First-in-human phase 1/2 study of the first-in-class SUMO-activating enzyme inhibitor TAK-981 in patients with advanced or metastatic solid tumors or relapsed/refractory lymphoma: phase 1 results

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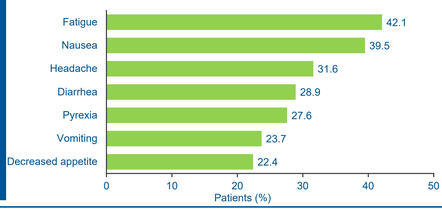
Question What is the safety and tolerability profile of the novel SUMOylation inhibitor subasumstat (TAK-981), and what is the RP2D?

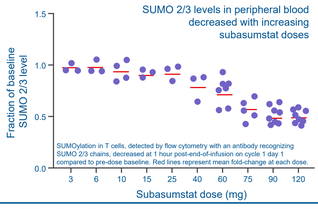
Investigation Patients with advanced/metastatic solid tumors or R/R lymphomas (N=76) — Subasumstat IV 3–40 mg BIW or 60–120 mg QW/BIW — Treated in 21-day cycles for up to 1 year or until disease progression, unacceptable toxicity, or other withdrawal criteria met

Results

Most common TEAEs (any grade)



Pharmacodynamics



RP2D

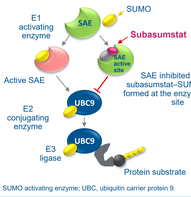
- MTD determined as 120 mg BIW
- Dose-related pharmacodynamics, with strongest evidence of biological activity at doses ≥60 mg BIW
- 90 mg BIW selected as the RP2D for subasumstat

Conclusions Subasumstat had a manageable safety profile up to MTD of 120 mg BIW, with evidence of SUMOylation inhibition and type I IFN pathway activation at doses ≥60 mg. The RP2D was determined as 90 mg BIW; evaluation of anti-tumor activity at this dosage is ongoing in the phase 2 expansion portion of this study.

Subasumstat (TAK-981)

- Subasumstat, previously known as TAK-981, is a first-in-class, investigational, SUMO-activating enzyme inhibitor, and is the first small-molecule inhibitor of SUMOylation to enter clinical trials
  - SUMOylation is a post-translational modification in which SUMO proteins are activated and covalently attached to substrate proteins[1]
  - SUMOylation has a central role in constraining type I interferon (type I IFN)-dependent responses[2]
- By blocking SUMOylation **(Figure 1)**, subasumstat promotes type I IFN-dependent innate immune responses and can enhance antitumor adaptive immunity[3,4]
- Here we report dose-escalation phase data from the first-in-human study of subasumstat conducted in patients with advanced/metastatic solid tumors or relapsed/refractory (R/R) lymphomas

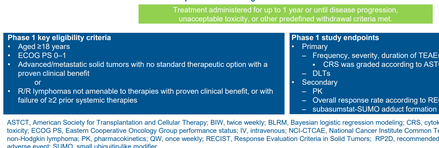
Figure 1. Mechanism of subasumstat inhibition of the SUMOylation enzyme cascade[3]



SAE, SUMO activating enzyme; UBC, ubiquitin carrier protein 9.

Methods

Figure 2. Phase 1/2, open-label, dose-escalation and dose-expansion study — ClinicalTrials.gov: NCT03648372



Phase 1 key eligibility criteria
- Aged ≥16 years
- ECOG PS 0–1
- Advanced/metastatic solid tumors with no standard therapeutic option with a proven clinical benefit
  or
- R/R lymphomas not amenable to therapies with proven clinical benefit, or with failure of ≥2 prior systemic therapies

Phase 1 study endpoints
- Primary
  - Frequency, severity, duration of TEAEs according to NCI CTCAE version 5.0
    - CRS was graded according to ASTCT Consensus Grading for CRS
  - DLTs
- Secondary
  - PK
  - Overall response rate according to RECIST version 1.1 or Lugano classification
  - subasumstat-SUMO adduct formation and SUMO pathway inhibition

ASTCT, American Society for Transplantation and Cellular Therapy; BIW, twice weekly; BLRM, Bayesian logistic regression modeling; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; SUMO, small ubiquitin-like modifier.

