DISCOVERY OF A NOVEL, SELECTIVE SIK3 INHIBITOR FOR THE TREATMENT OF ULCERATIVE COLITIS, CROHN'S DISEASES AND OTHER AUTOIMMUNE DISEASES

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O3R-5671, a highly selective SIK3 inhibitor designed to overcome prior SIK inhibitor safety limitations, demonstrated dose-dependent efficacy in preclinical IBD models and has entered phase 1 clinical testing.

KEY POINTS

- O3R-5671 is a sub-nanomolar potency SIK3 inhibitor with low activity against SIK1, SIK2, and the broader human kinome, designed to inhibit multiple cytokines including TNFα, IL-12, and IL-23 while inducing IL-10 secretion.
- In preclinical models, O3R-5671 demonstrated dose-dependent efficacy in two distinct mouse IBD models and showed activity comparable to an IL-23 blocking antibody in T-cell transfer colitis.
- Six-week GLP toxicity studies in rats and dogs established NOAELs supporting human dosing with doses predicted to be pharmacologically active with a large safety margin, and the compound is clean on hERG.
- Cross-species pharmacokinetic modeling predicts a flat human PK profile with TNFα IC70 coverage for 24 hours after a single dose and a 210-fold safety window.
- A phase 1 clinical trial is ongoing; the first dose cohort has been completed safely and confirmed the predicted flat PK profile, with a second cohort underway and a deep biomarker plan addressing circulating TNFα and IL-23.
- The presenter stated he firmly believes O3R-5671 has potential to change the treatment paradigm in UC and Crohn's disease by combining TNFα and IL-23 inhibition in a single molecule.

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