PAXIS: A Randomized, Double-Blind, Placebo-Controlled, Dose Finding Phase 2 Study (Part 1) Followed by an Open-Label Period (Part 2) to Assess the Efficacy and Safety of Pacritinib in Patients with VEXAS Syndrome

David B. Beck[1], Mael Heiblig[2,3], Sinisa Savic[4], Marcela A. Ferrada[5], Arsene Mekinian[6], Onima Chowdhury[7,8], Danielle Hammond[9], Lachelle D. Weeks[10], Carmelo Gurnari[11,12], Yohei Kirino[13], Sophie Georgin-Lavialle[14], Sarah A. Buckley[15], Bryan G. Harder[15], Sandra Goble[15], Matthew J. Koster[16]*

*[1]NYU School of Medicine, New York, NY; [2]Lyon-Sud Hospital, Hospices Civils de Lyon, Paris, France; [3]Université Claude Bernard, Lyon, France; [4]University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, UK; [5]University of Maryland School of Medicine, Baltimore, MD; [6]AP-HP.Sorbonne Université – Hôpital Saint-Antoine, Paris, France; [7]Oxford University Hospitals' NHS Foundation Trust, Oxford, UK; [8] Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK; [9]The University of Texas MD Anderson Cancer Center, Houston, TX; [10]Dana Farber Cancer Institute, Boston, MA; [11]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy; [12]Translational Hematology and Oncology Research Department, Taussig Cancer Center, Cleveland Clinic, Clevland, OH; [13]Yokohama City University Graduate School of Medicine, Yokohama, Japan; [14] Sorbonne university, Tenon hospital, DMU3ID, CEREMAIA, ERN RITA, Paris, France; [15]Sobi, Inc., Waltham, MA; [16]Mayo Clinic, Rochester, MN; *Former employee*

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Disclosures

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VEXAS syndrome is a severe systemic auto-inflammatory disease

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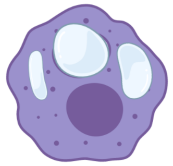
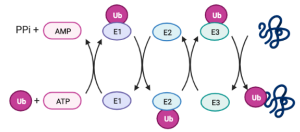
- Caused by somatic *UBA1* mutation restricted to myeloid cells[1]
- Presents with inflammation in multiple organ systems[1]
- A subset of patients have concomitant hematologic disorders such as myelodysplastic syndrome (MDS)[1]
- Glucocorticoids (GCs) are the mainstay of treatment[1,2]
- Associated with high mortality[3] due to complications of disease and immunosuppressive therapy
- Unmet need for safe and effective therapies to control inflammation and improve quality of life[4]

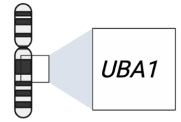
V **Vacuoles:**
Vacuolated myeloid and erythroid precursors



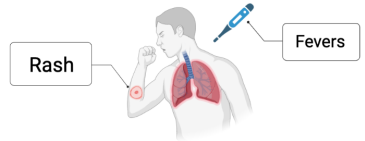
E **E1-Enzyme:**
Mutations in *UBA1* lead to lack of cytoplasmic E1 enzyme



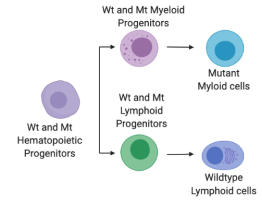
X **X-linked:**
UBA1 gene located on X chromosome



A **Autoinflammatory:**
Severe inflammation, steroid dependent



S **Somatic:**
Mutations in UBA1 restricted to myeloid origin cells



[1] Beck DB, et al. NEJM 2020. [2] Grayson P, Patel BA, and Young NS, Blood. 2021.
[3] Georgin-Lavialle S, et al. Br J Dermatol. 2022. [4] Mekinian AM, et al. Arthritis & Rheumatology, 2025.

