GLPG0634m1, a major metabolite of the JAK1-selective inhibitor GLPG0634, is also JAK1-selective and efficient in the rat CIA model.

Cécile Belleville-Da Costa1, Didier Merciris1, Beatrice Vayssière1, Nicolas Houvenagel1, Alain Monjardet1, Liên Lepeschine1, Sonia Dupont1, Thierry Christophe2, Monica Borgonovi2, Philippe Clément-Lacroix1, Christel Menet3, Luc Van Rompaey1, Reginald Brys2, René Galién1

1 Galapagos SASU, Romainville, France; 2 Galapagos NV, Mechelen, Belgium

Introduction

GLPG0634 is an oral JAK inhibitor that displays a high selectivity for JAK1 over JAK2 in human whole blood assays (around 30-fold) and over JAK3 and TYK2 in biochemical assays. Encouraging efficacy and safety profiles were shown in two 4-week Phase 2a studies with GLPG0634. A phase 2b program in RA and a Phase 2 trial in Crohn’s diseases are currently ongoing.

GLPG0634’s major metabolite, GLPG0634m1, has a long half-life (21-27 h) in human and might contribute to the clinical efficacy of the parent compound observed in RA patients.

Here, we characterize the pharmacological properties of the GLPG0634m1, its activity on JAK-driven pathways and its efficacy in the rat CIA (collagen-induced arthritis) model.

Methods

- Biochemical analysis of compound potency was performed using an in vitro ATP-competitive radiometric kinase assay.
- In the STAT phosphorylation assays, whole blood was triggered for 20 minutes with IL-6, IL-2, IFNα or GM-CSF. White blood cells were labelled with pSTAT1 or pSTAT3 antibodies and analysed by flow cytometry.
- Arthritis was induced in Dark Agouti rats with 2 intradermal injections of bovine type II collagen and treatments were administered for 14 days after disease onset.
- The clinical score was obtained by combining paw swelling and Larsen scores.
- The histological score included pannus severity, bone and cartilage lesion and infiltration index.
- LC-MS/MS was used to measure steady-state GLPG0634m1 concentrations in rat plasma.

Comprehensive JAK selectivity of GLPG0634 and its main metabolite, in whole blood from various species shown by measurement of IL-2- and GM-CSF-induced STAT5 phosphorylation by flow cytometry.

Conclusions

- While displaying a lower potency compared to its parent molecule, GLPG0634m1 has a similar JAK1 selectivity and comparable general kinase selectivity as assessed in a 451 kinase panel.
- Oral administration of this metabolite reduces inflammation and provides structural protection in the rat CIA model to the same extent as parental etanercept.
- This effect is supported by JAK1 inhibition and appears independent of JAK2 inhibition.
- These findings, together with the high expression and long half-life of this metabolite observed in phase 1 and phase 2 clinical studies, strongly suggest that it may contribute to the clinical efficacy of the parent compound GLPG0634 in RA.

Impact of GLPG0634m1 on the development of arthritis in the rat CIA model: GLPG0634m1 is as efficacious as etanercept in reducing the development of arthritis in rat as measured by clinical score (A) and histological analysis (B). Pharmacokinetic analysis of GLPG0634m1 (C) shows that metabolite concentrations in CIA rat plasma are compatible with JAK1 inhibition but not with JAK2 inhibition.

Disclosures: All authors are employees of Galapagos. AbbVie has provided funding to Galapagos for the development of GLPG0634.