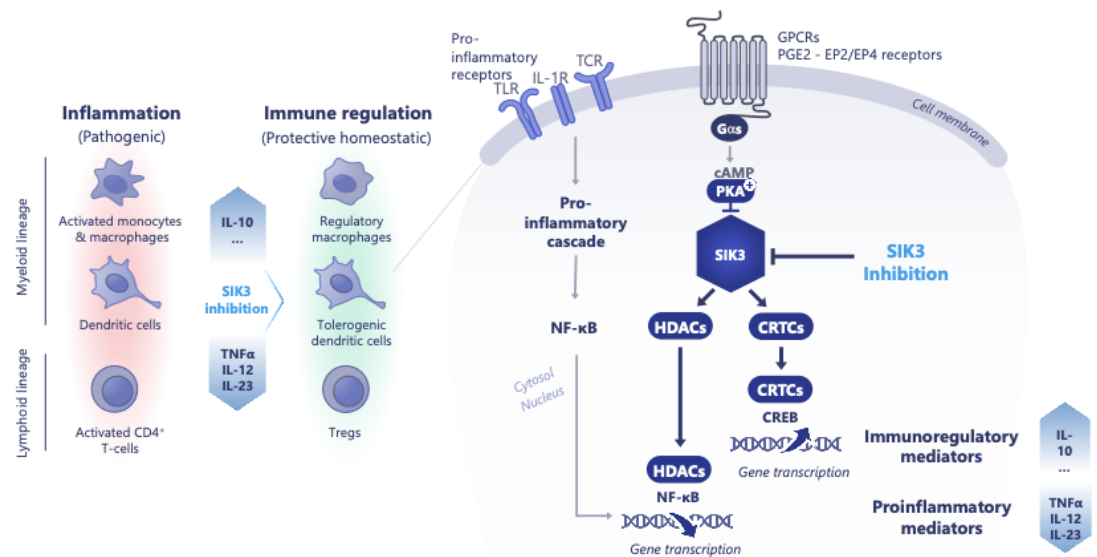


Background

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 an adverse decreased in bone marrow hematopoietic cellularity in rat toxicology studies. In clinical trials, the dual SIK2/SIK3 inhibitor GLPG3970 demonstrated some clinical activity in patients with ulcerative colitis and psoriasis. However, safety concerns related to the human Ether-à-go-go-Related Gene (hERG) and SIK2 inhibition, and insufficient target coverage impeded further development of the compound.

COL-5671 is a potent and selective oral SIK3 inhibitor that downregulates the expression of multiple pathogenic cytokines, including TNF α , IL-23, TL1A and IL-12, and is designed to avoid off-target effects of first-generation SIK inhibitors. The prodrug, COL-5671-PRO, was engineered to optimize PK properties and target coverage, and is active in translational mouse models of ulcerative colitis.



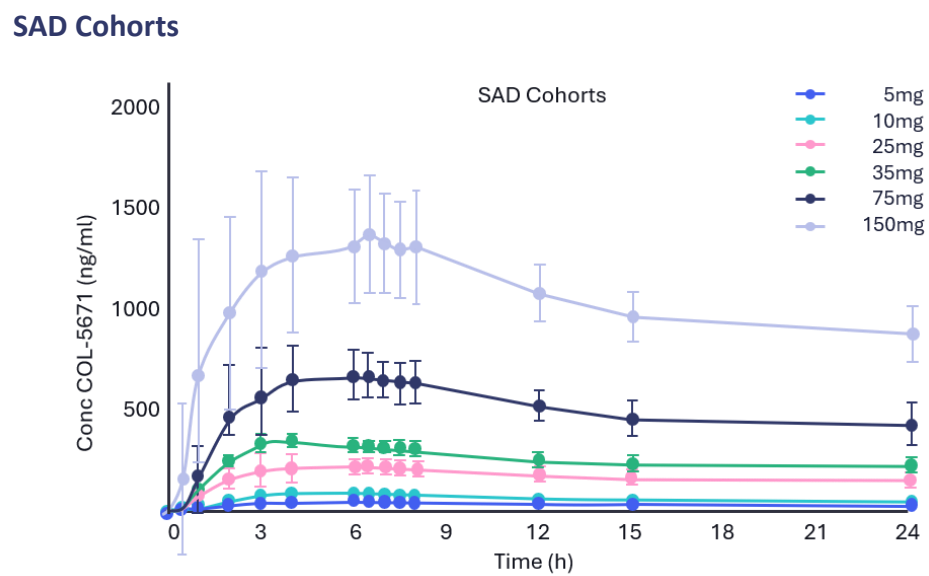
Selective inhibition of SIK3, but not SIK2, suppresses key pathogenic cytokines in primary human immune cells