VEXAS syndrome causes a hyper-inflammatory response

- Mutated myeloid cells have multiple elevated inflammatory gene signatures[1]
- Innate immune signaling activated by NFκB drives inflammatory cytokines (IL-6, IL-8, IL-18, TNFα)[2]
- Most anti-inflammatory strategies target single cytokines or single inflammatory pathways (anti-IL-6, anti-IL-1, anti-TNFα, JAK inhibitors)[3-5]
- No agent targeting NFκB-mediated inflammation has been attempted in VEXAS syndrome

***UBA1* somatic mutation:** mutation in myeloid progenitors leads to defective tagging of misfolded proteins for destruction

Accumulation of misfolded protein: cytoplasmic vacuolization in myeloid progenitors

Hyperinflammatory response: including NFκB-related cytokines (IL-6, IL-8, IL-18, TNFα)

[1] Wu Z, et al. Cell Rep Med. 2023. [2] Kosmider O, et al. Nat Commun. 2024. [3] Bourbon E, et al. Blood. 2021. [4] Hadjadj J, et al. Ann Rheum Dis. 2024. [5] Kirino Y, et al. Ann Rheum Dis. 2021.
Image source: Wikimedia commons

Pacritinib: a unique oral kinase inhibitor that targets multiple inflammatory pathways (IRAK1/NFκB and JAK2/STAT)

- Approved in the U.S. for treatment of patients with myelofibrosis who have severe thrombocytopenia (platelet count <50 ×10^9/L)[1]
- Does not inhibit JAK1, potentially preserving T cell proliferation compared to JAK1/2 inhibitors[2-4]
- Inhibits the hepcidin regulator ACVR1, possibly associated with improvement in inflammatory anemia[5]
- Approved dose in myelofibrosis is 200 mg BID

Pacritinib inhibition profile[2,5]

C_{max} (unbound) at 200 mg BID: 213 nM

Target	IC_{50}, nM
IRAK1	13.6
JAK1	1280.6
JAK2	6.0
JAK3	18.3
TYK2	27.0
ACVR1	16.7
FLT3 (ITD)	13.4
CSF-1R	39.5

ACVR1, activin receptor-like kinase-2; BID, twice daily; Cmax, maximum serum concentration; IC50, half-maximal inhibitory concentration; IRAK1, interleukin-1 receptor–associated kinase; JAK, Janus associated kinase; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; STAT, signal transducer and activator of transcription; TLR, toll-like receptor

[1] VONJO Prescribing Information. Sobi Inc.; 2025. [2] Singer JW, et al. J Exp Pharmacol. 2016.
[3] Singer JW, et al. PLoS One. 2019. [4] Betts BC, et al. PNAS. 2018 [5] Oh ST, et al. Blood Adv. 2023.

PAXIS schema, Part 1: double-blind placebo-controlled dose-finding study

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Key Eligibility

- VEXAS syndrome
- Active inflammatory disease in the past 6 months
- GC dose 15-45 mg daily
- Prior therapy washout