Results

Patients

- Seventy-six patients received subasumstat at 10 dose levels (3–40 mg BIW, 60–120 mg QW/BIW; **Table 1**)

Table 1. Enrollment by subasumstat dose

	Subasumstat dose, mg												
	3 mg BIW	6 mg BIW	10 mg BIW	15 mg BIW	25 mg BIW	40 mg BIW	60 mg QW	60 mg BIW	75 mg QW	75 mg BIW	90 mg QW	90 mg BIW	120 mg QW	120 mg BIW	Total
n	5	3	4	3	4	4	6	7	6	6	7	8	5	8	76

- Patient baseline demographics and disease characteristics are summarized in **Table 2**
- At data cut-off, 13 patients (17.1%) were receiving the study drug
- Among patients who had discontinued treatment, the most common reason was disease progression (57.9%)
- Other reasons for discontinuation included adverse event (AEs; 10.5%), symptomatic deterioration (7.9%), and withdrawal by patient (6.6%)

Table 2. Patient baseline demographics and disease characteristics

Characteristic	N=76
Median age, years (range)	61 (38–79)
Female, n (%)	42 (55.3)
Tumor type, n (%)	
Colorectal	20 (26.3)
Pancreatic	7 (9.2)
Kidney	5 (6.6)
Breast	4 (5.3)
Head & neck	4 (5.3)
Melanoma	4 (5.3)
Prostate	4 (5.3)
Adrenal	3 (3.9)
Non-small cell lung cancer	3 (3.9)
Endometrial	2 (2.6)
Appendix	2 (2.6)
Other*	18 (23.7)
Median number of prior lines of therapy (range)	4 (1–10)

*Other tumor types occurring in 1 patient only were: anal, bladder, cervical, cholangiocarcinoma, diffuse large B-cell lymphoma, gallbladder, liver, biliary, salivary gland, bile duct, chordoma, desmoid, peritoneal carcinoma, small cell lung cancer, thoracic, thyroid, unknown – colon or small bowel, and uterine.

DLTs and determination of MTD

- A total of 4 DLTs were observed in 62 evaluable patients (those who received all cycle 1 doses or experienced a DLT during cycle 1) **(Table 3)**
- The maximum tolerated dose (MTD) was determined to be 120 mg BIW, based on BLRM in 40 DLT-evaluable patients on BIW dosing schedules

Table 3. DLTs reported during dose-escalation

Subasumstat dose level	N	n with DLTs during cycle 1	Description of TEAEs	Action taken
60 mg BIW	7	1	Transient grade 3 ALT/AST elevation	Subasumstat reduced to 40 mg BIW
90 mg BIW	8	1	Grade 3 recurrent pneumonitis	Study treatment discontinued
120 mg BIW	8	2	Grade 3 stomatitis (n=1)	Subasumstat reduced to 90 mg BIW
			Grade 3 cognitive disturbance (n=1)	Study treatment discontinued

ALT, alanine aminotransferase; AST, aspartate transaminase

Safety and tolerability profile

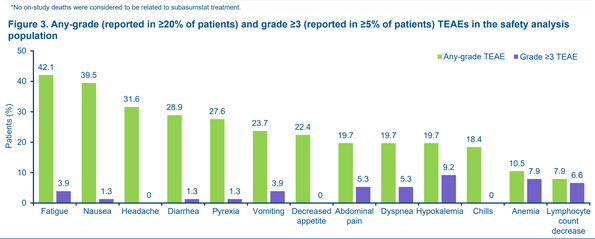
- At data cut-off of 30 Apr 2021, median treatment duration in the safety analysis population (n=76) was 2 cycles (range: 1–12)
- TEAEs in the safety analysis population are summarized in **Table 4**
- The most common TEAEs (reported in ≥20% of patients) were fatigue (42.1%), nausea (39.5%), headache (31.6%), diarrhea (28.9%), pyrexia (27.6%), vomiting (23.7%), and decreased appetite (22.4%) **(Summary panel)**
- Grade ≥3 TEAEs reported in ≥5% of patients were hypokalemia (9.2%), anemia (7.9%), lymphocyte count decreased (6.6%), dyspnea (5.3%), and abdominal pain (5.3%) **(Figure 3)**
- CRS was reported in a total of 9 patients (11.8%), of whom 5 had grade 1 CRS and 4 had grade 2 CRS
  - All cases of grade 2 CRS resolved within 12 hours of onset with oral antipyretics, supportive oxygen and/or IV fluids

