Sponsor: Sanofi **Drug substance(s):** isatuximab	**Study Identifiers:** U1111-1189-4706; NCT03194867; EudraCT Number: 2017-001431-39 **Study code:** TCD14906

Title of the study:

A Phase 1/2 study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with relapsed/refractory multiple myeloma

Study center(s):

30 sites screened and 29 sites randomized at least 1 patient in 10 countries including Australia, Brazil, Canada, Czech Republic, France, Greece, Hungary, Italy, Spain, and United States.

Study period:

Date first patient screened: 21 February 2018

Date study completion: 05 April 2023

Study Status: Completed

Phase of development: 1/2

Objectives:

The primary objectives were:
To determine the safety and tolerability of the combination of isatuximab and cemiplimab.
Phase 2 only: To compare the overall response rate (ORR), defined as complete response (CR) + very good partial response (VGPR) + partial response (PR) of the combination of isatuximab and cemiplimab versus isatuximab alone in patients with relapse and refractory multiple myeloma (RRMM) based on International Myeloma Working Group (IMWG) criteria.
The secondary objectives were:
To determine the following efficacy measurements (Phase 2 only):
• Clinical benefit rate (CBR), CR + VGPR + PR + minimal response (MR),
• Duration of response (DOR),
• Time to response (TTR),
• Progression free survival (PFS),
• Overall survival (OS).
To determine the pharmacokinetic (PK) profile of isatuximab and cemiplimab when given in combination.

To assess the immunogenicity of isatuximab and cemiplimab when given in combination.

Methodology:

This was a Phase 1/2 study to evaluate the safety, tolerability, efficacy and PK of isatuximab in combination with cemiplimab in RRMM. The study was conducted in 2 parts. Phase 1 (run-in) was to confirm the feasibility of the isatuximab/cemiplimab combination. Phase 2 was to further evaluate the safety, efficacy, and PK of the combination versus isatuximab monotherapy. Patients were randomized in a 1:1:1 in 3 arms or 1:1 in 2-arms study using Interactive Response Technology (IRT).

Number of patients:

Planned: 3 to 18 patients in Phase 1 and 105 patients in Phase 2

Randomized: 3 patients in Phase 1 and 106 patients in Phase 2

Treated: 3 patients in Phase 1 and 105 patients in Phase 2

Evaluated:

Safety: 3 patients in Phase 1 and 105 patients in Phase 2

Efficacy: 3 patients in Phase 1 and 106 patients in Phase 2

Pharmacokinetics: 108 patients in Phase 2

Diagnosis and criteria for inclusion:

Patients were ≥18 years old and must have had a known diagnosis of multiple myeloma (MM) with evidence of measurable disease. Patients must have received prior treatment with an immunomodulatory drug (IMiD) and at least 3 prior lines of therapy and must have achieved MR or better with any antimyeloma therapy.

Study products

Investigational medicinal products: Isatuximab and cemiplimab

Formulation:

- Isatuximab: 20 mg/mL (500 mg/25 mL) in 20 mM histidine, 10% (w/v) sucrose and 0.02% (w/v) polysorbate 80, pH 6.0 buffer.
- Cemplimab: 50 mg/mL in 10 mL vials with 5.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline and 0.2% (w/v) polysorbate 80, pH 6.0.

Route of administration: Intravenous (IV) infusion

Dose regimen:

Isatuximab

- For isatuximab alone as control, and at DL1 and DL-1: 10 mg/kg QWx4 followed by Q2W (ie, on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond, of a 28-day cycle).
- For DL-2: 10 mg/kg Q2W (ie, on Days 1 and 15 every cycle, of a 28-day cycle).

Cemplimab

- For DL1: 250 mg Q2W (ie, on Days 1 and 15 every cycle, of a 28-day cycle).
- For DL-1 and DL-2: 250 mg Q4W (ie, on Day 1 in every cycle, of a 28-day cycle).

