Sponsor: Sanofi **Drug substance(s):** isatuximab	**Study Identifiers:** IND: 151491; EudraCT/EU trial number: 2020-003880-24; NCT04661033; WHO: U1111-1255-5350 **Study code:** ACT16832

Title of the study:

A multicenter, open-label, non-randomized, Phase 1b/2 study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with warm autoimmune hemolytic anemia

Study center(s):

One study center each from France, Germany, Italy, Netherlands, the United Kingdom, and the United States participated in the study.

Study period:

Study initiation date: 09 September 2021 (signed informed consent)

Early study termination date: 26 June 2023 (date of last observation from last participant)

Study Status: Terminated. Study discontinuation based on strategic sponsor decision; not driven by any safety concerns.

Phase of development: Phase 1/Phase 2

Objectives:

Primary

- Part A: To evaluate the safety and tolerability of subcutaneous injections of isatuximab in adults with wAIHA.
- Part B: To evaluate the efficacy of the selected dose in adults with wAIHA.

Secondary

Part A (Cohorts 2 and 3 only)

- To evaluate the efficacy of isatuximab in adults with wAIHA.
- To evaluate the durability of response to isatuximab and time to response.
- To evaluate the impact of isatuximab treatment on fatigue.

Part B:

- To evaluate the safety and tolerability of isatuximab in adults with wAIHA.
- To evaluate the durability of response to isatuximab and time to response.
- To evaluate the impact of isatuximab treatment on fatigue.

Parts A (all Cohorts) and B

- To evaluate the effect of isatuximab on markers of hemolysis.
- To characterize the PK profile of isatuximab in adults with wAIHA.
- To evaluate the immunogenicity of isatuximab.

Methodology:

This was a Phase 1b/2 open-label, non-randomized, multicenter study to evaluate the safety, pharmacokinetics (PK), and efficacy of subcutaneous (SC) isatuximab in adults with wAIHA. The study was to be conducted in 2 parts: Part A for safety and dose-finding, and Part B for assessment of the efficacy of the selected dose regimen. Approximately 17 to 23 participants were expected to be enrolled, depending on the number of participants in Part A who received the regimen chosen for Part B.

Part A was planned to be conducted in 2 to 3 cohorts. Cohort 1 consisted of 3 participants who received 2 doses of isatuximab 140 mg (1 mL) SC administered 2 weeks apart. Cohort 2 was planned to open following a review of available safety, PK, and pharmacodynamics (PD) data after the 3 participants in Cohort 1 completed the Day 43 visit. Cohort 2 was planned to consist of 3 participants who were to receive isatuximab SC given every 2 weeks (Q2W) through Day 71 (total of 6 doses). The dose for Cohort 2 was to be either 70 mg (0.5 mL), 140 mg (1 mL), or 280 mg (2 mL), which was to be determined based on the safety profile, PK, and PD observed in Cohort 1. A dose of 280 mg was selected for Cohort 2.

Once the 3 participants in Cohort 2 completed the Day 85 visit, an analysis of the available safety, PK, and PD data was to be performed, and a decision was to be made to either enroll 3 participants as an additional optional dose-finding cohort (Cohort 3) in which a dose up to 560 mg (4 mL) was to be investigated, or Part B was to be opened. A decision was made to open Cohort 3 to investigate a dose of 560 mg. Part B was planned to open once available safety, PK, and PD data through the Day 85 visit from the participants of Cohort 3 were reviewed. However, the study was stopped after opening Cohort 3 for non-safety reasons and, as a result, Part B was not performed.

Participants in Cohort 1 who experienced no response by the end of the treatment period, or a response that subsequently waned while still in follow-up, could be retreated, after completing the Day 43 visit, with 6 administrations of the dose selected for Cohort 2, Cohort 3, or Part B. Such participants continued to be followed for at least 24 weeks from the first retreatment dose, but their response to the additional doses were not included for any analyses other than listings.