Table 4. Summary of TEAEs with subasumstat

	Subasumstat dose												
n (%)	3 mg BIW (n=5)	6 mg BIW (n=3)	10 mg BIW (n=4)	15 mg BIW (n=3)	25 mg BIW (n=4)	40 mg BIW (n=4)	60 mg QW (n=6)	60 mg BIW (n=7)	75 mg QW (n=6)	75 mg BIW (n=6)	90 mg QW (n=7)	90 mg BIW (n=8)	120 mg QW (n=5)	120 mg BIW (n=8)	Total (N=76)
TEAEs	4 (80.0)	3 (100)	4 (100)	3 (100)	4 (100)	4 (100)	5 (83.3)	6 (85.7)	6 (100)	5 (83.3)	7 (100)	8 (100)	4 (80.0)	8 (100)	71 (93.4)
Related to subasumstat	2 (40.0)	2 (66.7)	3 (75.0)	1 (33.3)	4 (100)	3 (75.0)	3 (50.0)	3 (42.9)	6 (100)	4 (66.7)	7 (100)	7 (87.5)	4 (80.0)	8 (100)	57 (75.0)
Grade ≥3 TEAEs	2 (40.0)	2 (66.7)	3 (75.0)	1 (33.3)	2 (50.0)	2 (50.0)	1 (16.7)	4 (57.1)	0	4 (66.7)	5 (71.4)	6 (75.0)	3 (60.0)	6 (75.0)	41 (53.9)
Related to subasumstat	0	0	1 (25.0)	0	1 (25.0)	0	0	2 (28.6)	0	1 (16.7)	3 (42.9)	2 (25.0)	1 (20.0)	4 (50.0)	15 (19.7)
TEAEs leading to discontinuation	1 (20.0)	0	0	0	0	0	0	0	0	1 (16.7)	0	4 (50.0)	1 (20.0)	2 (25.0)	9 (11.8)
Related to subasumstat	0	0	0	0	0	0	0	0	0	0	0	1 (12.5)	1 (20.0)	1 (12.5)	4 (5.3)
Serious AEs	3 (60.0)	2 (66.7)	3 (75.0)	1 (33.3)	2 (50.0)	2 (50.0)	1 (16.7)	2 (28.6)	0	3 (50.0)	2 (28.6)	5 (62.5)	2 (40.0)	5 (62.5)	33 (43.4)
Related to subasumstat	0	0	0	0	1 (25.0)	0	0	2 (28.6)	0	0	0	1 (12.5)	1 (20.0)	2 (25.0)	7 (9.2)
On-study deaths*	1 (20.0)	0	0	0	0	1 (25.0)	0	1 (14.3)	0	1 (16.7)	0	2 (25.0)	0	0	6 (7.9)

*No on-study deaths were considered to be related to subasumstat treatment.

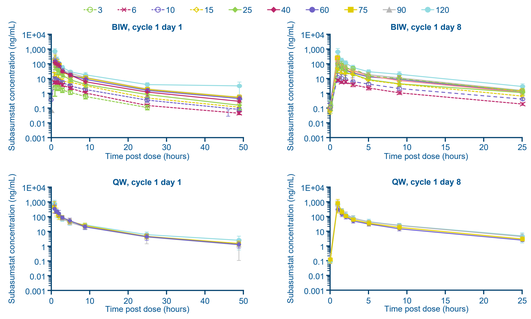
Figure 3. Any-grade (reported in ≥20% of patients) and grade ≥3 (reported in ≥5% of patients) TEAEs in the safety analysis population



Pharmacokinetics and pharmacodynamics

- Subasumstat exhibited linear PK in the dose range 60–120 mg, with approximately dose-proportional exposure **(Figure 4)**
- The mean terminal half-life of subasumstat 60–120 mg ranged from 7.7–10.8 hours on cycle 1 day 1, and 3.8–6.0 hours on cycle 1 day 8, with no evidence of accumulation at these dose levels

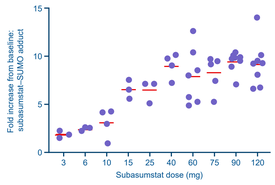
Figure 4. Mean plasma concentration versus time profiles of subasumstat following IV infusions by dose and schedule*



*Different PK sample collection periods were used for the determination of half-life on cycle 1, day 1 and cycle 1, day 8, as shown in the figure.

