Parabilis Medicines Reports Early Clinical Evidence that Zolucatetide Reduces Polyp Burden in a Patient with Familial Adenomatous Polyposis

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Preliminary clinical data presented at the InSiGHT Biennial Meeting demonstrate significant reductions in duodenal polyposis and the size of the co-existing desmoid tumor in a patient from the ongoing Phase 1/2 trial of zolucatetide

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Parabilis Medicines, a clinical-stage biopharmaceutical company committed to creating extraordinary medicines for people living with cancer using its Helicon™ peptide platform to drug historically undruggable targets, today announced preliminary clinical and preclinical data at the 11th Biennial Meeting of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) supporting the therapeutic potential of its lead investigational candidate, zolucatetide — the first and only direct inhibitor of the β-catenin:TCF interaction — in patients with familial adenomatous polyposis (FAP).

In the company's ongoing Phase 1/2 trial, a patient with FAP and an associated desmoid tumor treated with zolucatetide demonstrated significant improvement in duodenal polyposis at 60 weeks following initiation of treatment. Substantial reductions in polyp number and size compared with a pre-treatment evaluation nearly two years prior were observed, consistent with downstaging from Spigelman stage II to stage I. The patient also sustained a 52.2% reduction in desmoid tumor diameter. No treatment-related serious adverse events or discontinuations have been reported.

Complementary preclinical findings confirmed dose dependent inhibition of β-catenin transcriptional activity in APC mutant tumor cells leading to reduced polyp formation in a mouse model of FAP at exposures relevant to the ongoing clinical trial. Together with the observed clinical activity, these findings support direct β-catenin inhibition as a disease-modifying approach in FAP.

"Patients with FAP face a lifetime of intensive surveillance and often prophylactic colectomy, yet there are no approved therapies," said Mathai Mammen, M.D., Ph.D., Chairman, CEO and President of Parabilis Medicines. "These early findings suggest that directly inhibiting β-catenin, the key driver of tumor formation in FAP, may offer a new way to intervene at the source of disease. Our goal is to move beyond managing polyp burden and toward altering the course of disease for patients suffering from FAP."

FAP is a rare inherited disorder, impacting an estimated 34,000 people in the U.S., caused by germline loss-of-function mutations in the *APC* gene, leading to persistent activation of Wnt/β-catenin signaling and the development of hundreds to thousands of pre-cancerous colorectal adenomas with near-inevitable progression to colorectal cancer if left untreated. Management often requires prophylactic colectomy at a young age — a life-altering surgery — yet it does not prevent continued Wnt-driver manifestations, such as duodenal polyposis, rectal polyposis and occasionally desmoid tumors. These realities underscore the need for systemic therapies that directly target the underlying molecular driver of disease.

The Wnt/β-catenin pathway is a central oncogenic driver across a broad spectrum of rare and common solid tumors, implicated in millions of cancer cases annually. Despite its well-established role in tumor biology, direct inhibition of β-catenin — particularly its interaction with TCF transcription factors, the key downstream node within the pathway — has until now been considered "undruggable."

Beyond FAP, zolucatetide is being evaluated across a broad range of rare and common Wnt/β-catenin-driven tumor types, with early clinical data demonstrating single-agent activity in desmoid tumors – an indication that received Fast Track Designation from the FDA late last year, adamantinomatous craniopharyngioma (ACP), hepatocellular carcinoma (HCC; shared at the JP Morgan Healthcare Conference) and several other tumor types. Data also support further evaluation of rational combination approaches in biologically complex tumors, including for the treatment of microsatellite-stable colorectal cancer.

The company plans to share additional data readouts in 2026 from its ongoing Phase 1/2 trial of zolucatetide, in which more than 150 patients have been dosed to date.

About Zolucatetide (Previously FOG-001)

Zolucatetide is an investigational first-in-class competitive inhibitor of β-catenin interactions with the T-cell factor (TCF) family of transcription factors and is currently in clinical development. By directly targeting the β-catenin:TCF protein-protein interaction, zolucatetide is intended to block the Wnt signaling pathway irrespective of the various APC and β-catenin mutations that typically drive disease.

Zolucatetide combines key features that distinguish it from previously reported Wnt/β-catenin pathway modulators: zolucatetide acts inside the cell where it binds directly to the key oncogenic driver β-catenin; and zolucatetide blocks the Wnt pathway at the key downstream node, disrupting the interaction between β-catenin and the TCF transcription factors, thereby abrogating the

signal transmission by which Wnt pathway mutations are believed to drive oncogenesis.

Zolucatetide is currently being evaluated in a Phase 1/2 clinical trial in patients with locally advanced or metastatic solid tumors. Zolucatetide has received Fast Track Designation for the treatment of desmoid tumors from the U.S. Food and Drug Administration (FDA).

About the Phase 1/2 trial of Zolucatetide

Zolucatetide is being evaluated in a Phase 1/2 multicenter, open-label study (NCT05919264) assessing its safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity. The trial includes dose-escalation and dose-expansion phases and is testing zolucatetide both as a monotherapy and in combination with other anticancer agents in patients with advanced or metastatic solid tumors likely or known to harbor a Wnt pathway–activating mutation (WPAM).

About Parabilis Medicines

Parabilis Medicines is a clinical-stage biopharmaceutical company dedicated to creating extraordinary medicines that unlock high-impact protein targets long-considered undruggable. Leveraging over a decade of proprietary data, laboratory innovations, and AI- and physics-based algorithms, the company has developed a new class of stabilized, cell-penetrant alpha-helical peptides – Helicons™ – capable of modulating intracellular proteins that are inaccessible to traditional drug modalities.

Headquartered in Cambridge, Mass., Parabilis is advancing a focused pipeline of multiple first-in-class therapies across both rare and common cancers. Its lead candidate, zolucatetide (previously known as FOG-001), is the first direct inhibitor of the interaction between β-catenin and the T-cell factor (TCF) family of transcription factors, implicated in colorectal cancer, desmoid tumors, and a range of other Wnt/β-catenin-driven tumors. Parabilis is also advancing investigational degraders of ERG and allosteric AR^{ON} for the treatment of prostate cancer, as well as other preclinical programs.

Learn more about how the company is advancing a new generation of precision cancer medicines with the potential to meaningfully alter the trajectory of disease for patients in need: www.parabilismed.com.

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