The First-in-Class SIK3 Inhibitor O3R-5671 Demonstrates Optimal Pharmacokinetics and Potent and Sustained Pharmacodynamic Activity in Human Participants

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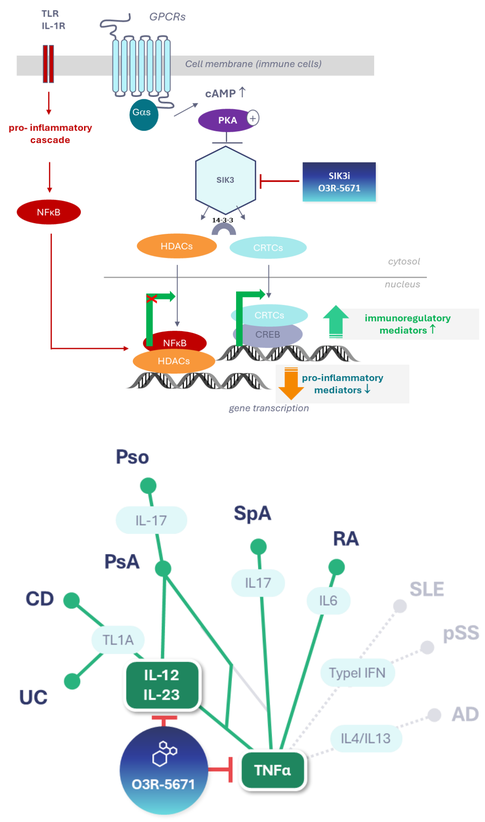
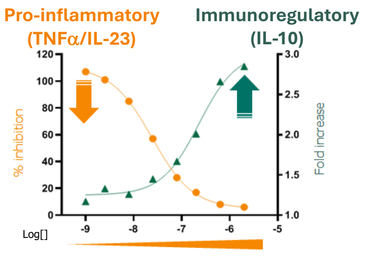
Onco3R Therapeutics
Right team - Right strategy - Right drugs

Background

Treatment options for inflammatory bowel disease (IBD) are limited by low remission rates and loss of response. Most therapies target single pathogenic pathways and while combinations of biologics targeting different pathogenic cytokines can increase clinical remission rates, dosing schedules are inconvenient.

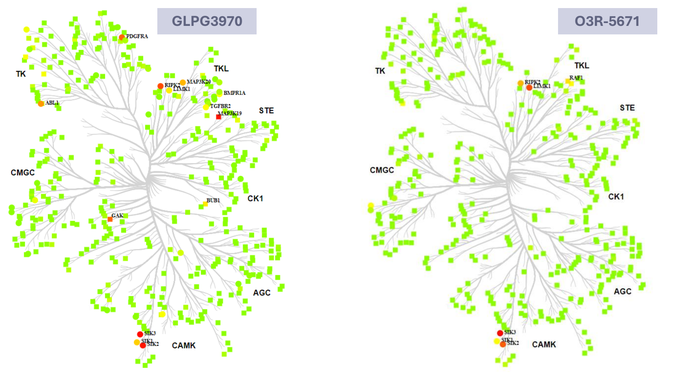
Salt-inducible kinases (SIKs), a subfamily of serine/threonine kinases in the AMP-activated protein kinase (AMPK) family, act as key regulators of immune cell signalling. Three SIK isoforms exist: SIK1, SIK2 and SIK3. SIK inhibitors targeting multiple isoforms have been investigated. The SIK2 inhibitor G2001501 showed adverse bone marrow decreased hematopoietic cellularity in 2-wk rat toxicology studies. In clinical trials, the dual SIK2/SIK3 inhibitor GLPG3970 demonstrated some activity in patients with ulcerative colitis and psoriasis. However, safety concerns related to hERG inhibition and SIK2 inhibition, and insufficient target coverage impeded further development of the compound.