Randomization

- N = 78
- 1:1:1
- Stratified by baseline GC dose

Treatment*

Pacritinib 200 mg BID

Pacritinib 100 mg BID
+ Placebo BID

Placebo BID

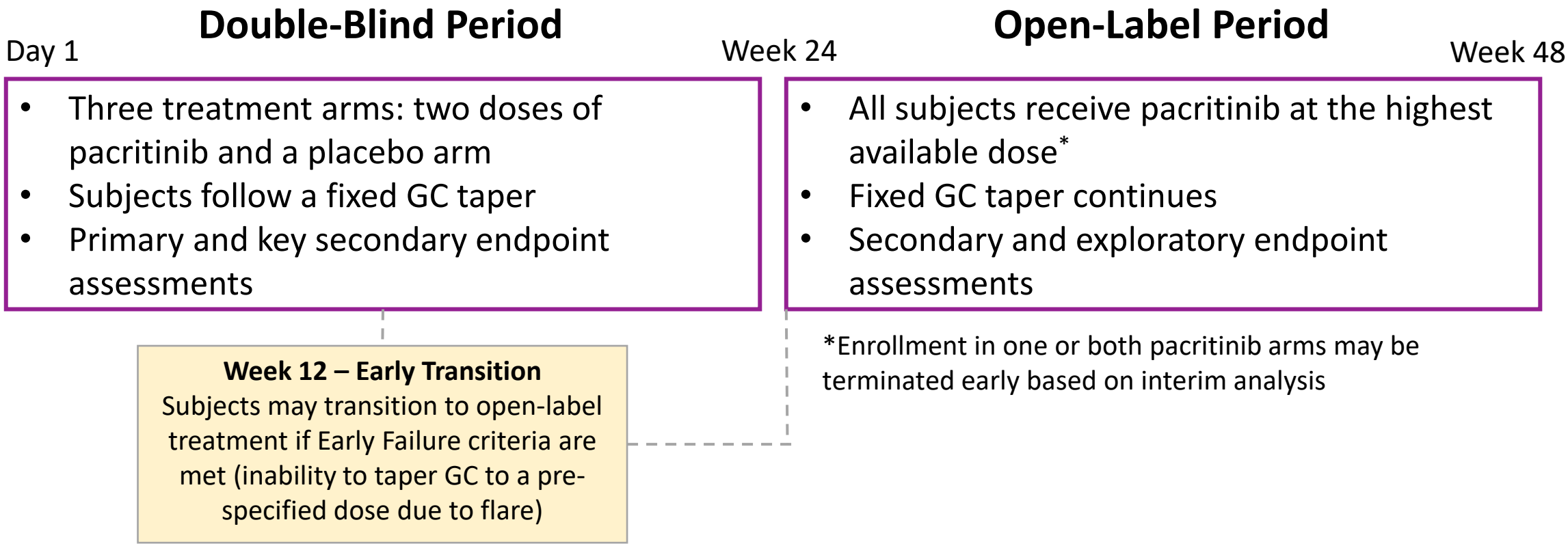
*With fixed GC taper

Primary Endpoint

Overall Clinical Response by Week 24, defined as a flare-free interval lasting ≥8 consecutive weeks after successful GC taper, with GC dose ≤10 mg during entire interval

BID, twice daily; GC, glucocorticoid; mg, milligrams

PAXIS schema, double blind (Part 1) period and open label (Part 2) period



GC, glucocorticoid

Select eligibility criteria

Key Inclusion Criteria

- VEXAS syndrome (UBA1 M41 or splice site mutation), with active disease within past 6 months
- GCs (prednisone/prednisolone) 15-45 mg/day ongoing for ≥4 consecutive weeks
- Platelet count ≥25 × 10^9/L
- Absolute neutrophil count ≥500/µL
- Peripheral blasts <5%

Key Exclusion Criteria

- Prior allogeneic stem cell transplant
- Current use of systemic GCs for conditions other than VEXAS syndrome
- Exposure to non-GC anti-inflammatory therapy within protocol-defined washout timeframes*
- Exposure to HMAs within the last 6 months, or >6 cycles at any time
- High-risk MDS, or MDS requiring HMA therapy
- ≥9 units of RBC transfusion in prior 90 days

GC, glucocorticoid; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; RBC, red blood cell

*Anti-CD20 agents (e.g., rituximab): 180 days, Anti-IL-23 agents (e.g., ustekinumab): 90 days, Anti-TNFα except for etanercept (e.g., infliximab): 60 days, Canakinumab: 60 days, Intravenous anti-IL-6 agents (e.g., tocilizumab): 42 days, Subcutaneous anti-IL-6 agents: 28 days, Anti-IL-17 agents (e.g., secukinumab): 28 days, Anti-integrins (e.g., vedolizumab): 60 days, Intravenous immunoglobulin: 28 days, Danazol, immunomodulatory imide drugs (ImiDs), luspatercept, or thrombopoietin receptor agonists: 28 days, Cytotoxic chemotherapy: 28 days, Etanercept: 21 days, Oral Janus kinase (JAK) inhibitors: 14 days, Anti-IL-1 agents except for canakinumab: 14 days, Any other non-GC anti-inflammatory therapy (e.g., mycophenolate, azathioprine, cyclosporine, sulfasalazine, methotrexate): 14 days

