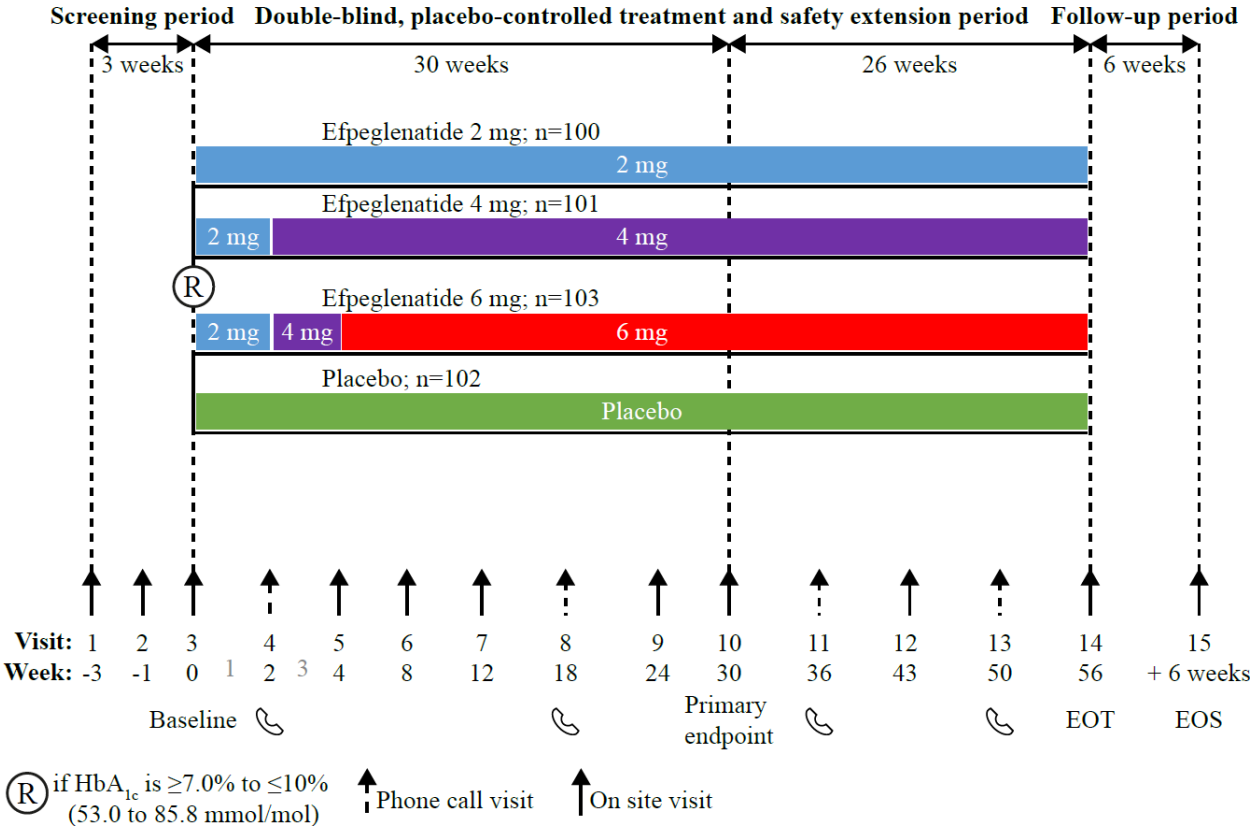
**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

