ATLAS: A randomized, double-blind, placebo-controlled, adaptive seamless phase 2/3 study to assess the safety and efficacy of momelotinib in patients with VEXAS syndrome

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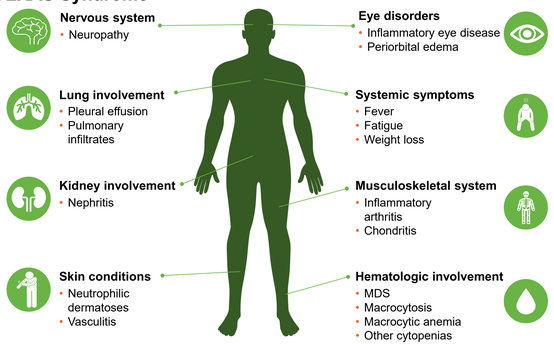
ATLAS is a randomized, double-blind phase 2/3 trial of momelotinib plus GCs vs placebo plus GCs in patients with VEXAS syndrome

Digital poster

Introduction

- VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a rare clonal myeloid hematoinflammatory disorder caused by somatic *UBA1* mutations[1,2]
- This adult-onset autoinflammatory disease was first described in 2020 by Beck et al, and leads to severe multisystemic inflammation with rheumatologic, dermatologic, and hematologic involvement (**Figure 1**)[1-3]

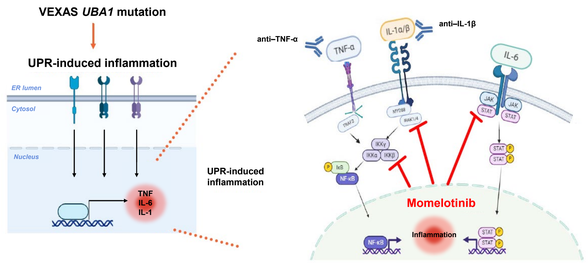
Figure 1: **Common Inflammatory and Hematologic Symptoms in VEXAS Syndrome[1,4]**



MDS, myelodysplastic syndrome; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

- Currently, there are no approved therapies for VEXAS; current non-glucocorticoid (GC) therapies are not steroid sparing and do little to slow disease progression[1]
- Janus kinase (JAK) inhibitors have shown promise for treating VEXAS, as the JAK-STAT signaling pathway is integral to inflammation and immune regulation[5-7]
- Momelotinib is a JAK1/JAK2/activin A receptor type 1 inhibitor that is approved for treating myelofibrosis with anemia[8]
  - Momelotinib's unique pharmacologic profile, including targeting of pathways such as TNF-α, IL-6, and IL-1 signaling, provides rationale for expansion beyond myelofibrosis to VEXAS (**Figure 2**)[9]
  - In a case report, momelotinib showed promise in 2 patients with VEXAS, representing the first experiences of momelotinib as a safe and effective treatment for VEXAS[10]
    - Both patients experienced an improvement in anemia and a decrease in inflammation, and momelotinib was well tolerated
  - In a single-center case report, 6 patients with confirmed VEXAS received momelotinib as authorized by the Regional Rare Disease Fund in Italy[11]
    - After 3 months of treatment, momelotinib led to a 2-g/dL increase in median hemoglobin (Hb) levels, along with decreases in median C-reactive protein levels (16 vs 25 mg/L at baseline), median GC dose (15 vs 20 mg/day), and median variant allele frequency (29.8% vs 67% at baseline)
    - Momelotinib had an acceptable safety profile with no life-threatening events
- Based in part on these case report data, momelotinib has received orphan drug status from the US Food and Drug Administration and European Medicines Agency for the treatment of VEXAS[12]

Figure 2: **Momelotinib Targets Pathways Implicated in VEXAS Pathophysiology[9]**

