# Phase 1b/2 study of the first-in-class SUMO-activating enzyme inhibitor TAK-981 in combination with monoclonal antibodies in patients with triple-class refractory multiple myeloma

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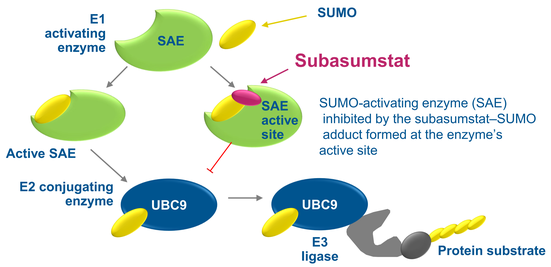
## SUMOylation pathway

- Reversible post-translational modification analogous to ubiquitination
  - Attaches a small, ubiquitin-like modifier (SUMO) to protein substrates (**Figure 1**)[1]
- Plays a central role in the immune system by regulating interferon type 1 (IFN-I) expression[2]
  - Reported to regulate cellular processes important for tumor cell proliferation and survival[3]
- Often overexpressed in multiple myeloma (MM)
  - Associated with poor outcomes[4]

## Subasumstat (TAK-981)

- First-in-class, small-molecule inhibitor of SUMO-activating enzyme[5]
  - Blocks SUMOylation cascade (**Figure 1**)
  - Increases IFN-I production and signaling in innate immune cells[6]
- In ex-vivo assays, subasumstat:
  - Activated the IFN-I pathway
  - Increased phagocytic activity of monocyte-derived macrophages
  - Increased natural killer (NK) cell cytotoxicity via IFN-I signaling[6]

**Figure 1. Inhibition of the SUMOylation cascade by subasumstat[5]**




## Rationale

- Ability of subasumstat to promote activation of macrophages and NK cells provides a rationale for combining it with monoclonal antibodies (mAbs) reliant on antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis
  - In-vivo studies show synergistic activity between subasumstat and rituximab, and between subasumstat and the anti-CD38 mAbs daratumumab and mezagitamab (TAK-079) (**Figure 2**)[7]

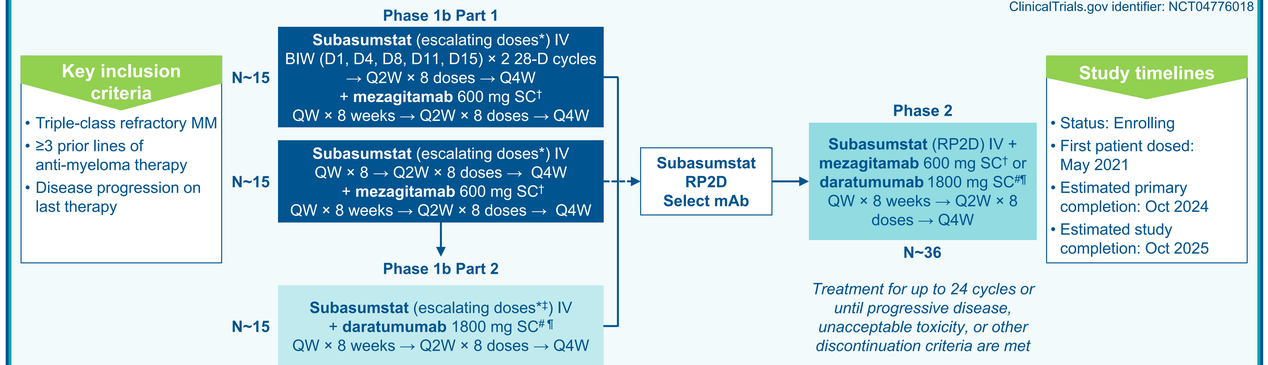
**Compared to daratumumab, mezagitamab shows:[8]**
- Lower affinity binding to CD38 expressed on red blood cells and platelets
- Greater affinity binding to CD38 on B and T lymphocytes

- MM patients with disease that is refractory to the three most effective classes of anti-myeloma therapies (proteasome inhibitors [PIs], immunomodulatory drugs [IMiDs], anti-CD38 mAbs) have a poor prognosis
  - Median OS, 9.2 months[9]
- Given the incurable nature of advanced MM and complex mechanisms of resistance, continued efforts to better understand MM biology at relapse and to translate this into effective combinations are needed
  - Combinations that engage the immune system to treat MM may offer substantial benefit

**Study design**: Phase 1b/2 open-label, multicenter study of **subasumstat (TAK-981)** in combination with mAbs in adults with RRMM

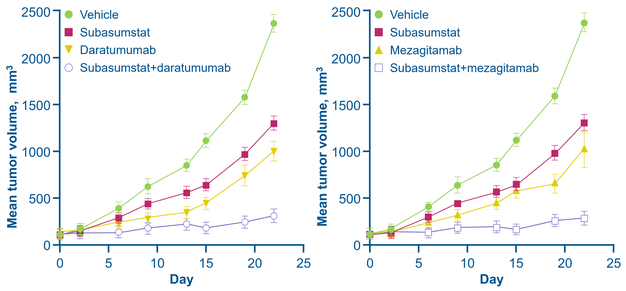
**Primary study objectives**: **Phase 1b**: Determine safety and tolerability, and select recommended phase 2 dose (RP2D) and schedule
**Phase 2**: Evaluate efficacy at the RP2D

ClinicalTrials.gov identifier: NCT04776018




*Dose escalation guided by an iBOIN design, along with consideration of other data. †RP2D from Phase 1b study of mezagitamab in relapsed/refractory MM (RRMM).[10] ‡Starting dose one dose level below RP2D/schedule defined in Part 1. #Daratumumab and hyaluronidase-fihj. ¶Approved dosage.[11]

**Figure 2. Synergistic combination of subasumstat with daratumumab or mezagitamab* in the Daudi tumor model†**




*Mezagitamab is an investigational anti-CD38 mAb being evaluated by Takeda for the treatment of hematologic malignancies, such as MM, and of autoimmune disorders.
†Eight-week-old female CB-17 severe combined immunodeficiency mice were inoculated subcutaneously (SC) in the flank with 2 x $10^6$ Daudi cells. When mean tumor volume reached ~100–200 $mm^3$, animals were randomized into treatment groups (n=8 each) and dosed intravenously (IV) with subasumstat, or intraperitoneally with daratumumab or mezagitamab, or with the combination of subasumstat+daratumumab or subasumstat+mezagitamab. Subasumstat, daratumumab, and mezagitamab were dosed at 7.5 mg/kg BIW for 3 weeks.