Primary endpoint (double-blind period only)

Overall Clinical Response (OCR): Flare-free interval lasting ≥8 weeks after successful GC taper, with GC dose ≤10 mg daily during the entire interval

	Endpoint Definition	Flare-free Interval	GC daily dose	CRP
Overall Clinical Response	Stringent Clinical Biochemical Response	≥8 consecutive weeks	≤5 mg	≤10mg/L
	Clinical Biochemical Response	≥8 consecutive weeks	≤10 mg	≤10mg/L **or** ≥50% reduced from baseline and a value ≤20mg/L
	Clinical Response	≥8 consecutive weeks	≤10 mg	
	Partial Clinical Response	≥8 consecutive weeks	≥50% reduced from baseline	
	Stable Disease	≥8 consecutive weeks	≤baseline	
	Non-Response	Not meeting other response criteria		

GC, glucocorticoid; CRP, C-reactive protein; mg, milligrams

Study endpoints and outcomes measures

Secondary Endpoints

- Best response
- Number of flare-free days with GC dose <10 mg daily
- Hematologic improvement
- Change in HRQoL
- PK/PD
- Safety

Exploratory Endpoints

- VEXAS-symptom assessment for (VEXAS-SAF)
- VEXAS-Disease Activity Index (VEXAS-DAI)
- Clinical Global impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C)
- Change in GC toxicity via the glucocorticoid toxicity index (GTI)
- *UBA1* variant allele frequency

GC, glucocorticoid; HRQoL, health-related quality of life; PK, pharmacokinetics; PD, pharmacodynamics

Established definition of VEXAS flare

- Developed based on consensus from an expert panel using Delphi methodology
- Supports the OCR primary endpoint
- Will be used to advance clinical trial design and conduct in VEXAS syndrome

Definition of VEXAS flare
A VEXAS flare is defined as an active inflammatory manifestation of VEXAS syndrome fulfilling at least one of the criteria below, for which an escalation in glucocorticoid therapy is indicated

Category A
Recurrence of one or more of the patient's prior documented VEXAS-related inflammatory manifestations

Category B
Development of one or more of the following inflammatory signs considered by the Investigator to be directly attributable to VEXAS syndrome

Category C
Development of any of the following inflammatory manifestations directly attributable to VEXAS syndrome per an independent adjudication committee

OCR, Overall Clinical Response

VEXAS-DAI is designed to measure active inflammation in patients with VEXAS

- A comprehensive DAI to measure clinically significant inflammatory activity in VEXAS within 13 organ systems
- Developed based on input from a multidisciplinary group of VEXAS experts in Rheumatology, Hematology, and Immunology
- Work is ongoing to validate this instrument in the PAXIS trial