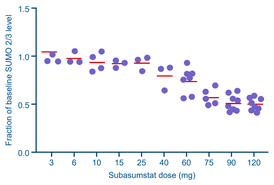
- Formation of subasumstat–SUMO adduct increased **(Figure 5)** while SUMO 2/3 conjugated protein levels decreased **(Figure 6)** with increasing subasumstat doses
- Markers of type I IFN induction (*CXCL10* mRNA) and innate immune response activation (CD69+ natural killer [NK] cells) also increased in a dose-related manner **(Figures 7 and 8)**

Figure 5. Target engagement: subasumstat–SUMO adduct formation in blood sampled from patients on BIW dosing schedule



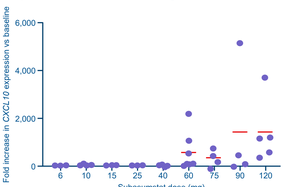
Blood samples were collected on cycle 1 day 1 pre-dose and at multiple timepoints after subasumstat administration. Target engagement in T cells was detected by flow cytometry with an antibody recognizing the subasumstat-SUMO adduct formed during the inhibition of the SUMO-activating enzyme by subasumstat; cycle 1 day 1 signal increased at 1 hour post-end-of-infusion compared to the background level observed pre-dose (baseline).
Red lines represent mean fold-change at each dose.

Figure 6. SUMO 2/3 levels in blood sampled from patients on BIW dosing schedule



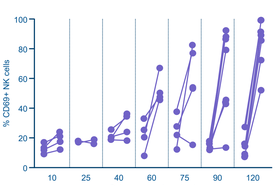
SUMOylation in T cells, detected by flow cytometry with an antibody recognizing SUMO2/3 chains, decreased at 1 hour post-end-of-infusion on cycle 1 day 1 compared to pre-dose baseline.
Red lines represent mean fold-change at each dose.

Figure 7. Upregulation of *CXCL10* expression in blood sampled from patients on BIW dosing schedule



Upregulation of mRNA levels of *CXCL10*, an IFN-ß-regulated gene, in peripheral blood. Gene expression was measured using Nanostring *n*Counter at cycle 1 day 1 pre-dose and at several timepoints post-dose. Data for maximum increase at 8 or 24 hours, relative to pre-dose, is shown.
Red lines represent mean fold-change at each dose.

Figure 8. NK cell activation in blood sampled from patients on BIW dosing schedule



NK cell activation in peripheral blood measured by flow cytometry. Percentage of CD69+ NK cells at cycle 1 day 1 pre-dose and at 24 hours post-end-of-infusion is shown by patient for each dose level.

Determination of biologically effective dose and RP2D

- Dose-dependent activity across a range of pharmacodynamic measures indicates that subasumstat is biologically active at doses of ≥60 mg, as evidenced by biomarkers of type I IFN pathway and NK cell activation
- Together with the safety data, these data support a RP2D of 90 mg BIW
- The dosing schedule taken forward to the phase 2 dose expansion phase of the trial is 90 mg BIW for 3 cycles, with the option to decrease the treatment schedule to a QW regimen based on tolerance and efficacy

Tumor responses

- One partial response was observed with subasumstat 40 mg BIW in a patient with R/R , human epidermal growth factor receptor 2 (HER2)-negative, hormone receptor-positive breast cancer who had received 8 prior lines of therapy
- This patient's response was observed after 3 cycles of subasumstat 40 mg BIW and deepened when the dose was escalated from subasumstat 40 mg to 60 mg. subasumstat treatment was discontinued after 12 cycles due to disease progression
- Thirteen patients (17.1%) had stable disease
- Anti-tumor activity of subasumstat is being investigated further in the ongoing dose-expansion phase of the trial

Conclusions

The MTD of single-agent subasumstat (TAK-981) was 120 mg BIW, while clear evidence of inhibition of SUMOylation was seen at doses of 60–120 mg BIW

The data generated in this study support continued subasumstat development for treatment of solid tumors and lymphoma, with a RP2D of 90 mg BIW

The phase 2 study expansion is ongoing in patients with advanced/metastatic non-small-cell lung, cervical, and colorectal cancer, and in R/R non-Hodgkin lymphoma

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Disclosures

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