Inspired by patients.
Driven by science.

Prematurely Ended - Statement

Statement on Discontinuation of the study
Name of Sponsor: UCB Biopharma SRL
Study No: CAI001
Product: zampilimab
Title: A Multicenter, Randomized, Placebo-Controlled Investigator-Blind, Participant-Blind Study to Evaluate Safety/Tolerability, Pharmacokinetics, and Pharmacodynamics of Zampilimab in Adult Kidney Transplant Recipients With Chronic Allograft Injury
Phase: Phase 1/2
Study Period: Approximately 680 days
Centres: planned in 20 sites
Number of Subjects: 3 enrolled
Publications: NA
Statement on discontinuation of the study: The study ended prematurely due to recruitment challenges and out licensing zampilimab. The full data set will not be posted, as the study was investigating a rare disease with a high risk of patient identification due to low enrolment (patient privacy/confidentiality issue). Partial results are shared in the following CSR synopsis.

CLINICAL STUDY REPORT SYNOPSIS: CAI001

Name of company: UCB Biopharma SRL	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Zampilimab	**Volume**: Not applicable	
Name of active ingredient: Zampilimab	**Page:** Not applicable	

Title of study: A Multicenter, Randomized, Placebo-Controlled, Investigator-Blind, Participant-Blind Study to Evaluate Safety/Tolerability, Pharmacokinetics, and Pharmacodynamics of Zampilimab in Adult Kidney Transplant Recipients with Chronic Allograft Injury

Investigators: This was a planned multicenter study. Due to premature termination, 2 investigators enrolled 3 study participants.

Study sites: This clinical study was planned to be conducted at approximately 20 study sites in Europe.

Publication (reference): None

Study period: Approximately 680 days **First participant enrolled:** 02 Dec 2019 **Last participant completed:** 04 May 2022	**Phase of development:** Phase 1/2

Objectives:

The primary objective of the study was to investigate the safety and tolerability of zampilimab when administered as repeat intravenous (iv) doses in kidney transplant recipients with Chronic Allograft Injury (CAI).

The secondary objective of the study was to evaluate the PK of zampilimab when administered as repeat iv doses in kidney transplant recipients with CAI.

The exploratory objectives of this study were to evaluate the effect of repeat dosing with zampilimab on renal function and kidney transplant histology associated with CAI; to determine zampilimab target occupancy and target engagement by measuring transglutaminase 2 (TG2) expression and activity in kidney transplant tissue, plasma, and urine; to explore the effects of repeat dosing with zampilimab on exploratory biomarkers in systemic and tissue samples; and to explore the immunogenicity of zampilimab following repeat-dose administration. Due to premature termination of the study, not all exploratory variables were analyzed.

Methodology: CAI001 was a safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), Investigator-blind, participant-blind, multicenter study in adult kidney transplant recipients with declining kidney function and moderate to severe fibrosis

Name of company: UCB Biopharma SRL	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Zampilimab	**Volume**: Not applicable	
Name of active ingredient: Zampilimab	**Page:** Not applicable	

associated with CAI. As this was the first zampilimab study in a patient population, the study evaluated the effect of repeat dosing with zampilimab in a maximum of 12 participants.

Study participants were to undergo individual dose up titration for the initial 8 weeks; an abridged Safety Monitoring Committee (SMC) was responsible for oversight of safety and PK data supporting dose escalation decisions. The SMC composition and responsibilities are detailed in the SMC charter.

Potential participants could be identified and referred from another center (referral center) to a study site for further evaluation.

The study comprised a Screening Period (maximum 35 days), Treatment Period (up to a maximum of 505 days) and a Safety Follow-Up Period (up to 140 days after the last investigational medicinal product [IMP] administration).

The CAI001 study commenced on May 2019. From then until November 2021, the CAI001 study faced recruitment challenges. During this time, zampilimab was out licensed. Therefore, a decision was made to discontinue the CAI001 study. At the time of study termination, all currently enrolled study participants continued with SFU visits as per the protocol.

This abbreviated clinical study report presents an analysis of available data for variables supporting the primary (safety/tolerability), secondary (PK), and select exploratory (PD) objectives.

Number of participants (planned and analyzed): A maximum of 12 participants were planned to be randomized (9 active and 3 placebo) in the study.

