

Phase 1/2 UMBRELLA trial evaluating isatuximab in combination with novel agents in relapsed or refractory multiple myeloma: Study design to evaluate isatuximab with dexamethasone and belumosudil or evorpaccept

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Introduction

- Multiple myeloma (MM) accounts for 1% of all cancers and approximately 10% of all hematologic malignancies¹
- Despite therapeutic advancements, heavily pretreated patients with relapsed/refractory MM (RRMM) continue to have a poor prognosis²
- Individuals with RRMM who have progressed through multiple lines of therapy require novel targeted therapies
- Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with other therapies for RRMM, transplant-ineligible newly diagnosed MM, and in the EU, transplant-eligible newly diagnosed MM^{3,4}
- The ongoing multinational phase 1/2 UMBRELLA trial (NCT04643002) evaluates Isa combined with novel agents in RRMM
- We present the design of 2 open and ongoing UMBRELLA substudies evaluating **belumosudil + Isa + dexamethasone (dex)** and **evorpaccept + Isa + dex**, respectively
- The objectives are to determine the recommended dose of belumosudil and evorpaccept in combination with Isa and dex and evaluate their clinical benefit in different settings of RRMM**
- Other substudies are planned to open shortly

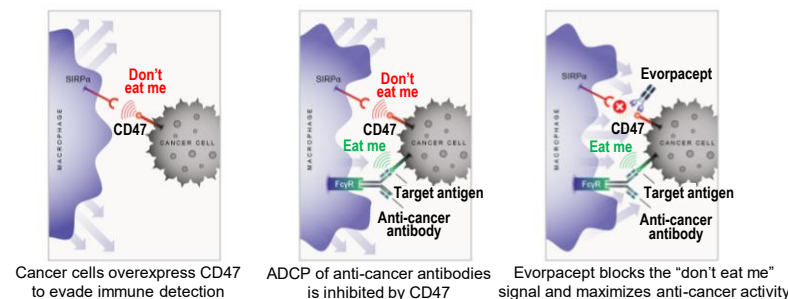
Belumosudil

- Belumosudil is an oral Rho-associated kinase 2 (ROCK2) selective inhibitor approved in several countries for chronic graft vs host disease
- It rebalances T-cell-mediated immune response and disrupts profibrotic signals

Evorpaccept

- Evorpaccept is a fusion protein composed of the N-terminal D1 domain of signal regulatory protein alpha (SIRPα) variant 1 genetically linked to a modified fragment crystallizable domain from human immunoglobulin (Ig) G1
- Evorpaccept binds CD47 to block the interaction with SIRPα and relieves the inhibition of phagocytosis (Figure 1)

Figure 1. Maximal antibody-dependent cellular phagocytosis (ADCP) requires 2 signals: (1) inhibition of the myeloid CD47 SIRPα checkpoint by evorpaccept, and (2) Fc gamma receptors binding to the Fc portion of the anti-cancer antibody bound to cancer cell



Methods

Key inclusion criteria

- Age ≥18 years (or country's legal age)
- Eastern Cooperative Oncology Group performance status of 0–1
- Received ≥2 prior lines of therapy for MM, including proteasome inhibitor and immunomodulatory drug
- RRMM with measurable disease:
 - Serum M protein ≥0.5 g/dL, using serum protein immunoelectrophoresis and/or
 - Urine M protein ≥200 mg/24 h, using urine protein immunoelectrophoresis and/or
 - Serum free light chain MM without measurable M protein in serum or urine per previous criteria (serum Ig free light chain ≥10 mg/dL and abnormal serum Ig kappa/lambda free light chain ratio <0.26 or >1.65)

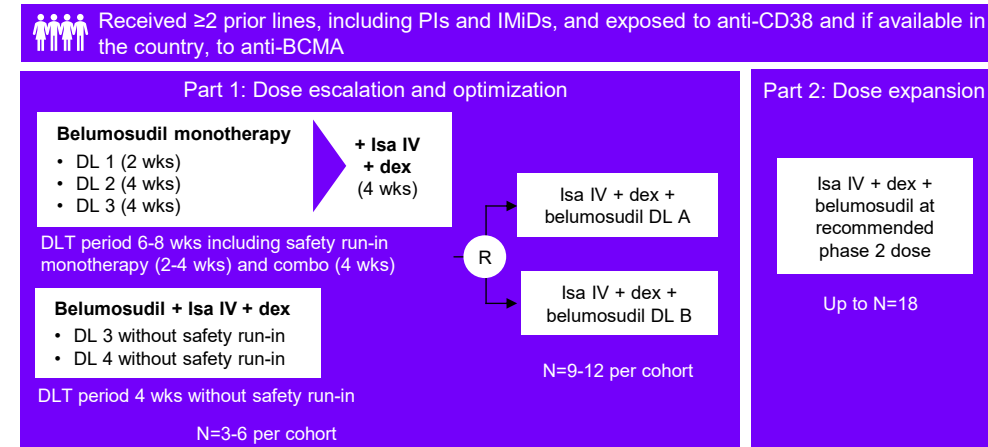
Key exclusion criteria

- Primary systemic amyloid light chain amyloidosis, plasma cell leukemia, monoclonal gammopathy of undetermined significance, or smoldering myeloma
- Any anti-MM drug treatment within 14 days before first study intervention administration, including dexamethasone