## Supplementary Information

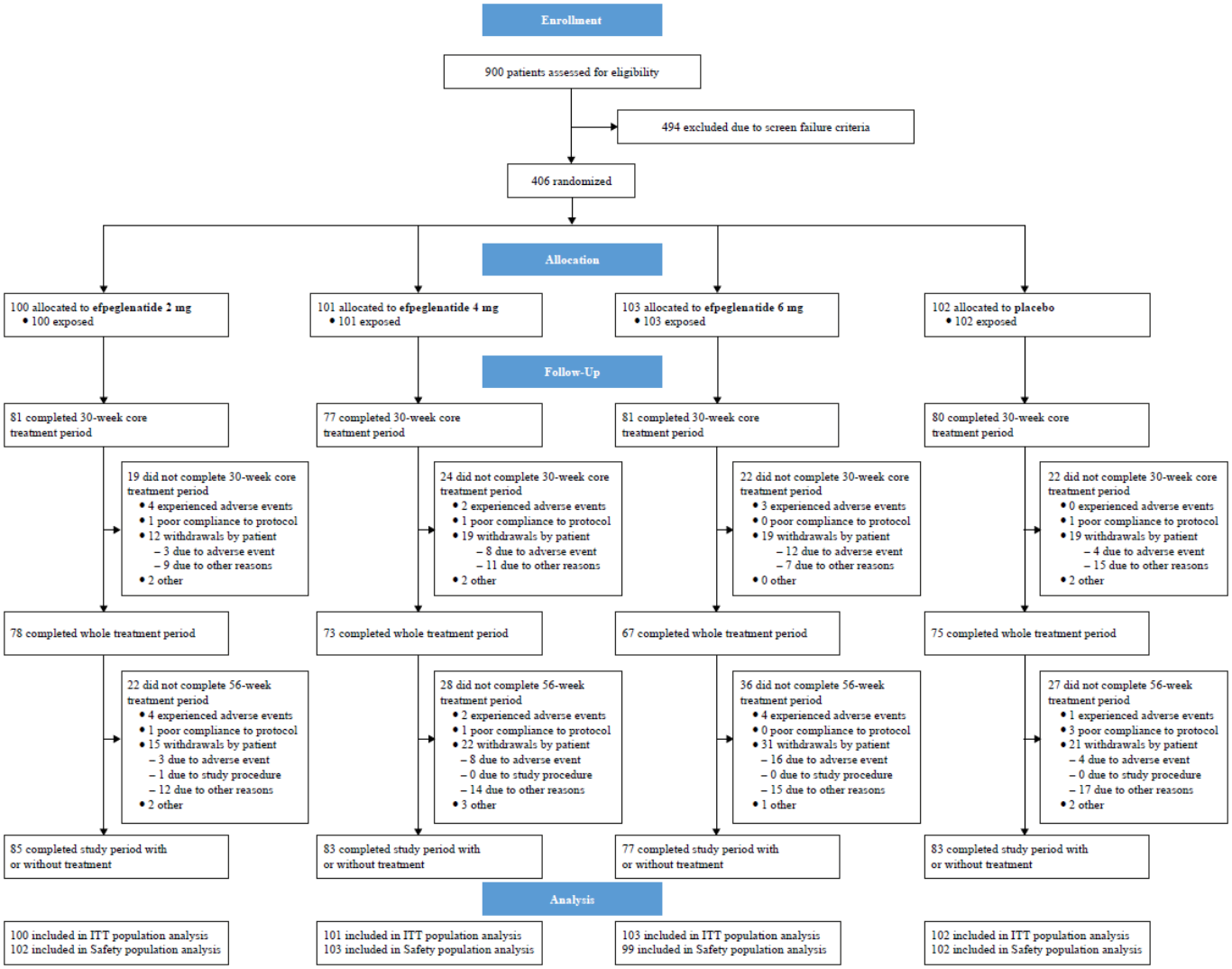
**Supplementary Figure 1**. Graphical study design




; phone call visit; EOS, end of study; EOT, end of treatment; R, randomized

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

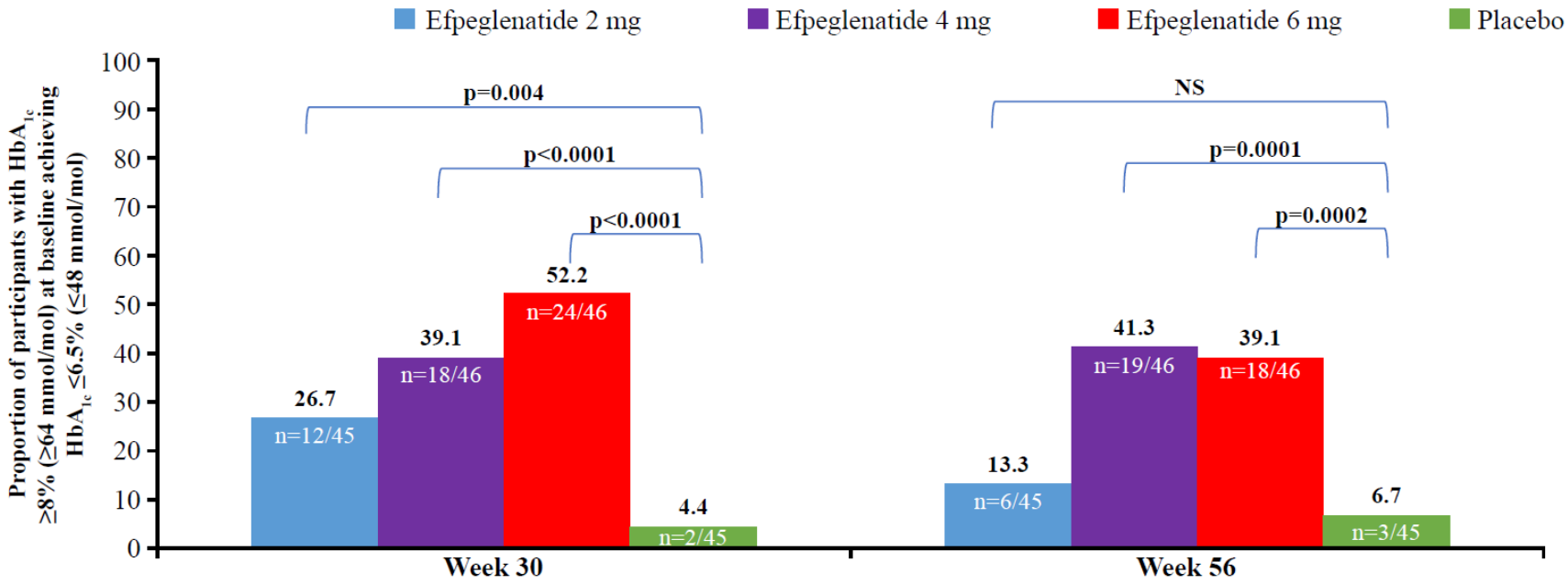
**Supplementary Figure 2.** Patient disposition