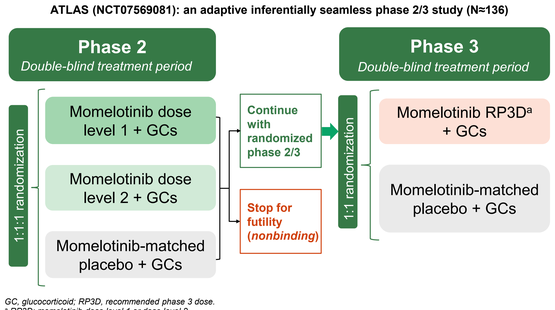


ER, endoplasmic reticulum; IL, interleukin; IRAK, interleukin receptor associated kinase; IKK, IκB kinase; JAK, Janus kinase; NF-κB, nuclear factor–κB; P, phosphate; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; TRAF2, TNF receptor associated factor 2; UBA1, ubiquitin-like modifier-activating enzyme 1; UPR, unfolded protein response; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Study Design[13,14]

- ATLAS (**NCT07569081** and **EU CT 2025-524416-11-00**) is a global, multicenter, double-blind, inferentially seamless phase 2/3 study that will enroll ≈136 patients (**Figure 3**)
- Phase 2 will integrate dose optimization and randomize patients, stratified by baseline GC dose, 1:1:1 to receive 1 of 2 doses of momelotinib or placebo for 26 weeks
  - Two doses of momelotinib will be evaluated to determine the recommended phase 3 dose (RP3D)
- A GC taper will be required during the treatment period; however, GC rescue therapy for flares is permitted
- If futility for momelotinib is not declared at the interim analysis, additional patients will be enrolled and randomized 1:1 to receive momelotinib at the RP3D or placebo
- All patients enrolled in phase 2 who have not met disease progression will remain blinded until phase 3 patients finish 26 weeks of treatment

Figure 3: **ATLAS Study Design[13,14]**



GC, glucocorticoid; RP3D, recommended phase 3 dose.
[a] RP3D: momelotinib dose level 1 or dose level 2.

Endpoints[13,14]

Table 1: **ATLAS Primary and Secondary Endpoints**

Primary objective	Endpoint
ORR at week 26	• CR or PR achievement at week 26 (based on VEXAS-related flares/symptoms and other disease features and GC tapering)
Secondary objectives	**Endpoints**
Identify the RP3D	• Percentage of patients with PR or CR at week 26 • PK concentrations of momelotinib and M21 • Selected safety endpoints
Evaluate efficacy measures	• Number of flare-free days[a] through the 26-week treatment period • Number of flare-free days[a] with GC dose ≤10 mg per day • DOR defined as the date of clinical response (CR or PR) to date of relapse • Percentage of patients achieving biochemical response • ORR at week 52
Evaluate HI-E	• HI-E evaluated by week 26 per IWG 2018 criteria
Evaluate patient-reported outcomes (eg, fatigue, physical functioning, and general quality of life)	• Change from baseline in SF-36 domain and summary scores • Change from baseline in EORTC IL 479 score • Change from baseline in PROMIS Physical Function Short Form 10b • Change from baseline in FACIT-Fatigue • Changes in from baseline in EQ-5D-5L index and VAS scores • Changes in PGIS scores • Changes in PGIC scores
Assess safety profile of momelotinib	• Incidence and severity of AEs and SAEs, and AEs leading to treatment discontinuation or dose modifications
Describe PK exposure of momelotinib and M21	• Plasma concentration of momelotinib and M21
OS	• Survival at 12, 24, and 36 months

AE, adverse event; CR, complete response; DOR, duration of response; EORTC IL, European Organisation for Research and Treatment of Cancer Item Library; EQ-5D-5L, European quality of life 5 dimensions, 5 level version; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; GC, glucocorticoid; HI-E, hematologic improvement – erythroid; IWG, International Working Group; M21, momelotinib metabolite 21; ORR, objective response rate; OS, overall survival; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; PR, partial response; PROMIS, Patient-Reported Outcomes Measurement Information System; RP3D, recommended phase 3 dose; SAE, serious adverse event; SF-36, 36-Item Short Form Survey; VAS, visual analog scale; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.
[a] Flare-free days are calendar days without clinical evidence of VEXAS flare and without treatment escalation. Total number of flare-free days is defined as the cumulative number of consecutive and nonconsecutive flare-free days.