- A family of 3 salt-inducible kinases (SIKs): SIK1, SIK2, SIK3
  - **activated** by liver kinase B1 (LKB1)
  - **suppressed** by cAMP/PKA
- SIK3 inhibition controls NFκB and CREB regulated gene expression in inflammatory conditions (HDACs / CRTCs substrates)

Improved human kinome selectivity profile of O3R-5671 compared to GLPG3970



None of the few off-target kinases have been confirmed in a cellular context

O3R-5671 is a potent and selective oral SIK3 inhibitor that inhibits multiple pathogenic cytokines including TNFα, IL-23 and IL-12 and is designed to avoid off-target effects of first-generation SIK inhibitors. The prodrug, O3R-5671-PRO, was engineered to optimize PK properties and target coverage, and is active in a translational mouse model of ulcerative colitis

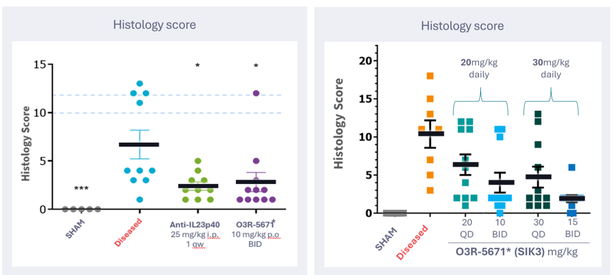
SIK3 inhibition suppresses key pathogenic cytokines in human primary immune cells, while SIK2 inhibition does not

	SIK2/SIK3 inhibitor	SIK3 inhibitor	SIK2 inhibitor
	GLPG3970	O3R-5671	G2001501
SIK1/2/3 ADPGlo IC_{50} (nM)	266 / 7.2 / 3.5	758 / 108 / 0.79	560 / 3.3 / 839
SIK1/2/3 nanoBRET cell IC_{50} (nM)	>18,463 / 706 / 590	>21,412 / >5,234 / 233	>1,420 / 10 / >3,753

Human Cell	trigger	Read-out	SIK2/SIK3 inhibitor GLPG3970	SIK3 inhibitor O3R-5671	SIK2 inhibitor G2001501
Monocyte	LPS	TNFα (4h)	248	96	>6,700
		IL-10 (4h)	>9,304 (25x)	>15,277 (4.0x)	
MdM (M-CSF)	LPS	TNFα	358	293	1,625
		IL-10	>4,800 (2.7x)	>4,500 (2.2x)	
MoDC[1] (GM-CSF +IL4)	LPS	TNFα	218 [3]	62	>6,667
		IL-12p40	178 [3]	49	87
		IL-10	Bell shape	Bell shape	
PBMC	αCD3/αCD28	TNFα	757	274	>6,667
		IL-2	776	685	1,682
		IFNγ	1922	4058	5,367

Legend: No activity | Inhibition IC_{50} (nM) | Induction EC_{50}nM (FC_{max})

O3R-5671 shows same activity range as anti-IL-23 biologics in the chronic and gold-standard T-cell transfer mouse model of human colitis

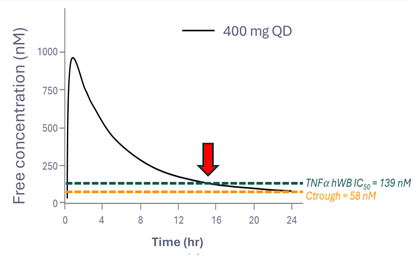


* O3R-5671 administered as O3R-5671-PRO prodrug

- O3R-5671 is active in a therapeutic mode and demonstrated equivalent efficacy to IL-23 mAb in the gold standard model of ulcerative colitis (chronic and long model, compared to short and acute models like e.g. DSS and anti-CD40 models)
- C_{min} identified as the driver of efficacy
- SIK2 inhibition is not required for maximum efficacy