SIK inhibitors with distinct selectivity profiles—including the SIK2/3 inhibitor GLPG3970, the SIK2 inhibitor GLPG5001, and the SIK3 inhibitor COL-5671 were evaluated in whole blood and in human primary monocyte, macrophage, dendritic cell, and T-cell systems to assess their ability to suppress stimulation-induced release of key cytokines. The data shown below demonstrate that selective SIK3 inhibition is sufficient to potently inhibit TNF α , IL-12p40, and IL-23.

		 Biochemical assay (Recombinant proteins)			 Whole blood	 Monocytes			 Macrophages		 Dendritic cells				 T Cells		
	Read-out	SIK1 IC ₅₀ (nM)	SIK2 IC ₅₀ (nM)	SIK3 IC ₅₀ (nM)	TNFα EC ₅₀ (nM)	TNFα	IL-23	IL-10	TNFα	IL-10	TNFα	IL-23	IL-12p40	IL-10	TNFα	IL-2	IFNγ
GLPG3970	SIK2/3 inhibitor	266	7.2	3.5	139	248	110	>9304 (25x)	358	>4800 (2.7x)	218	236	178	Bell shape	757	776	1922
GLPG5001	SIK2 inhibitor	560	3.3	839	>21,000	>6700	/	/	1625	/	>6667	n.d.	87	/	>6667	1682	5367
COL-5671	SIK3 inhibitor	758	108	0.79	24	96	32	>15277 (4.0x)	293	>4500 (2.2x)	62	51	49	Bell shape	274	685	4058

No activity
 Inhibition IC₅₀ (nM)
 Induction EC₅₀ (nM) – Max fold change

Pharmacokinetics



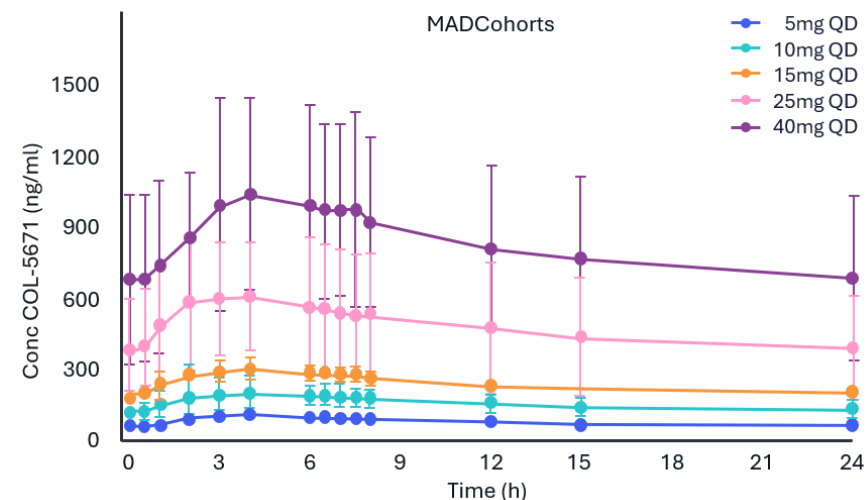
PK Parameters of COL-5671 in Plasma: SAD Cohorts						
Dose	5 mg	10 mg	25 mg	35 mg	75 mg	150 mg
C _{max} (ng/mL)	51.6 (15.9)	96.9 (12.2)	251.2 (16.9)	368.3 (8.4)	701.7 (11.3)	1503.5 (24.1)
AUC _{0-∞} (h*ng/mL)	1967.0 (23.5)	3983.5 (19.2)	12382.4 (27.3)	16178.7 (25.0)	28675.3 (23.0)	68809.4 (39.2)
T _{max} (h)	3.5 (73.3)	4.0 (27.4)	4.0 (29.6)	5.0 (45.7)	4.0 (32.3)	5.3 (60.9)
t _{1/2} (h)	27.7 (16.5)	29.7 (21.4)	34.7 (24.7)	29.8 (20.5)	27.7 (17.3)	33.5 (40.8)
C ₂₄ (ng/mL)	29.3 (27.1)	55.9 (8.2)	160.2 (20.8)	232.5 (17.3)	418.8 (21.4)	880.8 (15.5)