EOS, end of study; ITT, intent-to-treat analysis

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

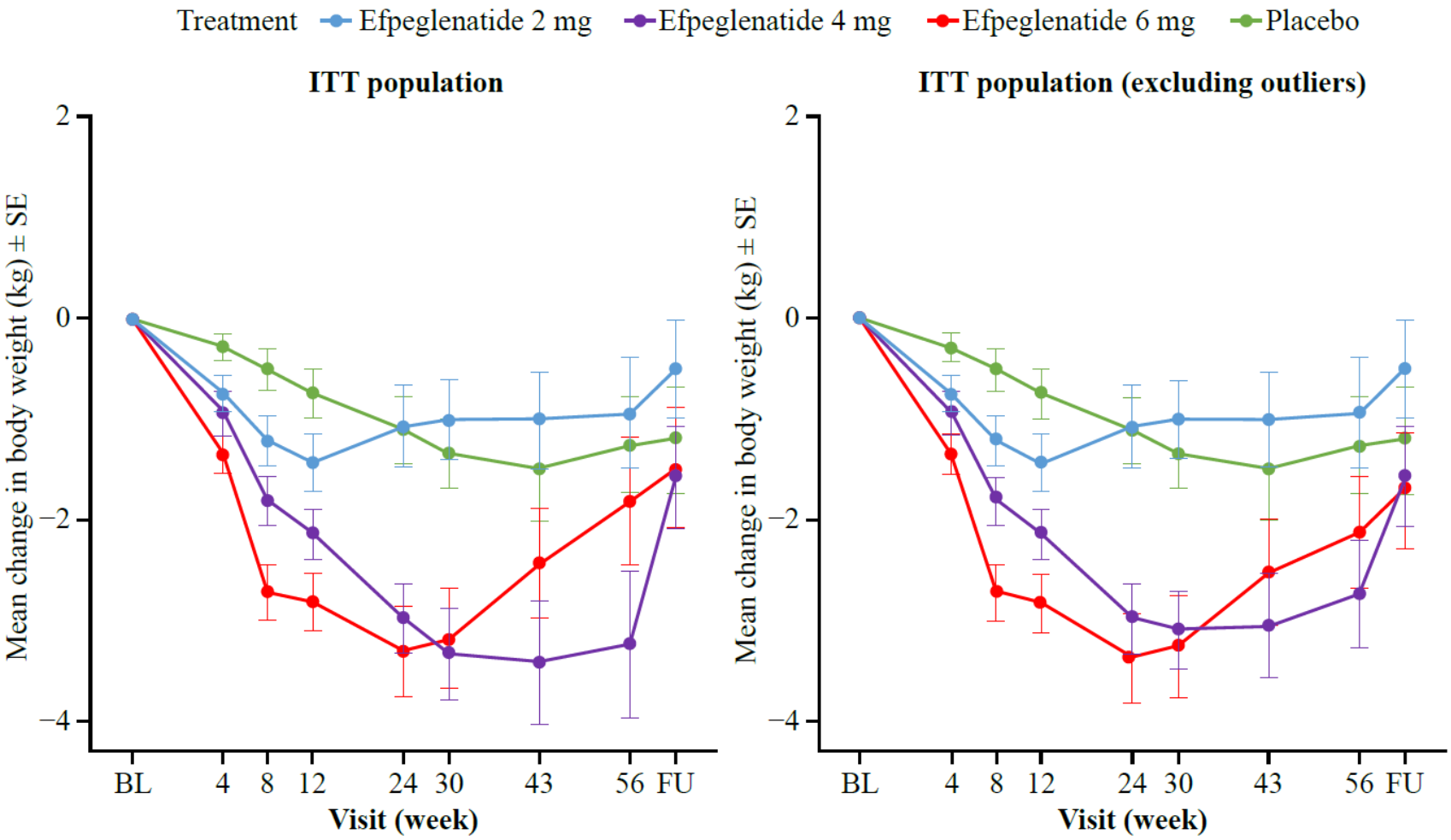
**Supplementary Figure 3.** Achievement of $HbA_{1c}$ ≤6.5% (48 mmol/mol) target in patients who had an $HbA_{1c}$ of ≥8% (64 mmol/mol) at baseline