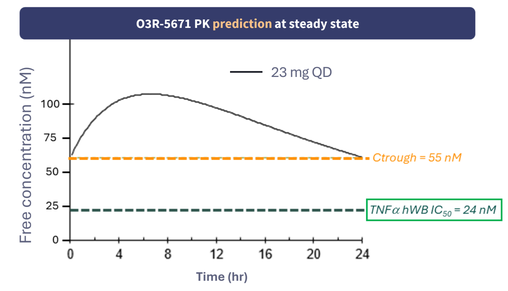
GLPG3970	
Selectivity	SIK2/SIK3 inh. (SIK2-related toxicities)
Off-targets	hERG → QTc prolongation
PK	Suboptimal target coverage

GLPG3970 Plasma exposures (HV) at steady state



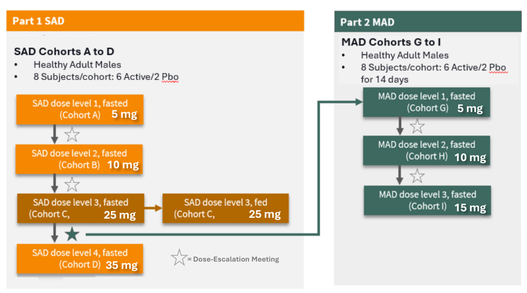
Onco3R O3R-5671	
Selectivity	SIK3 selective
Off-targets	No hERG; clean on kinome
PK	Low projected dose and optimal target coverage

O3R-5671 PK prediction at steady state



First-in-Human Study Results

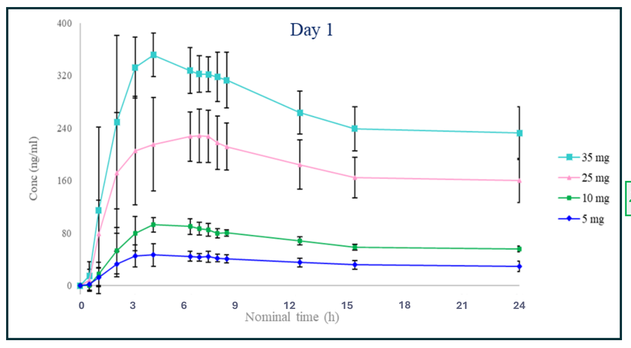
Methods



Randomized, placebo-controlled, double-blind Phase 1 study: 64 healthy male participants have received single or multiple ascending doses of O3R-5671-PRO or a placebo QD. PK samples were drawn pre-dose and post-dose and analyzed by LC-MS/MS. PD samples were drawn simultaneously and whole blood was stimulated with LPS for 20 hours prior to TNFα quantification in plasma by MSD V-PLEX immunoassay.

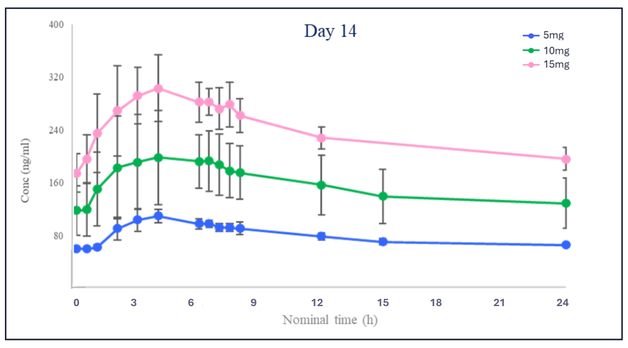
1. First SAD Cohorts Confirm the Flat PK profile and Accumulation is observed in the MAD Cohorts