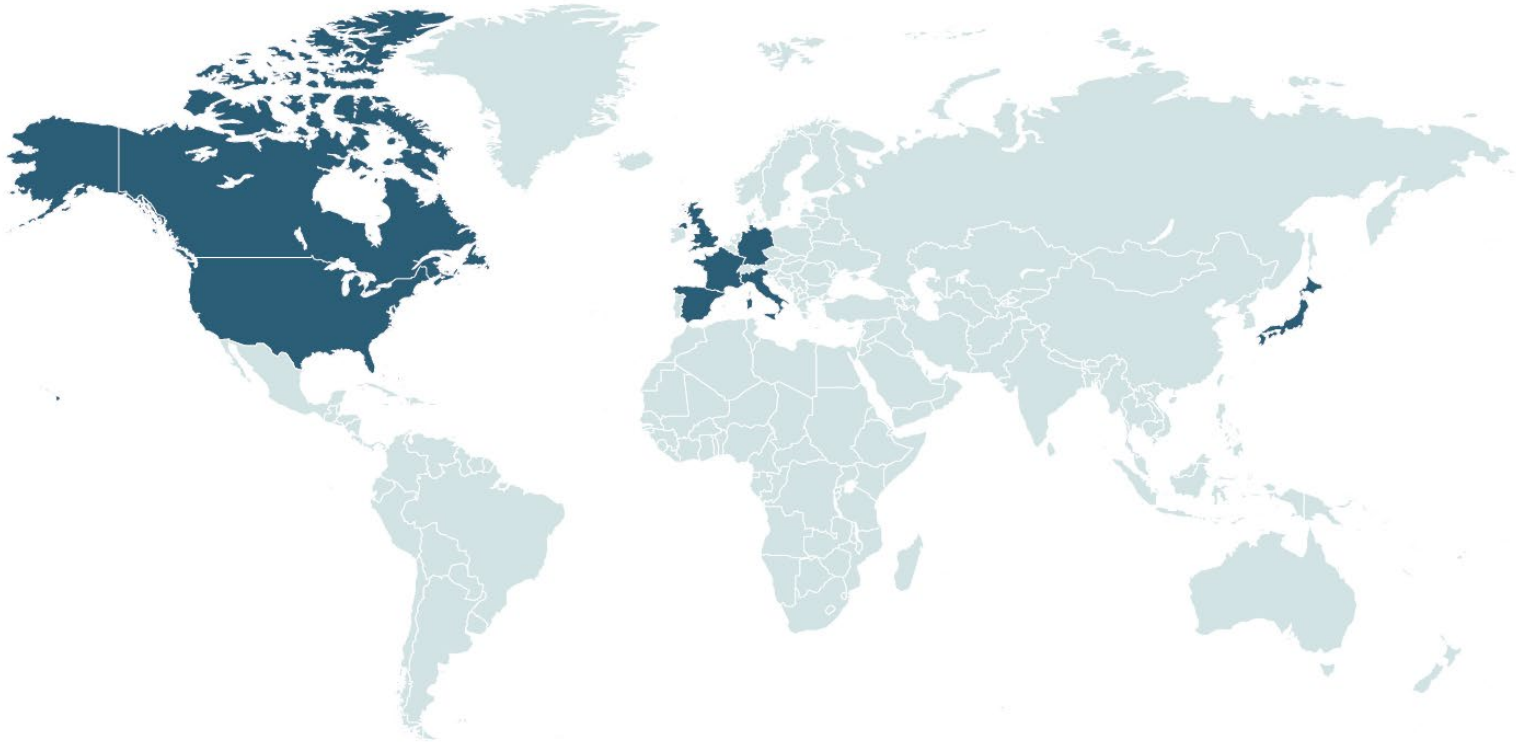
Domain	Items	Max. Score
Inflammatory-type rash	2	4
Chondritis	3	3
Periorbital involvement	1	2
Genitourinary involvement	1	3
Ophthalmologic involvement	5	4
Pulmonary involvement	3	4
Cardiovascular involvement	3	4
Neurologic involvement	5	4
Oral/gastrointestinal involvement	3	4
Renal involvement	1	4
New thrombosis/thromboembolism	1	0
Joint involvement	1	2
Constitutional symptoms	2	2
Total	**31 items**	**40**

Novel features of the PAXIS trial

- The PAXIS trial is the first prospective, randomized, placebo-controlled therapeutic study in VEXAS
- Mechanism of action of pacritinib (IRAK1/NFκB, JAK2/STAT inhibition) targets key molecular pathophysiological features of VEXAS
- The primary endpoint is based on disease-specific response criteria and the consensus definition of a VEXAS flare (*Weeks LW, et al. ACR 2025 Poster 0260*)
- Exploratory outcomes measures
  - VEXAS-SAF
  - VEXAS-DAI (*Byram K, et al. ACR 2025 Oral presentation 0777*)
  - Glucocorticoid Toxicity Index
- An independent adjudication committee will be used to adjudicate flares on study

PAXIS recruitment status

- Recruitment for PAXIS is ongoing in 40 sites across 8 countries
  - Canada, France, Germany, Italy, Japan, Spain, United Kingdom, and the United States
- NCT06782373
- EUCT: 2024-516347-41-00



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Questions?