Noninvestigational medicinal products: Acetaminophen, ranitidine, diphenhydramine, and methylprednisolone

Formulation:

- Acetaminophen: 650 to 1000 mg
- Ranitidine: 50 mg
- Diphenhydramine: 25 to 50 mg
- Methylprednisolone: 100 mg

Routes of administration:

- Acetaminophen: per oral (PO)
- Ranitidine: IV
- Diphenhydramine: IV
- Methylprednisolone: IV or PO

Dose regimen: Patients received premedication 30 to 60 minutes prior to the start of the isatuximab infusion.

Duration of treatment: 28 days per cycle. Patients continued treatment until disease progression, unacceptable adverse events (AEs), consent withdrawal, or any other reason.
Duration of observation: An initial screening period of 21 days, treatment period of 28 days per cycle, a follow-up period up to 90 days after treatment discontinuation and a further follow-up period of beyond 90 days after the last dose of study treatments until death or study cut-off date, whichever occurred first.

Criteria for evaluation:
Safety: AEs, including dose limiting toxicities (DLTs) during Phase 1 only, reported by the patient or noted by the Investigator. Standard hematology and blood chemistry.
Efficacy: The second co-primary endpoint of the study was to determine the efficacy of the combination as assessed by ORR. Overall response rate was defined as the proportion of patients with CR (including sCR), VGPR and PR as assessed by Investigators using the IMWG response criteria.
The secondary efficacy variables included CBR, DOR, TTR, PFS, and OS.
Immunogenicity: ADA incidence for isatuximab and cemiplimab were calculated, respectively.
Pharmacokinetics: The following PK parameters were calculated from plasma concentrations of isatuximab and serum concentrations of cemiplimab using noncompartmental analysis (NCA): concentration observed at the end of an IV infusion (C_{eoi}), maximum concentration observed (C_{max}), time to reach C_{max} (t_{max}), last concentration observed above the lower limit of quantitation (C_{last}), time of Clast (t_{last}), area under the concentration-time curve (AUC) calculated using the trapezoidal method from time zero to tlast (AUC_{last}), AUC from 0 to 168 hours ($AUC_{0\text{-}168h}$ for isatuximab), AUC from 0 to 336 hours ($AUC_{0\text{-}336h}$ for cemiplimab), AUC from 0 to 672 hours ($AUC_{0\text{-}672h}$ for cemiplimab Q4W schedule only), and concentrations observed before treatment administration during repeated dosing (C_{trough}).

Immunogenicity and pharmacokinetic sampling times and bioanalytical methods:
Samples for isatuximab antidrug antibodies (ADA) measurement were obtained each cycle prior to dosing, at the end of treatment (EOT), and during the FUP. The analysis was performed in plasma using validated polyethylene glycol precipitation and acid dissociation assay (PandA) (DOH1297).
Samples for cemiplimab ADA measurement were obtained prior dosing at Cycle 1 and Cycle 2 and thereafter every third cycles (ie, C5, C8, C11, C14, etc) until the last study treatment, then at EOT and FUP. The analysis was performed in serum using a validated bridging immunoassay (REGN2810-AV-17008-VA-01V2).
The PK profile of isatuximab was evaluated after the first administration on Cycle 1 from blood samples collected prior dosing, at the end of infusion (EOI), 4 hours after the EOI then at 72 and 168 hours. Additional blood samples were sparsely collected thereafter during Cycle 1 and beyond (eg, prior dosing, EOI, EOI + 1 hour) and at the EOT. Isatuximab concentrations were measured in plasma, using validated immunoassay (DOH1586) with a lower limit of quantitation (LLOQ) of 5.00 µg/mL.
The PK profile of cemiplimab was evaluated over Cycle 1 from blood samples collected prior dosing, at EOI, 4 hours after the EOI, then at 72, 168, 336, and 672 hours (cemiplimab Q4W only). Additional blood samples were sparsely collected during Cycle 1 and beyond (eg, prior dosing, EOI) and at EOT and FUP. Cemiplimab concentrations were measured in serum, using validated immunoassay (REGN2810-AV-14109-VA-01V2) with a LLOQ of 0.078 mg/L.