NS, not significant

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

**Supplementary Figure 4.** Mean change in body weight – ITT population/ITT population excluding outliers




BL, baseline; FU, follow-up, ITT, intent-to-treat

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

**Supplementary Table 1.** Key Inclusion/exclusion criteria

| | |
|---|---|
| **Inclusion criteria** | |
| 1 | Patients were ≥18 years of age at the time of signing the informed consent |
| 2 | Patients with type 2 diabetes and treated with diet and exercise |
| 3 | $HbA_{1c}$ between 7.0% and 10.0% (53–86 mmol/mol; inclusive) measured by the central laboratory at Screening |
| 4 | Capable of giving signed informed consent as described in Appendix 1 of the protocol, which included compliance with the requirements and restrictions listed in the ICF and in the protocol |
| **Exclusion criteria** | |
| 1 | Clinically relevant history of GI disease associated with prolonged nausea and vomiting, including (but not limited to) gastroparesis, unstable and not controlled gastroesophageal reflux disease within 6 months prior to screening or history of surgery affecting gastric emptying |
| 2 | History of pancreatitis (unless pancreatitis was related to gallstone and cholecystectomy had been performed) and pancreatitis during previous treatment with incretin therapies, chronic pancreatitis, and pancreatectomy |
| 3 | Personal or family history of MTC or genetic conditions that predisposes to MTC (multiple endocrine neoplasia syndromes) |
| 4 | Retinopathy or maculopathy with one of the following treatments, either recent (within 3 months prior to screening) or planned: intravitreal injections or laser or vitrectomy surgery |
| 5 | Body weight change of ≥5 kg within the last 3 months prior to screening |
| 6 | Systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg at Randomization |
| 7 | End stage renal disease as defined by estimated glomerular filtration rate (by MDRD) of <15 mL/min/1.73 $m^2$ |
| 8 | Known presence of factors that interfered with the $HbA_{1c}$ measurement (e.g., specific hemoglobin variants, hemolytic anemia) compromising the reliability of $HbA_{1c}$ assessment or medical conditions that affected interpretation of $HbA_{1c}$ results (blood transfusion or severe blood loss in the last 3 months prior to Randomization, any condition that shortens erythrocyte survival) |
| 9 | Any clinically significant abnormality identified either in medical history, during physical examination, laboratory tests, ECG, or vital signs at the time of screening or any AE during the Screening Period which, in the judgment of the investigator, precluded safe participation in the study and interpretation of the study results |
| 10 | Laboratory findings at the Screening Visit: |

| | |
|---|---|
| | - ALT or AST >3 times the ULN or total bilirubin >1.5 times the ULN (except in case of documented Gilbert's syndrome)<br>- Amylase and/or lipase: >3 times the ULN laboratory range<br>- Calcitonin ≥5.9 pmol/L (20 pg/mL) |
| 11 | Patients receiving antidiabetic drug treatment within 3 months prior to screening |
| 12 | Systemic glucocorticoid therapy (excluding topical, intra articular, or ophthalmic application, nasal spray or inhaled forms) for more than 10 consecutive days in the last 3 months prior to screening |
| 13 | Gastric surgery or other gastric procedures intended for weight loss within 2 years prior to screening, or planned during study period |
| 14 | Exposure to any investigational drugs in the last 4 weeks or 5 half-lives, whichever was longer, prior to screening |
| 15 | Concomitant enrollment in any other clinical study involving an investigational study treatment or any other type of medical research |
| 16 | Hypersensitivity to any of the study treatments, or components thereof, or to any GLP-1 RAs |
| 17 | History of drug or alcohol abuse within 6 months prior to the time of screening |
| 18 | Pregnant (demonstrated by serum pregnancy test at Screening) or breastfeeding women |
| 19 | Women of childbearing potential not willing to use highly effective method(s) of birth control or who were unwilling to be tested for pregnancy during the study period and for at least 5 weeks after the last dose of study intervention |
| 20 | Patient was an employee of the Sponsor, or was the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol |
| 21 | Any country related specific regulation that could prevent the patient from entering the study |
| 22 | Individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities |
| 23 | No confirmation of complete recording of the 24-hour ECG performed during Screening Period |
| 24 | Patients unwilling or unable to comply with study procedures as outlined in the protocol |
| 25 | Patients who withdrew consent during the Screening Period (starting from signed ICF) |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GI, gastrointestinal; ICF, informed consent form; MDRD, Modification of Diet in Renal Disease; MTC, medullary thyroid cancer; ULN, upper limit of normal

