| **Clinical Study Report Synopsis** | |
|---|---|
| Drug Substance | MEDI3506 /tozorakimab |
| Study Code | D9183C00001 |
| Edition Number | 1.0 |
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| NCT Number | NCT 04170543 |

# A Phase IIb Randomised, Double-blind, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of MEDI3506 in Subjects with Diabetic Kidney Disease

**Study dates:** First subject enrolled: 11 December 2019
Last subject last visit: 16 May 2023

**Phase of development:** Therapeutic exploratory (II)

**International Co-ordinating Investigator:** N/A

**Sponsor's Responsible Medical Officer:** PPD

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

## Study centre(s)

The Study (D9183C00001) was conducted in a total of 99 sites in 7 countries: Argentina, Canada, Chile, Peru, South Korea, Japan and US. Each site had its own Principal Investigator. There was no International Co-ordinating Investigator assigned for this study.

## Publications

Please refer to (Hofherr et al 2024) in the aCSR reference list Section 15.

## Objectives and criteria for evaluation

**Table S1 Objectives and Endpoints**

| Objectives | Endpoints | Reported in the aCSR |
|---|---|---|
| Primary | | |
| To evaluate the effect of tozorakimab (MEDI3506) on albuminuria in participants with DKD | Change from baseline to Day 169 (Week 24) in Urine albumin-creatinine ratio (UACR) compared with placebo. Central laboratory UACR results will be blinded to Investigators and Sponsor team starting from Visit 3 (Day 1) up to and including the EOS Visit (Day 230). | Yes, with simplification |
| Secondary | | |
| To evaluate safety and tolerability of tozorakimab (MEDI3506) with and without dapagliflozin in participants with DKD | Measures of safety and tolerability including but not limited to:<br>• Incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs)<br>• Assessment of vital signs (Systolic blood pressure [SBP], Diastolic blood pressure [DBP], heart rate, respiratory rate and body temperature)<br>• Electrocardiogram (ECG)<br>• Left ventricular ejection fraction (LVEF) as measured by echocardiogram<br>• B-type natriuretic peptide (BNP)<br>• Laboratory assessments (haematology, clinical chemistry, and urinalysis)<br>• For participants testing positive for COVID-19 during the intervention and follow-up periods, the number and proportion of participants with adverse events (AEs) / serious adverse events (SAEs), as well as the number and proportion of participants with COVID-19 AEs/SAEs, and the proportion of asymptomatic participants. | Yes, in full. |
| To describe the PK and immunogenicity of tozorakimab (MEDI3506) in participants with DKD | Tozorakimab (MEDI3506) serum concentrations and anti-drug antibody (ADA) incidence occurring throughout the study. | Yes, with simplification |
| To evaluate the effect of MEDI3506 in combination with ACEi or ARB with and without dapagliflozin on albuminuria in participants with DKD | • Proportion of participants with > 30% reduction in UACR at Day 169 (Week 24)[a]<br>• Proportion of participants with > 40% reduction in UACR at Day 169 (Week 24)[a]<br>• Proportion of participants with > 50% reduction in UACR at Day 169 (Week 24)[a]<br>• Change from baseline to Day 85 (Week 12) in UACR<br>• Change from Day 85 (Week 12) to Day 169 (Week 24) in UACR | Yes, with simplification |

[a] Planned logistic regression analysis to model the UACR reduction for secondary endpoint "Proportion of participants with > 30, > 40 or > 50% reductions in UACR at Day 169" was not performed.

### Study design

This was a Phase IIb, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of tozorakimab in adult participants with DKD; defined as participants with T2DM and an eGFR of 25 to 75 mL/min/1.73 m2 with a urine albumin:creatinine ratio (UACR) in the range of 100-3000 mg/g.

During study Phase IIb, 575 participants on stable dose of ACEi or ARB were randomised at Visit 3 (Day 1) to receive tozorakimab or placebo SC [redacted].