Statistical methods:

Unless otherwise specified, analyses were descriptive and performed separately for Phase 1 and Phase 2 patients, based on the analysis population including the In-to-treat (ITT)/Randomized, All-treated (AT)/Safety, DLT evaluable, PK, immunogenicity, and biomarker populations.
All efficacy analyses would be performed using the all ITT population in Phase 2 unless otherwise specified.
For ORR, a 95% 2 sided confidence interval(s) (CI) would be computed using Clopper-Pearson.
For Phase 2 randomization, the Fisher's exact test was performed to compare the ORR in control arm vs each of the combination arm, using a 1-sided significance level of 0.10 with Hochberg adjustment, (at time of primary analysis of ORR; ie, cut-off date 6 months after last patient first dose). If the maximum p-value (of 2 p-values) was less than 0.1, the null hypothesis for both combination arms would be rejected; else if minimal p-value was less than 0.05, the null hypothesis would be rejected for this corresponding arm only. If only one combination arm was continued in addition to the control arm, then ORR would be tested using a 1-sided significant level of 0.05.
Subgroup analyses of best overall response (BOR) would be performed including but not limited to the following variables: age, number of previous lines of therapy, international staging system (ISS) staging at study entry, high-risk cytogenetics, baseline creatinine clearance, refractory to prior antimyeloma therapies, and PD-L1 level at baseline.

The secondary efficacy endpoints DOR, TTR, PFS, and OS would be analyzed using the Kaplan-Meier method.

Summary Results:

Population characteristics:
During Phase 1, 3 patients were enrolled and treated, 2 patients were male and 1 was female. All 3 patients were aged between 63 and 68 years and had an Eastern Cooperative Oncology Group performance score (ECOG-PS) of 0 or 1. All patients received treatment, with 2 patients who discontinued treatment due to progressive disease and 1 patient who withdrew from the study.
In Phase 2, 34 patients in the Isa arm, 35 patients in the Isa+CemQ2W arm, and 36 patients in the Isa+CemQ4W arm were randomized and treated. A majority of patients discontinued treatment due to progressive disease (97.1% in the Isa arm, 80.6% in the Isa+CemQ2W arm, and 77.8% in the Isa+CemQ4W arm). All demographics were similar among the 3 arms.
Safety results:
A total of 175 cycles in the Isa arm, 239 cycles in the Isa+CemQ2W arm, and 198 cycles in the Isa+CemQ4W arm were started.
More than 90% of patients in all 3 arms experienced at least 1 TEAE (100% in the Isa arm; 97.3% in the Isa+CemQ2W arm, and 94.3% in the Isa+CemQ4W arm) and more than 50% of patients had Grade ≥3 TEAEs in all 3 arms (51.5% in the Isa arm; 51.4% in the Isa+CemQ2W arm, and 65.7% in the Isa+CemQ4W arm).
The number of patients with treatment related TEAEs of any grade was similar between all arms with 24 (72.7%) in the Isa arm, 24 (64.9%) in the Isa+CemQ2W arm, and 25 (71.4%) in the Isa+CemQ4W arm. The number of patients with Grade ≥3 treatment related TEAEs was greatest in the Isa+CemQ4W arm (10 [28.6%]) in comparison to the Isa (2 [6.1%]) and Isa+CemQ2W (5 [13.5%]) arms.
In the Isa arm, 17 (51.5%) patients experienced TESAEs, of which 2 (6.1%) patients had treatment related TESAEs including hematuria, proteinuria, and parainfluenzae virus infection. In the Isa+CemQ2W arm, 17 (45.9%) patients experienced TESAEs and 4 (10.8%) patients had treatment related TESAEs including epistaxis, thrombocytopenia, pulmonary embolism, pyrexia, and neutropenia. In the Isa+CemQ4W arm, 21 (60.0%) patients experienced TESAEs, of which 9 (25.7%) patients had treatment related TESAEs including encephalomyelitis, sepsis, pulmonary sepsis, colon neoplasm, diarrhea, IRR, encephalitis, pneumonia, and anemia.
One patient had a secondary malignancy colon neoplasm in the Isa+CemQ4W arm.