Primary endpoints

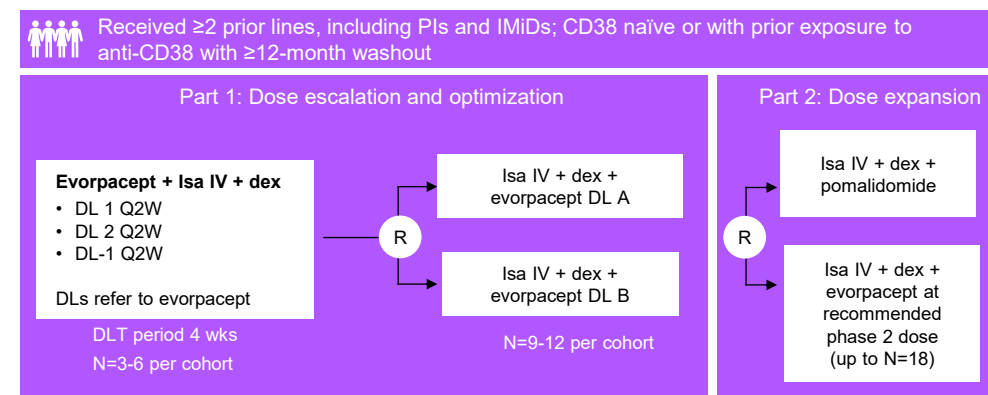
- Part 1:** Determination or confirmation of the dose based on treatment-emergent adverse events, serious adverse events, dose-limiting toxicities, and laboratory parameters
- Part 2:** ≥Very good partial response (VGPR; for controlled substudies) or overall response rate (ORR; defined as proportion of participants with stringent complete response [sCR], complete response [CR], VGPR, or partial response [PR]), according to 2016 International Myeloma Working Group criteria

Figure 2. Study design: belumosudil, isatuximab, and dexamethasone



DLs refer to belumosudil. Part 1 Cycle 1 for DL 1, DL 2, and the first DL 3 will last 6-8 weeks to evaluate belumosudil as monotherapy for 2-4 weeks. Otherwise, treatment cycles will last 4 weeks. DL 1 will be switched to DL 2 once DL 2 is cleared. BCMA=B-cell maturation antigen; CD38=cluster of differentiation 38; dex=dexamethasone; DL=dose level; DLT=dose-limiting toxicity; IMiD=immunomodulatory drug; Isa=isatuximab; IV=intravenous; PI=proteasome inhibitor; R=randomized; wk=week.

Figure 3. Study design: evorpaccept, isatuximab, and dexamethasone



Treatment cycles will last 4 weeks. BCMA=B-cell maturation antigen; CD38=cluster of differentiation 38; dex=dexamethasone; DL=dose level; DLT=dose-limiting toxicity; IMiD=immunomodulatory drug; Isa=isatuximab; IV=intravenous; PI=proteasome inhibitor; Q2W, every 2 weeks; R=randomized; wk=week.

Methods (continued)

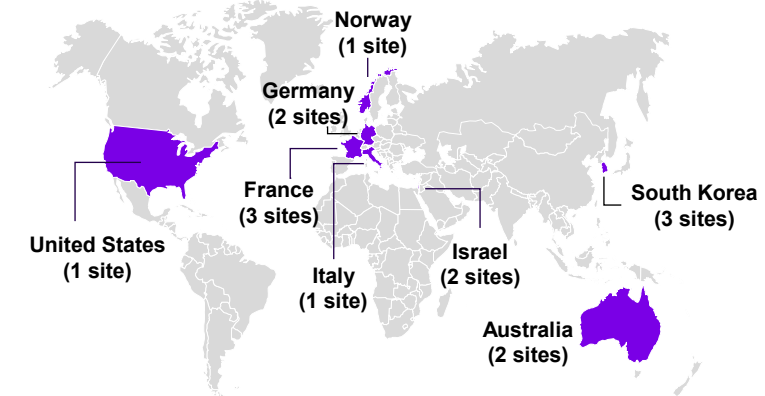
Key secondary endpoints

- Efficacy:** ORR and VGPR; clinical benefit rate (defined as the proportion of individuals with sCR, CR, VGPR, PR, or minimal response); duration of response; time to first response; time to best response; progression-free survival; overall survival
- Safety/tolerability:** Adverse events, serious adverse events
- Pharmacokinetics:** Concentration of the novel agents and Isa (Cycle 1 trough concentration)
- Immunogenicity:** Incidence of anti-drug antibodies
- Patient experience:** Patient-reported outcomes for health-related quality of life and symptoms

Status of Studies

The substudy with belumosudil is in dose escalation and the substudy with evorpaccept is in dose optimization as of February 26, 2026

15 study sites, 8 countries, 50 participants (across both studies)



References: 1. Rajkumar SV. *Am J Hematol.* 2018;93(8):981-1114. 2. Dimopoulos MA, et al. *Clin Lymphoma Myeloma Leuk.* 2022;22(7):460-473. 3. Isatuximab. Prescribing information. Sanofi; 2025. 4. Isatuximab. Summary of product characteristics. Sanofi; 2025.

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Disclosures: Schjesvold, Pianko, Touzeau, and Cerchione report honoraria from Sanofi. Schjesvold, Parmar, Garderet, Metzler, and Cerchione report consulting or an advisory role for Sanofi. Pianko and Touzeau report research funding/support from Sanofi. Cerchione reports participation on speakers' bureaus for Sanofi. Baakil, Andre, Kiwan, and Oprea are employees of Sanofi.

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