The study consisted of a 35-day screening period, up to 24-week (168 days) treatment period, the EOT visit (Day 169), and a 10-week (70 days) safety follow up after last dose. An interim analysis was performed for this study when ≥ 70% of participants completed their Day 85 (Week 12) visit to evaluate change from baseline in UACR as well as AEs, and other safety parameters.

The study started in November 2019 as a Phase IIa study, and it was paused by March 2020 due to the COVID-19 pandemic. It was resumed in June 2020 and amended to a Phase IIb study in July 2020, with additional tozorakimab dose levels and the requirement for dapagliflozin treatment in the second half of the treatment period. Therefore, the Phase IIb study treatment consisted of two periods: period 1 (12 weeks) where treatment with dapagliflozin was not mandated and period 2 (12 weeks) that consisted of treatment with tozorakimab and dapagliflozin.

### Target subject population and sample size

**Target population:** Adults with T2D with an estimated eGFR of 25–75 mL/min/1.73 m2 and a UACR of 100–3000 mg/g. Patients were receiving a stable dose of an ACEi or ARB for at least 6 weeks before screening. Patients with a documented intolerance to ACEi or ARBs were also eligible. Patients taking an SGLT2i had to be on a stable dose for at least 4 weeks before randomisation. Key exclusion criteria were a diagnosis of CKD other than DKD, HbA1c >10.5%, serum potassium >5.5 mmol/L that could not be adjusted by appropriate management, and a history of clinically significant heart disease.

**Sample size:** A sample size of 565 participants randomised using a 95:95:95:140:140 ratio to receive either 30, 60 mg, 120 mg, or 300 mg tozorakimab MEDI3506 or matching placebo was planned to give approximately 85:85:85:125:125 evaluable participants per group. This would have provided at least 85% power for the 300 mg arm and 80% power for the 30, 60, and 120 mg arms to detect a 30% reduction in change from baseline to Day 169 (Week 24) in UACR between each tozorakimab treatment group and placebo group (or placebo/tozorakimab (MEDI3506) ratio of 1.429) with a one-sided alpha of 0.05 without multiplicity adjustment, assuming a coefficient of variation of 1.31 or standard deviation of 1.0 in log scale.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

| | |
|---|---|
| **IP:** CCI / MEDI3506<br>**Provider:** AstraZeneca | CCI |
| **IP:** Placebo<br>**Provider:** AstraZeneca | |
| **IP:** Dapagliflozin,<br>**Provider:** AstraZeneca | CCI |

HDPE = high-density polyethylene; w/v = weight/volume.

Both tozorakimab and placebo were packaged into single vial kits with a unique number printed on all labels within the kit (ie, the outer carton label and the label of the vial within the carton). Dapagliflozin was provided in bottle and was labelled in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

### Duration of treatment

Participants were dosed tozorakimab subcutaneouslyCCI over a 168-day treatment period. For the second half of the study, all participants received 10 mg dapagliflozin by mouth daily from Day 85 until Day 168.

Following the signing of informed consent, participants were assessed for study eligibility during a screening period of up to 35 days (Day -37 to Day -3) followed by a 168-day (24 week) treatment period and a 70-day (10 week) follow-up period.

**Statistical methods**

The primary efficacy analysis of change from baseline to Day 169 (Week 24) in UACR compared to placebo (on treatment with dapagliflozin as standard of care) was based on the Per Protocol Population. UACR was log-transformed and analysed using mixed model repeated measures (MMRM) method adjusting for fixed categorical effects of treatment, visit, and treatment-by-visit interaction, randomisation stratification factors, and the continuous covariates of baseline log UACR and baseline log UACR-by-visit interaction.

The secondary efficacy analysis of change from baseline to Day 85 (Week 12) in UACR and change from Day 85 (Week 12) to Day 169 (Week 24) in UACR was analysed similarly to that of the primary efficacy analysis and was based on the Full Analysis Set and Per Protocol Population. For the proportions of subjects with > 30%, > 40%, and > 50% reduction in UACR was summarised based on the Full Analysis Set and the Per Protocol Population.