All study participants randomized to zampilimab received all doses during the Up-Titration Period, were treated during the Maintenance Period, and attended SFU Visit 1, SFU Visit 2 and SFU Visit 3

Diagnosis and main criteria for inclusion: Participant had to be at least 18 years old; had received a functioning living or deceased donor allograft and was≥1 year post-transplantation; had a Baseline (Screening) biopsy showing Grade II or III IF/TA (≥25% IF/TA), had progressive loss in kidney function observed after the first-year post-transplant, defined as an estimated glomerular filtration rate (eGFR) decline of ≥3mL/min/year for at least 24 months prior to screening, with a minimum of 2 documented measurements per year (minimum of 4 documented measurements in the 24-month period, performed at least 1 month apart); and had an eGFR ≥30mL/min/1.73m^2 for a period of 6 months up to Screening.

Name of company: UCB Biopharma SRL	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Zampilimab	**Volume**: Not applicable	
Name of active ingredient: Zampilimab	**Page:** Not applicable	

Test product, dose(s) and mode of administration, batch number(s):

[redacted]

The batch numbers for zampilimab in this study were as follows: 327211, 324051, 320794, 320792, 312658, 278571, 262180, and 278567.

Duration of treatment: For each study participant, the study was planned to last a maximum of up to 680 days, as follows:

- Screening Period of up to 35 days
- Treatment Period of up to a maximum of 505 days
- SFU Period of up to 140 days

Reference therapy, dose(s) and mode of administration:

Placebo was provided locally as commercial source of 0.9% sodium chloride aqueous solution (physiological saline, preservative free) in 10mL plastic ampoules for iv infusion. The batch numbers for placebo were as follows: 336429, 262182, 312659, and 324046.

Criteria for evaluation:

Safety:

The primary safety variable was:

- Adverse events
  - Adverse events occurring during the study (ie, after the signing of the Informed Consent Form, including any pretreatment and post-treatment periods required by the protocol, were reported in the electronic Case Report Form even if no IMP was taken but specific study procedures were conducted. Other safety variables:
- All clinical laboratory testing (hematology, clinical chemistry, and urinalysis), except urine pregnancy test, was performed at the central laboratory. Urine pregnancy tests were performed at the clinical site by clinical study personnel.
- Vital signs (blood pressure [systolic and diastolic], pulse rate, and body temperature [oral]), 12-lead electrocardiogram (ECG) readings, and physical examinations were performed as outlined in the Schedule of Study Assessments. Local tolerability was

Name of company: UCB Biopharma SRL	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Zampilimab	**Volume**: Not applicable	
Name of active ingredient: Zampilimab	**Page:** Not applicable	

assessed at each dosing visit, following cannulation but prior to the infusion start, and then during the infusion and safety monitoring period.

Pharmacokinetics:

The serum concentration of zampilimab was characterized. Serum and urine samples were collected according to the Schedule of Study Assessments.

Pharmacodynamics:

Exploratory PD variables also included, but were not limited to, kidney function (eGFR and protein:creatinine ratio) and kidney transplant histology associated with CAI, TG2 expression, TG2 activity (target engagement), and TG2 binding (target occupancy) (in tissue); TG2 levels in plasma and urine; TG2 crosslink products (ε[γ-glutamyl] lysine) in tissue and urine. Immunoglobulin G was assessed in serum and urine, and IgM was assessed in serum. The study was terminated prematurely, and not all planned analyses were conducted. For details on assessments reported in this study, see Table 4-1 of the abbreviated clinical study report.

Biopsy procedure:

Percutaneous kidney biopsies were scheduled to be performed at Screening (Baseline) and post-Baseline as indicated in the Schedule of Study Assessments.

Summary and conclusions:

Subject disposition:

All 3 of the study participants (100%) in the RS who started the study also completed the study. All study participants randomized to zampilimab received all doses during the Up-Titration Period, were treated during the Maintenance Period, and attended SFU Visit 1, SFU Visit 2, and SFU Visit 3; there were no discontinuations due to AEs or any other reason.

Safety results:

Extent of exposure

- Over the study (Up-Titration Period and Maintenance Period), the median duration of exposure was 504 days (range: 392 to 700 days).
- During the Maintenance Period, no study participants received a reduced dose of zampilimab [redacted] due to lack of tolerability of zampilimab [redacted].