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

**Supplementary Table 2. Open-label rescue medication: threshold criteria***

| Time in study | Threshold |
|---|---|
| From Randomization up to and including the scheduled week 8 visit (Visit 6) | FPG >15.0 mmol/L (>270 mg/dL) |
| After the week 8 visit up to and including the scheduled week 12 visit (Visit 7) | FPG >13.3 mmol/L (>240 mg/dL) |
| After the week 12 visit (Visit 7) to and including the end of the 30-week Core Treatment Period | FPG >11.1 mmol/L (>200 mg/dL) or $HbA_{1c}$ ≥8% (64 mmol/mol) |
| After the week 30 Visit (Visit 10) to and including the end of the treatment period | FPG >8.9 mmol/L (>160 mg/dL) or $HbA_{1c}$ ≥7% (53 mmol/mol) |

FPG, fasting plasma glucose

*If a patient's FPG reading exceeded the appropriate threshold for 3 successive days, then a central laboratory FPG and $HbA_{1c}$ measurement was arranged to confirm hyperglycemia. If a central laboratory rescue alert was received, this needed to be re-tested and confirmed before rescue medication could be initiated. Details of these measurements were not shared with investigators while the study was ongoing, although investigators were made aware that an alert had been received. Patients requiring glycemic rescue were still able to receive their allocated study treatment, which remained blinded until the end of the study unless investigators considered a change to be necessary for safety reasons.

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

**Supplementary Table 3.** Details of treatment-emergent adverse events of special interest (AESIs), and adverse events requiring specific monitoring (AERSMs) by prespecified grouping and preferred term (Safety population), treatment-induced ADAs (ADA population) and changes in vital signs during the whole on-treatment period

| **Category/ Preferred Term n (%)** | **Efpeglenatide 2 mg** | **Efpeglenatide 4 mg** | **Efpeglenatide 6 mg** | **Placebo** |
|---|---|---|---|---|
| **Patients with any TEAE of special interest (AESI)** | 1 (1.0) | 3 (2.9) | 1 (1.0) | 0 |
| Pregnancy | 0 | 0 | 0 | 0 |
| Symptomatic overdose with study treatment/non-study treatment | 0 | 0 | 0 | 0 |
| Increase in ALT >3 x ULN | 1 (1.0) | 3 (2.9) | 1 (1.0) | 0 |
| **Patients with any AERSM** | 9 (8.8) | 6 (5.8) | 8 (8.1) | 7 (6.9) |
| Severe GI events | 4 (3.9) | 2 (1.9) | 1 (1.0) | 1 (1.0) |
| Pancreatic events | 2 (2.0) | 0 | 3 (3.0) | 2 (2.0) |
| Selected cardiovascular event | 2 (2.0) | 2 (1.9) | 1 (1.0) | 4 (3.9) |
| Calcitonin and thyroid C-cell neoplasm | 1 (1.0) | 0 | 0 | 0 |
| Acute renal failure | 1 (1.0) | 1 (1.0) | 0 | 0 |
| Diabetic retinopathy complications | 0 | 0 | 4 (4.0) | 0 |
| **Severe GI events [a]** | 4 (3.9) | 2 (1.9) | 1 (1.0) | 1 (1.0) |
| Gastrooesophageal reflux disease | 0 | 0 | 1 (1.0) | 0 |
| Abdominal distension | 0 | 1 (1.0) | 0 | 0 |
| Abdominal pain upper | 1 (1.0) | 0 | 0 | 0 |
| Colitis | 1 (1.0) | 0 | 0 | 0 |
| Constipation | 0 | 1 (1.0) | 0 | 0 |
| Diarrhea | 1 (1.0) | 0 | 0 | 1 (1.0) |
| Functional gastrointestinal disorder | 0 | 1 (1.0) | 0 | 0 |
| Gastroenteritis | 1 (1.0) | 0 | 0 | 0 |
| **Pancreatic events [b]** | 2 (2.0) | 0 | 3 (3.0) | 2 (2.0) |
| Lipase increased | 1 (1.0) | 0 | 3 (3.0) | 1 (1.0) |