**Study population**

A total of 1575 patients were screened in 99 study centres. Of these, 599 were randomised in 82 study centres across 7 countries: Argentina, Canada, Chile, Japan, Peru, South Korea and US. Following the Phase IIb CSP, 575 out of the 599 patients were randomised in a 95:95:95:140:140 ratio to receive either tozorakimab 30, 60, 120, or 300 mg or placebo.

A group of 41 participants were excluded from the summary statistics. This aCSR is based on the summary statistics of 558 participants from study Phase IIb only.

The Phase IIb study was completed per protocol by a total of 427 participants. At the end of the study, all participants had either completed (N = 454) or discontinued (N = 104) the treatment; the most common reason for treatment discontinuation in the placebo and the total tozorakimab groups was “Other”. The number and reasons for discontinuations from treatment did not raise any concerns about the conduct of the study.

The first participant was randomised into the study on 20 August 2020 and the last participant completed their last study visit on 16 May 2023. The majority of study participants were white male. The median age of participants was 68 years and median weight 85.25 kg.

**Summary of efficacy results**

- The study did not meet its primary objective. No statistically significant, or clinically meaningful difference from placebo was demonstrated for any of the tozorakimab

treated groups in mean percent change of UACR from baseline at Day 169 (Week 24) as measured in PPP.

- Conclusions on mean percent change in UACR levels from baseline throughout the study treatment duration (up to Day 169, Week 24) did not change post sensitivity analysis.

- Addition of dapagliflozin at Week 12 caused reduction in UACR levels from baseline in all treatment groups including placebo.


**Summary of pharmacokinetic results**

Not Applicable.

**Summary of pharmacodynamic results**

Not Applicable.

**Summary of pharmacokinetic/pharmacodynamic relationships**

Not Applicable.

**Summary of pharmacogenetic results**

Not Applicable.

**Summary of safety results**

- Overall, tozorakimab administered alone or in combination with dapagliflozin was well tolerated.

- In total over 81% of study participants received all CCI doses of IP and the extent of exposure was consistent across all treatment groups.

- The proportion of participants reporting at least one TEAEs in the placebo and the tozorakimab treated groups was similar. A slightly higher proportion of participants in the placebo group compared with the tozorakimab total group reported AEs leading to discontinuation of IP.

- The proportion of participants in the placebo group who reported TEAEs was highest in the SOC Infections and infestations. The proportion of participants in the tozorakimab total group who reported TEAEs was highest in the SOC Metabolism and nutrition disorders followed by the SOC Vascular disorders.

- The most commonly reported (≥ 2% of participants in any treatment group) TEAESIs in the placebo and the tozorakimab total groups were of the PTs COVID-19 and oedema peripheral. Additionally, TEAESI of PT diarrhoea was reported by ≥ 2% of participants in the tozorakimab total group.

- TEAEs resulting in death were low (~1%) and reported by a similar proportion of participants in the placebo and the tozorakimab total groups.

- Highest proportion of participants in the placebo group and in the tozorakimab total group reported the majority of TESAEs in the SOC of Infections and infestations. The most common (≥ 2% of participants in any treatment group) TESAEs in tozorakimab treated participants were of the PTs atrial fibrillation and hyperkalaemia.

- IP discontinuation due to at least one TEAE leading to discontinuation was low and similar across all treatment groups.

- There were no Hy's Law or potential Hy's Law cases.

- There were no clinically important trends over time from baseline in haematology or clinical chemistry parameters.

- There were no meaningful trends in vital sign variables, ECGs, LVEF or BNP.

**Conclusion(s)**

- Treatment with tozorakimab alone or in combination with dapagliflozin from Day 85 onwards, did not demonstrate a clinical benefit in patients with DKD compared with placebo.

- Tozorakimab alone or in combination with dapagliflozin demonstrated an acceptable safety and tolerability profile.