Overall summary of treatment-emergent adverse events

- During the Up-Titration Period, all 3 study participants (100%) reported a total of 12 treatment-emergent adverse events (TEAEs); 1 TEAE, 7 TEAEs, and 4 TEAEs were

Name of company: UCB Biopharma SRL	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Zampilimab	**Volume**: Not applicable	
Name of active ingredient: Zampilimab	**Page:** Not applicable	

reported while receiving zampilimab [redacted], zampilimab [redacted], and zampilimab [redacted], respectively.

- During the Maintenance Period, all 3 study participants (100%) reported at least 1 TEAE; 17 TEAEs were reported in total.

Most common TEAEs

- No TEAEs were reported by more than 1 study participant during the Up-Titration Period.
- Overall and during the Maintenance Period, the most frequently reported TEAEs by preferred term were hypertension and corona virus disease 2019 (2 study participants [66.7%], each).

TEAEs by relationship

- One study participant (33.3%) had 2 related TEAEs of pruritis during the Up-Titration Period; 1 of which was mild in intensity on Day 2 following zampilimab [redacted] and 1 of moderate intensity following zampilimab [redacted] on Day 32. All TEAEs were nonserious, did not lead to discontinuation of IMP, nor to change in dose, and were considered resolved by Day 3 and Day 34, respectively.

Serious TEAEs

- No serious adverse events were reported during the study.

Discontinuations due to TEAE

- No study participants discontinued prematurely from the study due to an AE.

Deaths due to TEAE

- No deaths occurred during the study.

Other observations related to safety

- No clinically meaningful patterns of changes were observed in hematology, biochemistry values, vital signs, physical examination findings, or ECG findings.

Pharmacokinetics results:

- Following the first administration of zampilimab [redacted] iv on Day 1, the end of infusion median zampilimab serum concentration was [redacted].
- As expected, higher zampilimab serum concentrations were observed by Day 57; the end of infusion median zampilimab serum concentration was [redacted].
- During the Maintenance Period, predose zampilimab serum concentrations were maintained.

Name of company: UCB Biopharma SRL	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Zampilimab	**Volume**: Not applicable	
Name of active ingredient: Zampilimab	**Page:** Not applicable	

- The amount of zampilimab in urine was generally very low (within the microgram range) compared to the administered doses.

Pharmacodynamic results:

- Due to the small number of participants in this study, no conclusions can be drawn in regard to TG2 levels in plasma or IgG and IgM levels in serum and urine over time, and results should be interpreted with caution.
- At all time points observed, TG2 levels in urine were BLQ; there were no evaluable data at any time point for any study participant.
- There were no changes in adjudicated IF/TA scores 12 months posttreatment with zampilimab (collection time as specified in CAI001 protocol amendment 4 [05 Jun 2020]).
- Taking into account visit to visit variability, there was no overall change in the mean eGFR measurement or mean protein: creatinine ratio over time for study participants treated with zampilimab.
- For all 3 participants, the historical eGFR results during the 2 years prior to Screening show the downward trend required by the protocol inclusion criteria. For 2 participants, most/all eGFR results following treatment with zampilimab were no worse than their Baseline value and for the other participant, eGFR results fluctuated above and below their Baseline value.

  Considering the expected variability in eGFR data, overall, results are stable during the Treatment Period with a downward trend observed during the 4-month Safety Follow-Up Period following the last dose of zampilimab.

Conclusions:

- Overall, within a 3-year timeframe, only 3 participants were enrolled globally; in consequence, the study was terminated prematurely due to recruitment challenges.
- Treatment with zampilimab was well tolerated in all 3 study participants.
- No new safety concerns occurred in these 3 study participants with kidney transplants.
- Zampilimab PK was as expected from previous studies.
- No conclusions on exploratory PD variables can be drawn from the data reported in this study due to the small number of study participants in the study.

Report date: 13 Dec 2022

Approval Signatures

Name: CAI001-synopsis

Version: 2.0

Document Number: CLIN-000193886

Title: CAI001 - Synopsis

Approved Date: 15 Dec 2022

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 15-Dec-2022 05:26:27 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 15-Dec-2022 17:04:11 GMT+0000