| | | | | |
|---|---|---|---|---|
| Amylase increased | 0 | 0 | 1 (1.0) | 1 (1.0) |
| Pancreatitis chronic | 1 (1.0) | 0 | 0 | 0 |
| **Selected cardiovascular event [b]** | 2 (2.0) | 2 (1.9) | 1 (1.0) | 4 (3.9) |
| Suspected or Confirmed Cerebrovascular event | 0 | 1 (1.0) | 1 (1.0) | 0 |
| Vertebral artery stenosis | 0 | 0 | 1 (1.0) | 0 |
| Cerebral artery stenosis | 0 | 1 (1.0) | 0 | 0 |
| Suspected or confirmed myocardial infarction or unstable angina | 1 (1.0) | 0 | 0 | 4 (3.9) |
| Acute myocardial infarction | 0 | 0 | 0 | 1 (1.0) |
| Angina unstable | 0 | 0 | 0 | 1 (1.0) |
| Chest pain | 1 (1.0) | 0 | 0 | 0 |
| Coronary artery stenosis | 0 | 0 | 0 | 1 (1.0) |
| Myocardial infarction | 0 | 0 | 0 | 1 (1.0) |
| Suspected or Confirmed Heart Failure [c] | 1 (1.0) | 1 (1.0) | 0 | 1 (1.0) |
| Cardiac failure | 1 (1.0) | 1 (1.0) | 0 | 0 |
| Cardiac failure congestive | 0 | 0 | 0 | 1 (1.0) |
| Primary cause of cardiovascular death [d] | 0 | 0 | 0 | 0 |
| **Calcitonin and thyroid C-cell neoplasm [a]** | 1 (1.0) | 0 | 0 | 0 |
| Calcitonin increase | 1 (1.0) | 0 | 0 | 0 |
| Blood calcitonin increased | 1 (1.0) | 0 | 0 | 0 |
| Thyroid C-cell neoplasm | 0 | 0 | 0 | 0 |
| **Acute renal failure [a]** | 1 (1.0) | 1 (1.0) | 0 | 0 |
| Acute kidney injury | 0 | 1 (1.0) | 0 | 0 |
| Renal failure | 1 (1.0) | 0 | 0 | 0 |
| **Diabetic retinopathy complications [b]** | 0 | 0 | 4 (4.0) | 0 |
| Diabetic retinopathy | 0 | 0 | 2 (2.0) | 0 |
| Vision blurred | 0 | 0 | 2 (2.0) | 0 |
| **Patients with any treatment-induced ADA** | 4 (4.1) | 13 (12.7) | 16 (16.3) | 0 |
| Transient ADA response [e] | 1 (25.0) | 2 (15.4) | 2 (12.5) | 0 |
| Persistent ADA response [f] | 2 (50.0) | 10 (76.9) | 11 (68.8) | 0 |

| | | | | |
|---|---|---|---|---|
| Indeterminate ADA response [g] | 1 (25.0) | 1 (7.7) | 3 (18.8) | 0 |
| **Vital signs*** | | | | |
| Patients with abnormal ECG result, n (%) | | | | |
| Baseline | 42 (41.2) | 42 (40.8) | 43 (43.9) | 49 (48.0) |
| Week 56 | 33 (45.2) | 33 (46.5) | 26 (40.6) | 35 (48.6) |
| Systolic blood pressure, mmHg (mean [SD]) | | | | |
| Baseline | 138.0 (15.9) | 134.5 (13.5) | 138.4 (16.7) | 134.8 (14.6) |
| Week 56 | 132.8 (14.4) | 131.0 (17.2) | 135.3 (16.9) | 134.4 (15.4) |
| Diastolic blood pressure, mmHg (mean [SD]) | | | | |
| Baseline | 79.1 (10.3) | 81.6 (9.0) | 81.3 (9.2) | 80.5 (8.9) |
| Week 56 | 78.2 (10.3) | 78.6 (9.0) | 82.0 (9.6) | 78.7 (8.9) |
| Heart rate, bpm (mean [SD]) | | | | |
| Baseline | 70.3 (10.5) | 72.6 (10.4) | 71.7 (12.8) | 71.1 (11.5) |
| Week 56 | 71.1 (10.8) | 73.5 (8.4) | 75.2 (9.8) | 69.7 (11.4) |

ADA, anti-drug antibody. AESRM, adverse event requiring specific monitoring; ALT, alanine aminotransferase; CMQ, Customized MedDRA query; eCRF, electronic case report form; ECG, electrocardiogram; GI, Gastrointestinal; SMQ, Standardized MedDRA query; ULN, upper limit of normal

n (%) = number and percentage of patients

Safety population comprised efpeglenatide 2 mg (n=102), efpeglenatide 4 mg (n=103), efpeglenatide 6 mg (n=99) and placebo (n=102). ADA population comprised efpeglenatide 2 mg (n=98), efpeglenatide 4 mg (n=102) and efpeglenatide 6 mg (n=98). The Whole On-treatment Period is defined as the time from the first injection of study drug up to 30 days (7 days for hypoglycemia) after the last injection of study drug.