PK Parameters of Total COL-5671 in Plasma Under Fasting and Fed Conditions		
Dose (mg)	25 mg fasted	25 mg fed
C _{max} (ng/mL)	251.2 (16.9)	212.5 (26.1)
AUC _{0-∞} (h*ng/mL)	12382.4 (27.3)	12756.6 (29.7)
*T _{max} (h)	4.0 (29.6)	6.5 (55.5)
t _{1/2} (h)	34.7 (24.7)	36.2 (14.6)
Vd/F (L)	103.0 (18.5)	107.6 (23.2)
CL/F (L/h)	2.2 (27.7)	2.1 (29.9)

Data expressed as mean (%CV), except T_{max} expressed as median (%CV)

COL-5671-CL-101 Trial

MAD Cohorts



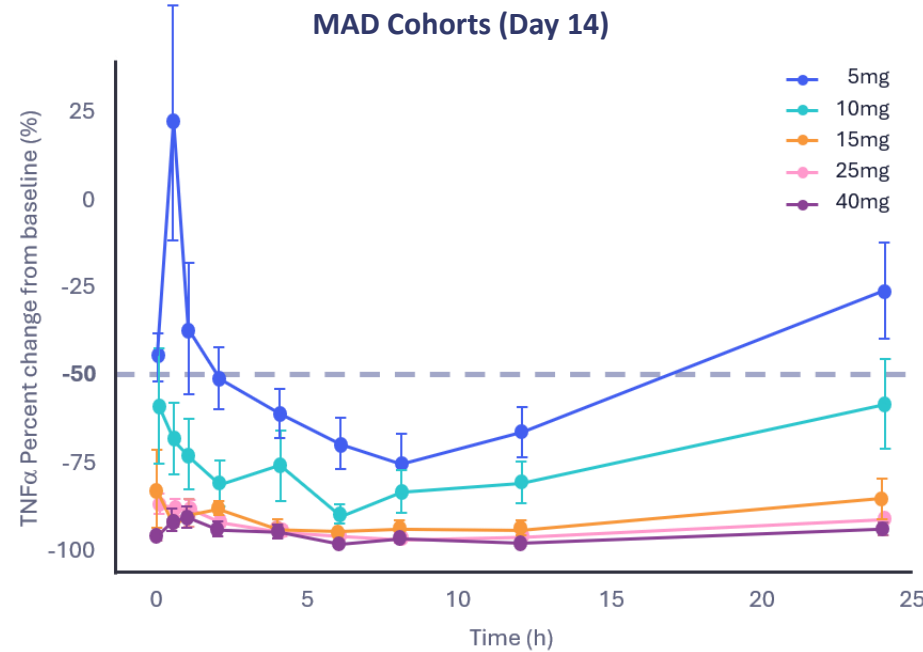
PK Parameters of COL-5671 in Plasma: MAD Cohorts					
Dose (mg)	5 mg q.d.	10 mg q.d.	15 mg q.d.	25 mg q.d.	40 mg q.d.
C _{max} (ng/mL)	108.0 (24.0)	207.0 (27.3)	307.8 (16.0)	601.0 (37.9)	1062.7 (39.2)
C _{1au} (ng/mL)	63.7 (31.0)	127.1 (30.1)	194.3 (8.8)	371.2 (53.5)	698.8 (54.3)
AUC _{0-12h} (h*ng/mL)	1864.4 (26.9)	3705.5 (29.4)	5619.8 (10.4)	10961.8 (49.4)	19801.1 (46.8)
T _{max} (h)	4.0 (0.0)	4.0 (35.0)	4.0 (31.5)	4.0 (46.5)	4.0 (27.2)
t _{1/2} (h)	29.6 (26.6)	31.0 (15.5)	29.1 (5.5)	30.4 (28.9)	34.7 (43.9)
C _{max} (ng/mL)	108.0 (24.0)	207.0 (27.3)	307.8 (16.0)	601.0 (37.9)	1062.7 (39.2)

Data expressed as mean (%CV), except T_{max} expressed as median (%CV)

Following single oral doses of COL-5671-PRO (5 to 150 mg) and q.d. administration of COL-5671-PRO (5 to 40 mg for 14 days), COL-5671-PRO was rapidly metabolized to COL-5671. PK for COL-5671 was dose proportional, showed a low peak to trough ratio and a long half-life (29-35 hours at steady state). Food did not meaningfully affect overall systemic exposure.