Part B was planned to enroll 8 to 14 participants who were to receive isatuximab SC Q2W for a total of 6 doses, at a dose determined by the totality of safety, PK, and PD data available from all participants in Part A. The maximum allowable dose in Part B was to be 560 mg. Approximately 14 participants in the study were to receive the isatuximab regimen selected for Part B. Thus, the number of participants in Part B were to range from 8 to 14, depending on the number of participants in Part A who received that same regimen in Cohorts 2 or 3.

All participants received isatuximab subcutaneously.

Number of study participants:

Approximately 17 to 23 participants were expected to be enrolled, depending on the number of participants in Part A who received the regimen chosen for Part B. Eight participants were enrolled in Part A. Part B was not conducted during the study.

Diagnosis and criteria for inclusion:

Males and females with a confirmed diagnosis of primary wAIHA or systemic lupus erythematosus (SLE)-associated wAIHA (without other SLE-related manifestations apart from cutaneous and musculoskeletal manifestations). Participants who have previously failed to maintain a sustained response after treatment with corticosteroids (corticosteroid-refractory or corticosteroid-dependent primary wAIHA).

Study products

Investigational medicinal product(s):

Isatuximab

- Formulation: Solution at a concentration of 140 mg/mL.
- Route of administration: SC injection.
- Dose regimen: SC Q2W; Cohort 1: 140 mg, Cohort 2: 280 mg, and Cohort 3: 560 mg.

Duration of study intervention:

The screening period was planned to be of 28 days, followed by a treatment period of 42 days (6 weeks) for Cohort 1 or 84 days (12 weeks) for the other participants in the study.

All participants were to be followed for at least 24 weeks from the first isatuximab dose. The total length of the study, including screening, was to be 28 weeks.

Criteria for evaluation:

Primary

- Part A: Standard clinical and laboratory parameters and adverse events.
- Overall response rate (R or CR) at Day 85. R was defined as an increase in Hb by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks. Biochemical evidence of hemolysis may still be present.

  CR was defined as Hb ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks.

Secondary

- Overall response rate (R or CR) at Day 85.

  R was defined as an increase in Hb by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks. Biochemical evidence of hemolysis may still be present.

  CR was defined as Hb ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks.
- Proportion of participants with durable Hb response by Day 169. Durable response was defined as Hb level ≥10 g/dL with an increase from baseline of ≥2 g/dL on three consecutive evaluable visits during the study period; with absence of transfusion and no rescue medication during the period of 3 consecutive visits and for at least 7 days (transfusions) and 4 weeks (rescue medication) prior to the first consecutive visit.
- Overall response rate at Day 169, median time to R or CR, median time to loss of R or CR (loss of R defined as Hb <10 g/dL at two consecutive visits at least 7 days apart and initiation of new treatment for anemia or increase in steroid dose; loss of CR was defined as Hb <11 g/dL [women] or <12 g/dL [men] at two consecutive visits at least 7 days apart), proportion of participants requiring rescue therapy (any wAIHA-directed therapy other than prednisone or transfusion) or splenectomy.
- FACIT-fatigue scale score at Day 85 and Day 169.
- Standard clinical and laboratory parameters and adverse events.
- Proportion of participants with durable Hb response by Day 169. Durable response was defined as Hb level ≥10 g/dL with an increase from baseline of ≥2 g/dL on three consecutive evaluable visits during the study period; with absence of transfusion and no rescue medication during the period of 3 consecutive visits and for at least 7 days (transfusions) and 4 weeks (rescue medication) prior to the first consecutive visit.
- Overall response rate at Day 169, median time to R or CR, median time to loss of R or CR (loss of R defined as Hb <10 g/dL at two consecutive visits at least 7 days apart and initiation of new treatment for anemia or increase in steroid dose; loss of CR was defined as Hb <11 g/dL [women] or <12 g/dL [men] at two consecutive visits at least 7 days apart), proportion of participants requiring rescue therapy (any wAIHA directed therapy other than prednisone or transfusion) or splenectomy.
- FACIT-fatigue scale score at Day 85 and Day 169.
- Change from baseline in LDH, haptoglobin, reticulocytes, and total bilirubin at 1, 2, 4, 8, 12, and 24 weeks
- PK parameters after subcutaneous administrations (including C_{max} and $AUC_{0\text{-}2\ week}$).
- Incidence and titer (if relevant) of anti-isatuximab antibodies.