Observed PK Profiles in SAD Cohorts



2x AUC_{24h}

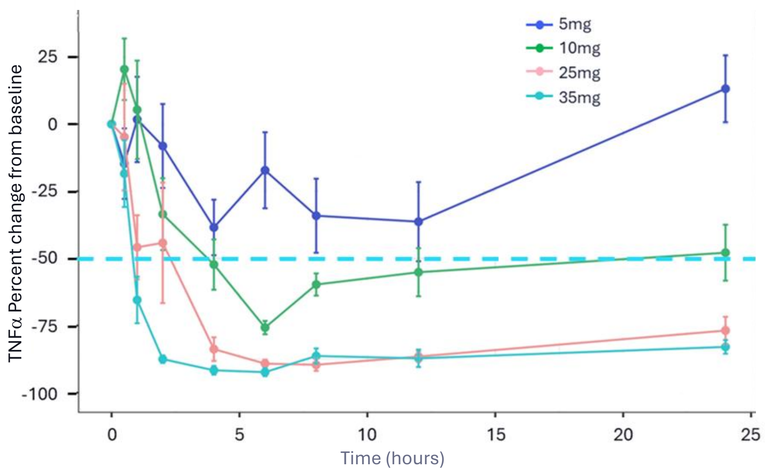
Observed PK Profiles at Steady State (MAD)



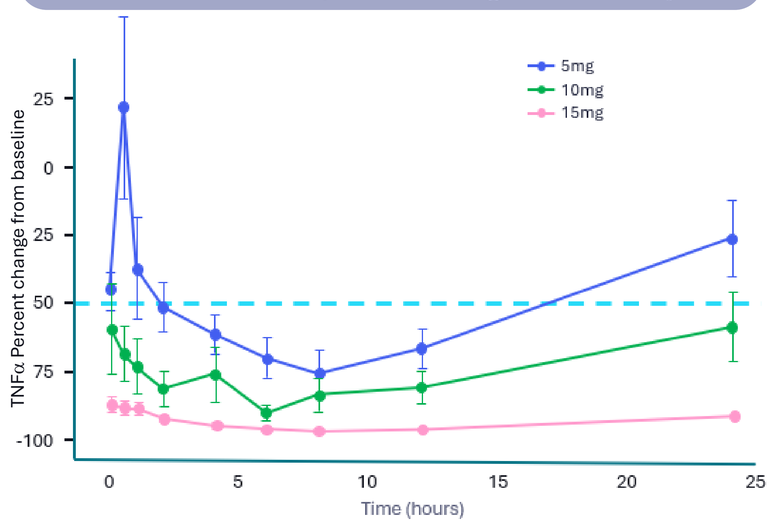
- Healthy volunteers' exposure data confirm the flat PK profile of O3R-5671 upon QD dosing
- Dose proportional exposure is observed after oral administration of O3R-5671
- Accumulation is observed at steady-state leading to an approximative doubling of the exposure compared to single-dose
- A food effect cohort (25mg single dose) demonstrated a minimal effect on PK parameters, with a 10% reduction in AUC and no effect on C_{trough}

2. Single doses of 10, 25 & 35 mg O3R-5671 and 5, 10 & 15 mg at steady state have stronger effect on PD marker than 400 mg of GLPG3970 that showed activity in Pso and UC