[a] AERSMs are identified via CMQ or SMQ;

[b] AERSMs are identified via eCRF;

[c] Suspected or confirmed heart failure includes suspected or confirmed heart failure led to unplanned hospitalization, led to urgent/unscheduled visit to emergency room or an urgent/unscheduled outpatient heart failure treatment unit, or infusion center, or office/practice visit, not followed by hospitalization, or occurred while patient was hospitalized for another reason as recorded in eCRF;

[d] Cardiovascular death includes death with primary cause recorded in eCRF as Acute Myocardial Infarction, Sudden cardiac death, Heart failure or cardiogenic shock, Stroke, Complication of cardiovascular procedure, Other cardiovascular cause, or Undetermined cause of death;

[e] Persistent ADA response is defined as treatment-emergent or treatment-boosted ADA detected at ≥2 sampling points during the study, where the first and last samples are separated by ≥16 weeks;

[f] Transient ADA response is defined as treatment-emergent or treatment-boosted ADA 1) detected at only one sampling point during the study (excluding the last sampling point) or 2) detected at ≥2 sampling points during the study, where the first and last samples are separated by <16 weeks and the last time point is ADA negative;

[g] Indeterminate ADA response is defined as treatment-emergent or treatment-boosted ADA where only the last sampling point is positive, and all previous samples are negative.

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

**Supplementary Table 4.** Hierarchical testing structure

| Endpoint type | Endpoints (prioritised order) | P value |
|---|---|---|
| **Primary** | 1. Change from baseline to week 30 in $HbA_{1c}$ (%) for efpeglenatide 6 mg versus placebo | p<0.0001 |
| | 2. Change from baseline to week 30 in $HbA_{1c}$ (%) for efpeglenatide 4 mg versus placebo | p<0.0001 |
| | 3. Change from baseline to week 30 in $HbA_{1c}$ (%) for efpeglenatide 2 mg versus placebo | p=0.0054 |
| **Secondary** | 1. $HbA_{1c}$ <7% (53 mmol/mol) at week 30 for efpeglenatide 6 mg versus placebo (yes/no) | p<0.0001 |
| | 2. $HbA_{1c}$ <7% (53 mmol/mol) at week 30 for efpeglenatide 4 mg versus placebo (yes/no) | p<0.0001 |
| | 3. Change from baseline to week 30 in body weight (kg) for efpeglenatide 6 mg versus placebo | p=0.0014 |
| | 4. Change from baseline to week 30 in body weight (kg) for efpeglenatide 4 mg versus placebo | p=0.0048 |
| | 5. $HbA_{1c}$ <7% (53 mmol/mol) at week 30 for efpeglenatide 2 mg versus placebo (yes/no) | p<0.0001 |
| | 6. Change from baseline to week 30 in FPG (mmol/L, mg/dL) for efpeglenatide 6 mg versus placebo | p<0.0001 |
| | 7. Change from baseline to week 30 in FPG (mmol/L, mg/dL) for efpeglenatide 4 mg versus placebo | p=0.0003 |
| | 8. Change from baseline to week 56 in body weight (kg) for efpeglenatide 6 mg versus placebo* | |

| | | |
|---|---|---|
| | 9. Change from baseline to week 56 in $HbA_{1c}$ (%) for efpeglenatide 6 mg versus placebo | |
| | 10. Change from baseline to week 56 in body weight (kg) for efpeglenatide 4 mg versus placebo | |
| | 11. Change from baseline to week 56 in $HbA_{1c}$ (%) for efpeglenatide 4 mg versus placebo | |
| | 12. Change from baseline to week 56 in $HbA_{1c}$ (%) for efpeglenatide 2 mg versus placebo | |
| | 13. Change from baseline to week 56 in body weight (kg) for efpeglenatide 2 mg versus placebo | |

*End of hierarchical testing procedure; all other p-values are exploratory only

**Efficacy and Safety of Once-Weekly Efpeglenatide Monotherapy Versus Placebo in Type 2 Diabetes: The AMPLITUDE M Randomized Controlled Trial**

**Supplementary Table 5.** Changes over time in a) absolute $HbA_{1c}$, b) FPG and c) body weight

A)