## Patient eligibility

***Inclusion criteria***
- Male or female patients aged ≥18 years
- Diagnosis of MM (IMWG criteria[12]) with documented disease progression on last therapy
- Measurable disease
- Prior stem cell transplant or considered transplant-ineligible
- Failed ≥3 prior lines of anti-myeloma therapy, including 1 anti-CD38 mAb
- MM disease that is triple-class refractory (refractory/intolerant to ≥1 PI and ≥1 IMiD, and refractory to ≥1 anti-CD38 mAb)
- Eastern Cooperative Oncology Group performance score 0–2
- Adequate organ function
- Prior chimeric antigen receptor T cell therapy is allowed

***Exclusion criteria***
- Treatment with systemic anticancer treatments or radiation therapy within 14 days or any investigational product within 5 half-lives of the first dose of study drug
- Diagnosis of primary amyloidosis, Waldenström's disease, monoclonal gammopathy of undetermined significance or smoldering MM, plasma cell leukemia, POEMS syndrome, myelodysplastic syndrome, or myeloproliferative syndrome
- Central nervous system and/or meningeal involvement
- Prior treatment with >1 anti-CD38 mAb

## Objectives and endpoints

**Phase 1b objectives**

***Primary:***
- Safety and tolerability
- RP2D

***Secondary:***
- Pharmacokinetics (PK) profile
- Preliminary efficacy (IMWG criteria[13])
- Target engagement (subasumstat–SUMO adduct formation) and SUMOylation pathway inhibition in blood

**Phase 1b endpoints**

***Primary:***
- Frequency and severity of TEAEs
- Dose-limiting toxicities (DLTs) in Cycle 1

***Secondary:***
- Subasumstat concentration–time data
- ORR, CBR, DOR, TTP, TTNT, PFS, OS
- Subasumstat–SUMO adduct formation and SUMOylation pathway inhibition in blood

**Phase 2 objectives**

***Primary:***
- Efficacy at RP2D (IMWG criteria[13])

***Secondary:***
- PK profile
- Further efficacy characterization
- Safety and tolerability

**Phase 2 endpoints**

***Primary:***
- ORR (≥PR)

***Secondary:***
- Subasumstat concentration-time data
- Frequency and severity of TEAEs
- CBR, DOR, TTP, TTNT, PFS, OS
- Proportion of MRD-negative patients by NGS
- MRD-negative rate at 1 year
- Durable MRD-negative rate

## Subasumstat dosing

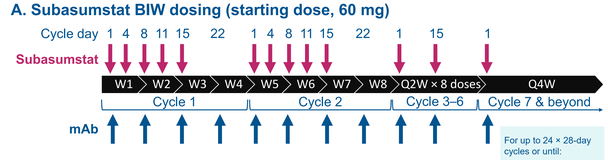
- Phase 1b Part 1: 1-hour IV infusion on initial BIW or QW schedule (**Figure 3A/B**) with SC mezagitamab 600 mg fixed dose (200 mg/2 mL)
- Phase 1b Part 2: Starting dose one dose level below RP2D/schedule defined in Part 1 with SC daratumumab 1800 mg and 30,000 units of hyaluronidase-fihj in 15 mL over approximately 5 min

- Dose escalation guided by Bayesian Optimal Interval Design with Informative Prior (iBOIN), with consideration of other safety clinical, PK, and pharmacodynamics data
  - iBOIN selects the true maximum tolerated dose (if any) with high accuracy by allocating more patients to dose levels with prior DLT probability closest to the target of 0.3

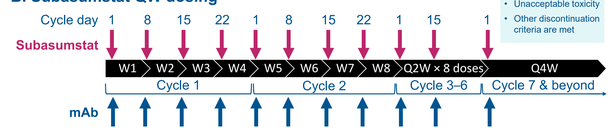
- Phase 2: At RP2D and schedule selected in Phase 1b with selected mAb. Phase 2 mAb will be selected by the sponsor following evaluation of Phase 1b data

**Figure 3. Combination dosing schedules**

**A. Subasumstat BIW dosing (starting dose, 60 mg)**




**B. Subasumstat QW dosing**

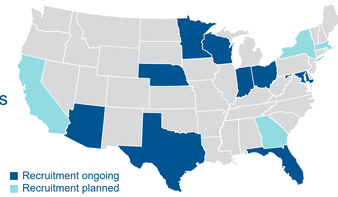



For up to 24 × 28-day cycles or until:
- Disease progression
- Unacceptable toxicity
- Other discontinuation criteria are met

On days that both agents are administered, mAb is administered at least 1 hour after completion of subasumstat infusion, except in Cycle 1 Day 1, when mAb is administered before subasumstat

## Enrollment

- Planned to enroll ~81 patients at 15 sites across the USA
- Recruitment is ongoing at sites in Texas (2 sites), Nebraska, Maryland, Minnesota, Florida, Arizona, Indiana, Wisconsin and Ohio

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