TNFα PD effects: 5, 10, 25 & 35 mg single dose

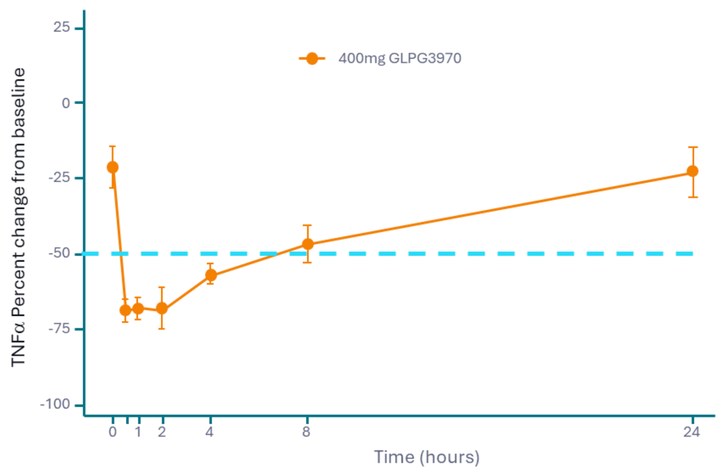


TNFα PD effects: 5, 10 & 15 mg MAD at day 14

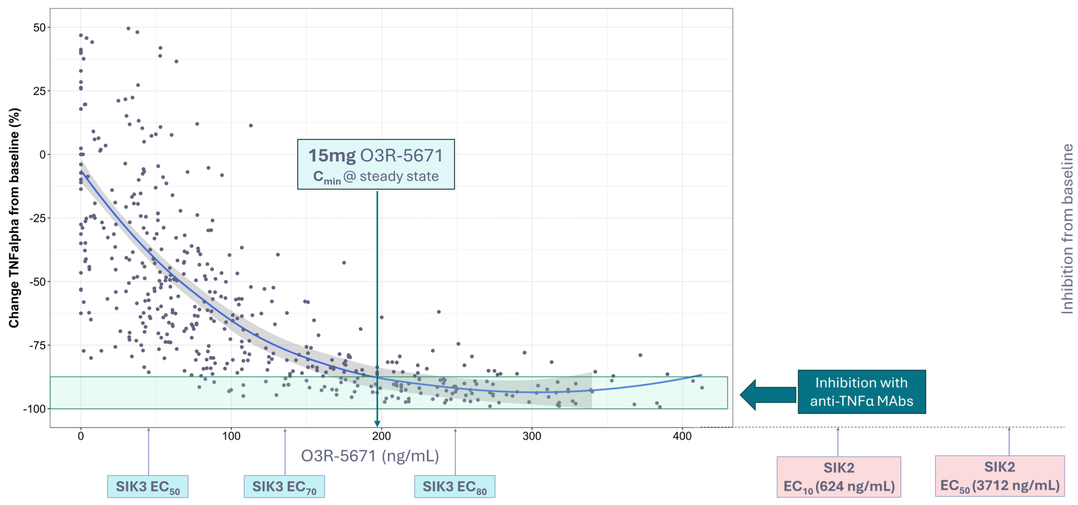


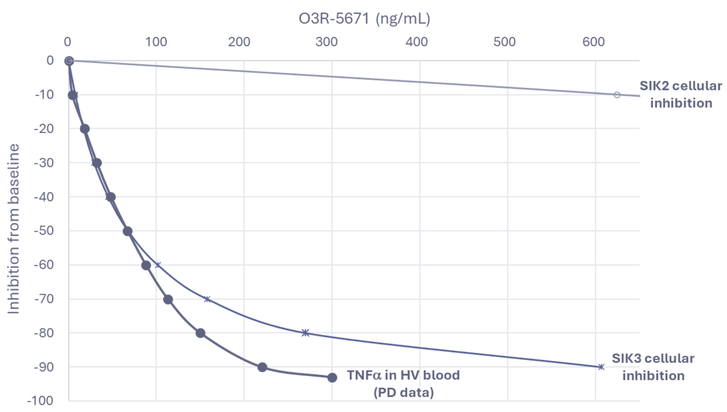
TNFα PD effects: 400 mg GLPG3970 (d14, MAD)

Historical Data



Linear regression analysis indicates that concentrations > 250 ng/mL leads to maximal TNFα inhibition in blood of human healthy volunteers and TNFα inhibition correlates with cellular SIK3, but not SIK2, inhibition





Conclusions

- PK/PD correlation data indicates that doses of 15 mg of O3R-5671 and above lead to maximum TNFα inhibition in the range of that achieved with biologics
- Concentrations maximally inhibiting TNFα correlate with SIK3 EC_{80} and do not inhibit SIK2
- O3R-5671 is safe and well tolerated* and dose escalation continues in the study
- O3R-5671 will be further developed in inflammatory diseases like Ulcerative colitis

* Study still blinded, safety and tolerability conclusion based on aggregated data for all subjects per cohort (6 active; 2 placebo)