| **Absolute $HbA_{1c}$ % (mmol/mol), mean ± SE** | **Baseline** | **Week 12** | **Week 30** | **Week 43** | **Week 56** | **Follow-up** |
|---|---|---|---|---|---|---|
| Efpeglenatide 2 mg (n=100) | 8.1 ± 0.9 (65 ± 9) | 6.8 ± 0.8 (51 ± 9) | 6.9 ± 1.0 (52 ± 11) | 6.9 ± 0.9 (52 ± 9) | 6.9 ± 0.9 (52 ± 9) | 6.8 ± 0.8 (51 ± 9) |
| Efpeglenatide 4 mg (n=101) | 8.1 ± 0.9 (65 ± 10) | 6.6 ± 0.6 (49 ± 7) | 6.6 ± 0.8 (49 ± 9) | 6.6 ± 0.7 (49 ± 8) | 6.6 ± 0.7 (49 ± 8) | 6.6 ± 0.7 (48 ± 8) |
| Efpeglenatide 6 mg (n=103) | 8.1 ± 1.0 (65 ± 10) | 6.5 ± 0.6 (47 ± 7) | 6.4 ± 0.7 (47 ± 7) | 6.6 ± 0.9 (48 ± 10) | 6.6 ± 1.0 (48 ± 11) | 6.4 ± 0.7 (47 ± 8) |
| Placebo (n=102) | 8.0 ± 0.9 (64 ± 10) | 7.9 ± 1.1 (63 ± 12) | 7.5 ± 1.0 (59 ± 11) | 7.6 ± 1.1 (59 ± 12) | 7.4 ± 0.9 (57 ± 10) | 7.5 ± 1.0 (59 ± 11) |

**B)**

| **FPG, mg/dL (mmol/L), mean ± SD** | **Baseline** | **Week 30** | **Week 56** |
|---|---|---|---|
| Efpeglenatide 2 mg (n=100) | 179.0 ± 47.5 (9.9 ± 2.6) | 135.5 ± 47.0 (7.5 ± 2.6) | 134.6 ± 31.3 (7.5 ± 1.7) |
| Efpeglenatide 4 mg (n=101) | 174.5 ± 49.5 (9.7 ± 2.8) | 123.3 ± 28.4 (6.8 ± 1.6) | 126.9 ± 25.6 (7.0 ± 1.4) |
| Efpeglenatide 6 mg (n=103) | 176.8 ±48.6 (9.8 ± 2.7) | 118.0 ± 23.4 (6.6 ± 1.3) | 126.5 ± 36.6 (7.0 ± 2.0) |
| Placebo (n=102) | 173.0 ± 56.7 (9.6 ± 3.2) | 154.7 ± 38.4 (8.6 ± 2.1) | 148.0 ± 31.5 (8.2 ± 1.8) |

**C)**

| **Body weight, kg, mean ± SD** | **Baseline** | **Week 30** | **Week 56** |
|---|---|---|---|
| Efpeglenatide 2 mg (n=100) | 98.0 ± 21.6 | 98.1 ± 21.4 | 97.7 ± 22.3 |
| Efpeglenatide 4 mg (n=101) | 95.2 ± 22.7 | 91.9 ± 22.9 | 90.4 ± 20.2 |
| Efpeglenatide 6 mg (n=103) | 96.4 ± 20.9 | 92.8 ± 20.8 | 92.7 ± 20.3 |
| Placebo (n=102) | 97.9 ± 22.7 | 95.5 ± 21.8 | 94.9 ± 22.0 |

FPG, fasting plasma glucose; SD, standard deviation; SE, standard error

**Supplementary Table 6**. Clinical narratives for patients excluded from body weight analyses

| **Patient number** | **#840002601024** | **#826000701014** |
|---|---|---|
| Treatment group | Efpeglenatide 6 mg | Efpeglenatide 4 mg |
| Age (years) | 50 | 45 |
| Sex | Female | Female |
| Race/ethnicity | White/Hispanic or Latino | White/not Hispanic or Latino |
| Country | United States | United Kingdom |
| Duration of diabetes (years) | 15.2 | 0.6 |
| Baseline $HbA_{1c}$ (%) | 7.9 | 7.3 |
| Baseline FPG (mmol/L) | 9.5 | 7.3 |
| Baseline eGFR | 376 | 120.5 |
| Baseline BMI ($kg/m^2$) | 33.5 | 48.1 |
| Baseline weight (kg) | 90 | 126 |
| Weight at week 30 (kg) | 93.1 | 102.9 |
| Weight at week 56 (kg) | 112 | 84.3 |
| Change in body weight (kg) | +22 | −40 |
| Change due to study drug? | No (assessed by authors) | No (assessed by authors) |
| Explanation for body weight change | Patient has history of hypo-/hyperthyroidism and initiated medication for this condition (methimazole) one month after study enrolment. The observed weight gain is considered likely to be caused by iatrogenic hypothyroidism, as a side effect of methimazole treatment. | Patient discontinued study drug at week 6 due to a GI adverse event, weight at week 8 was 124.6 kg (i.e. similar to baseline). Patient experienced weight loss of −21.7 kg between weeks 8 and 30, and a further weight loss of −18.6 kg between weeks 30 and 56. Since study drug was discontinued at week 8, it was considered unlikely to be responsible for this change. |

A figure showing the impact of excluding these patients from body weight analyses is shown in **Supplementary Figure 4**.