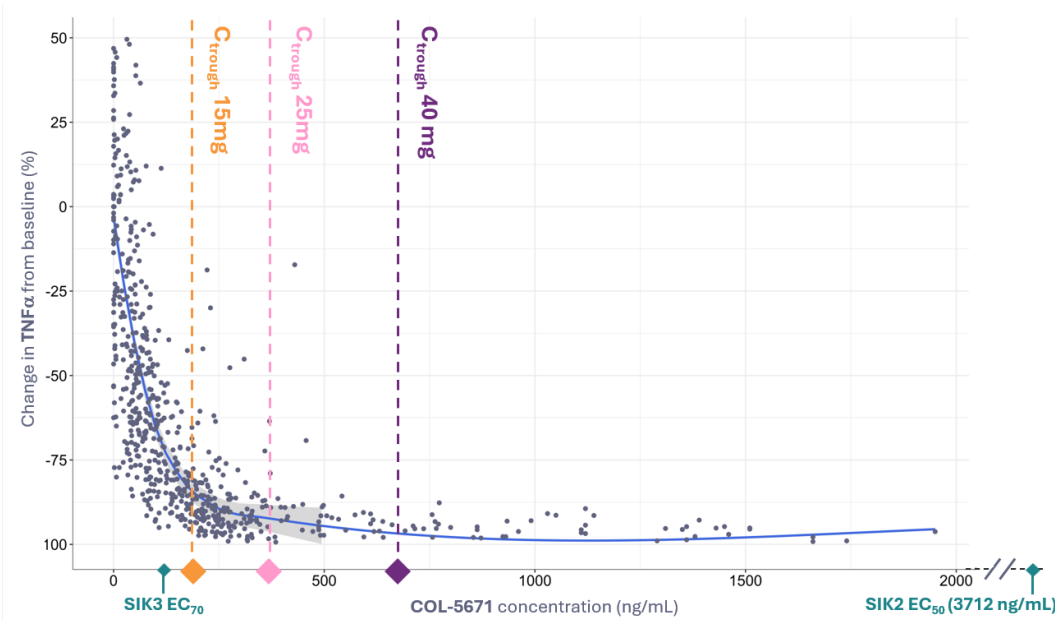
Pharmacodynamics

Samples from dosed subjects were stimulated with LPS and TNF α levels were measured to assess TNF α inhibition compared to baseline (no drug present).



COL-5671 demonstrated profound and sustained inhibition of TNF α at doses of 15mg and above in MAD cohorts

Regression analyses of COL-5671 concentration and TNF α inhibition indicate that doses of 15mg and above potentially inhibit TNF α at C_{trough}



Maximal TNF α inhibition is achieved with COL-5671 at concentrations well below the cellular EC₅₀ for SIK2 inhibition, yet above the SIK3 EC₇₀ threshold.

Safety

No dose-related trends were observed in the incidence of TEAEs, whether assessed by preferred term or system organ class. All TEAEs were Grade 1 or 2

	SAD		MAD	
	Pooled PBO N=12	Pooled COL-5671 N=36	Pooled PBO N=10	Pooled COL-5671 N=30
No subjects with at least one TEAE, n (%)	2 (16.7)	15 (41.7)	3 (30)	12 (40.0)
Serious TEAE, n (%)	0	0	0	0
Non-serious TEAE, n (%)	2 (16.7)	15 (41.7)	3 (30)	12 (40.0)
Grade ≥3 TEAE, n (%)	0	0	0	0
Treatment-related TEAE, n (%)	0	4 (11.1)	0	2 (6.7)
TEAE leading to discontinuation, n (%)	0	0	0	1* (3.3)
TEAE leading to IP interruption, n (%)	0	0	0	0
TEAE leading to IP withdrawal, n (%)	0	0	0	1* (3.3)
TEAE of special interest, n (%)	0	0	0	0

*one patient in the 25mg group discontinued study treatment (last intake on day 12) and the study due to Grade 2 influenza like illness considered related to study treatment by the investigator. PCR tests for common viruses were negative

Conclusions

COL-5671 is a potent and selective SIK3 inhibitor that has demonstrated:

- Favourable pharmacokinetic profile, characterized by a low peak-to-trough ratio, predictable dose–exposure relationship, prolonged half-life supporting once-daily dosing, and no requirement for dietary restrictions.
- Highly encouraging PD data demonstrating that doses as low as 15mg may offer profound and sustained TNF α inhibition
- A safety profile indicating that COL-5671 is safe and well tolerated at single doses up to 150mg and up to 40mg over 14 days

COL-5671 is being developed in a variety of inflammatory diseases including ulcerative colitis and psoriasis