Eligibility[13,14]

Select inclusion criteria

- ✓ Age **≥18 years *or*** of **legal age of consent** and can provide **signed informed consent**
- ✓ Confirmed **diagnosis of clinical VEXAS** defined by (a) documented evidence of canonical, pathogenic *UBA1* mutation and (b) inflammatory manifestations in ≥1 organ system
- ✓ Receiving **GC treatment** (prednisone/prednisolone) for ≥4 consecutive weeks that has been at a stable daily dose of 15 to 45 mg for ≥10 days prior to randomization
- ✓ **ECOG PS of ≤2**
- ✓ **Not pregnant or breastfeeding**
- ✓ Adequate **organ function** based on hematologic, hepatic, and renal function laboratory parameters

The disease history of patients will be obtained, including 1) clinical features such as organ involvement and flare history in patients previously diagnosed with VEXAS, and 2) features that warrant consideration of VEXAS testing in patients not yet diagnosed (eg, elevated inflammatory markers plus the presence of peripheral cytopenias, constitutional symptoms, and/or other common manifestations)

Select exclusion criteria

- ✗ >1 prior **ICU admission for VEXAS flare** within 6 months prior to randomization
- ✗ History of severe **steroid toxicity**
- ✗ High-risk/very high-risk **MDS** (IPSS-R score >3.5)
- ✗ Known **contraindication or hypersensitivity to momelotinib** and its metabolites or any of their excipients
- ✗ Inability to receive **PJP medical prophylaxis**
- ✗ **Presence of malignancies** and **other illnesses or medical conditions** as outlined in the study protocol

Select exclusion criteria: prior and concomitant therapies

- ✗ >1 **VEXAS-directed prior LOT** as specified in the study protocol
- ✗ **Ongoing adverse reactions from prior therapy that** have not recovered to grade ≤1 per NCI-CTCAE v6.0 or to the baseline status preceding prior therapy
- ✗ **GC therapy for non-VEXAS conditions**, systemic steroid use for >4 years, or inability to withdraw steroid treatment
- ✗ Non-GC anti-inflammatory biologic or nonbiologic therapy within specific timeframes prior to randomization
- ✗ **Prior solid organ transplant** (except corneal) or allogeneic or autologous stem cell transplant, or planned allogeneic HSCT for MDS or VEXAS within 1 year

ECOG PS, Eastern Cooperative Oncology Group performance status; GC, glucocorticoid; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IPSS-R, Revised International Prognostic Scoring System; LOT, line of therapy; MDS, myelodysplastic syndrome; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PJP, Pneumocystis jirovecii pneumonia; UBA1, ubiquitin-like modifier-activating enzyme 1; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Study Information

ATLAS will begin enrolling in Q3 2026

ClinicalTrials.gov

https://clinicaltrials.gov/study/NCT07569081

Study Contact

GSK Clinical Support: GSKClinicalSupportHD@gsk.com

Abbreviations

AE, adverse event; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC IL, European Organisation for Research and Treatment of Cancer Item Library; EQ-5D-5L, European quality of life 5 dimensions, 5 level version; ER, endoplasmic reticulum; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; GC, glucocorticoid; Hb, hemoglobin; HI-E, hematologic improvement – erythroid; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IL, interleukin; IPSS-R, Revised International Prognostic Scoring System; IRAK, interleukin receptor associated kinase; IKK, IκB kinase; IWG, International Working Group; JAK, Janus kinase; LOT, line of therapy; M21, momelotinib metabolite 21; MDS, myelodysplastic syndrome; NCI-CTCAE. National Cancer Institute Common Terminology Criteria for Adverse Events; NF-κB, nuclear factor–κB; ORR, objective response rate; OS, overall survival; P, phosphate; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PJP, Pneumocystis jirovecii pneumonia; PK, pharmacokinetic; PR, partial response; PROMIS, Patient-Reported Outcomes Measurement Information System; RP3D, recommended phase 3 dose; SAE, serious adverse event; SF-36, 36-Item Short Form Survey; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; TRAF2, TNF receptor associated factor 2; UBA1, ubiquitin-like modifier-activating enzyme 1; UPR, unfolded protein response; VAS, visual analog scale; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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