A total of 20 (60.6%) patients in the Isa arm, 23 (62.2%) patients in the Isa+CemQ2W arm, and 22 (62.9%) patients in the Isa+CemQ4W arm died during the on-treatment period or posttreatment period of the study. During the on treatment period, 1 (3.0%) patient in the Isa arm and 2 (5.4%) patients in the Isa+CemQ2W arm died due to disease progression. In the Isa+CemQ4W arm, 6 (17.1%) patients died during the on treatment period with AE being the most common cause of death (4 [11.4%] patients).
A total of 18 (54.5%) patients experienced IR in the Isa arm out of which 2 (6.1%) patients had Grade 1 IR and 16 (48.5%) patients had Grade 2 IR. A total of 15 (40.5%) patients experienced IR in the Isa+CemQ2W arm and all of them were Grade 2 IR. A total of 16 (45.7%) patients experienced IR in the Isa+CemQ4W arm out of which 2 (5.7%) patients had Grade 1 IR and 14 (40.0%) patients had Grade 2 IR. A trend was observed with lower incidence of IR when combining isatuximab to cemiplimab.
*One patient experienced a Grade 3 IR with Quincke's edema leading to hospitalization and IMP definitive discontinuation which was initially reported as a Grade 3 AE but erroneously changed to Grade 2 prior to DBL.

No positive ADA was observed for isatuximab and ADA incidence was of 2.7% for cemiplimab in this study.

Efficacy results:
The recommended single agent dose of isatuximab is 20 mg/kg. During this study, a dose of 10 mg/kg was used to allow for the assessment of cemiplimab contribution. The observed single agent response rate in this study, including patients without prior daratumumab therapy, appeared less than what has been historically observed.
The median duration of follow-up was 9.99 months (95% CI: 8.542 to 10.875) across all arms (N=106).
In the analysis for overall response, 4 patients (11.8%) in the Isa arm, 9 patients (25.0%) in the Isa+CemQ2W arm, and 8 patients (22.2%) in the Isa+CemQ4W arm were responders. The p-values of the Isa arm versus the Isa+CemQ2W arm as well as the Isa arm versus the Isa+CemQ4W arm were considered not statistically significant. As the p-values were greater than 0.1, the null hypothesis was failed to be rejected for both combination arms.
No CR was observed in any of the treatment arms. A similar number of patients in each arm achieved VGPR: 2 patients (5.9%) in the Isa arm, 3 patients (8.3%) in the Isa+CemQ2W arm, and 2 patients (5.6%) in the Isa+CemQ4W arm.
The clinical benefit (MR or better) appeared numerically higher in the Isa+CemQ2W arm (13 patients [36.1%]) and the Isa+CemQ4W arm (14 patients [38.9%]) compared with the Isa arm (8 patients [23.5%]). There were no responders (sCR, CR, VGPR, or PR) in any patients previously treated with daratumumab. The ORR in patients not previously treated with daratumumab was 17.4% in the Isa arm, 30.0% in the Isa+CemQ2W arm, and 32.0% in the Isa+CemQ4W arm.
The median number of months of PFS was similar for each arm: 2.89 months (95% CI: 1.971 to 3.811) for the Isa arm, 3.75 months (95% CI: 1.971 to 5.881) for the Isa+CemQ2W arm, and 3.02 months (95% CI: 2.793 to 5.158) for the Isa+CemQ4W arm.
In the analysis of OS, it was observed that the median time to death was still not reached for the Isa and Isa+CemQ2W arms and was 12.78 months for patients in the Isa+CemQ4W arm.
Pharmacokinetic results:
After the first administration of isatuximab at 10 mg/kg in combination with cemiplimab at 250 mg:
• Mean isatuximab Cmax and $AUC_{0\text{-}168h}$ assessed from 40 RRMM patients were 251 µg/mL and 21600 µg.h/mL, respectively. Exposure showed a moderate variability (CV% ranging from 26 to 31%). No effect of cemiplimab on isatuximab PK was observed.
• Mean cemiplimab Cmax, $AUC_{0\text{-}336h}$, and $AUC_{0\text{-}672h}$ were 73.8 mg/L, 481 mg.day/L, and 713 mg.day/L, respectively. Exposure showed a moderate variability (CV% ranging from 30 to 33%). No effect of isatuximab on cemiplimab PK was observed.
Overall, concomitant administration of cemiplimab did not appear to alter isatuximab exposure and vice versa.

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