Abbreviations: CR = Complete Response; FACIT = Functional Assessment of Chronic Illness Therapy; Hb = hemoglobin; LDH = lactate dehydrogenase; PK = pharmacokinetics; R = Response; wAIHA = warm autoimmune hemolytic anemia

Statistical methods:

For Part A, descriptive summaries of treatment-emergent adverse events (TEAEs) and potentially clinically significant abnormalities (PCSA) for standard clinical and laboratory parameters were provided in the safety population by dose level group and secondary endpoints were described by dose level group.

This study was stopped early due to non-safety reason and, as a result, Part B was not performed.

Summary Results:

Demographic and other baseline characteristics:

Eight participants were enrolled in the study of which 6 participants completed the study intervention period. The study included all White participants. There were 5 participants from 18 to 64 years of age group and 3 participants from 65 to 84 years of age group. The mean (standard deviation) age of study participants was 50.9 (19.3) years.

Exposure:

All participants from Cohort 1, two participants from Cohort 2, and one participant from Cohort 3 received study intervention as per the protocol. One participant from Cohort 2 received 2 of the planned 6 doses of the study intervention and permanently discontinued the study intervention. One participant from Cohort 3 received 4 of the planned 6 doses of the study intervention and permanently discontinued the study intervention.

Efficacy:

- Overall response rate for Hb was the secondary efficacy endpoint for Part A. No participants (0 out of 3) in Cohort 2 met the secondary efficacy endpoint of overall response rate. One out of 2 participants from Cohort 3 responded to the study intervention in absence of rescue medication from Day 15 to Day 85 corresponding to an overall response rate of 50% during this interval in Cohort 3.
- The mean absolute change from baseline (improvement) values of 7.3 and 12 points, respectively was observed on FACIT-Fatigue subscale score for Cohort 2 and Cohort 3.
- The absolute change from baseline showed slight improvement for markers of hemolysis. No participant had complete normalization of all hemolysis markers.

Safety results:

- The incidence of all TEAEs reported during the study was similar between the study cohorts. Nineteen TEAEs were reported in 6 out of 8 participants.
- TEAEs which met the criteria of Grade ≥3, serious adverse event (SAE)s, and adverse event of special interest (AESI)s were reported in one participant each from Cohort 1 and Cohort 3. One participant from Cohort 3 permanently discontinued study intervention and study due to a TEAE.
- TEAEs of headache, alanine aminotransferase increased, and edema peripheral were reported in 2 participants.
- Overall, 2 participants experienced SAEs during the study. SAEs of anemia, alanine aminotransferase increased, acute kidney injury, and liver injury reported in one participant from Cohort 1 were assessed as not related to the study intervention. Anemia is consistent with the underlying diagnosis of wAIHA. SAEs of infusion related reaction, sepsis, and alanine aminotransferase increased reported in another participant from Cohort 3 were assessed as related to the study intervention.
- TEAEs of sepsis and alanine aminotransferase increased led to permanent study intervention and study discontinuation.
- An AESI of increase in ALT >3 x ULN was reported in 2 participants.
- There were no TEAEs that resulted in death.
- There was no clinically meaningful change observed in the vital signs during the study.

Pharmacokinetic results:

- Following the first SC administration of 140, 280, and 560 mg isatuximab, a supra-dose proportionality associated with a high inter-subject variability was observed.
- Based on C_{trough}, a 19-fold and 1.35-fold accumulation ratio was observed at 280 mg and 560 mg, respectively.

Immunogenicity results:

• One participant each from Cohort 1 and Cohort 2 had post-baseline positive ADA.
Issue date: 21-May-2024