UNITED EUROPEAN GASTROENTEROLOGY
ueg week

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

Fabrice Kolb, PhD
Head of Immunology
Onco3R Therapeutics

October 6, 2025, Berlin

UNITED EUROPEAN GASTROENTEROLOGY

ueg week

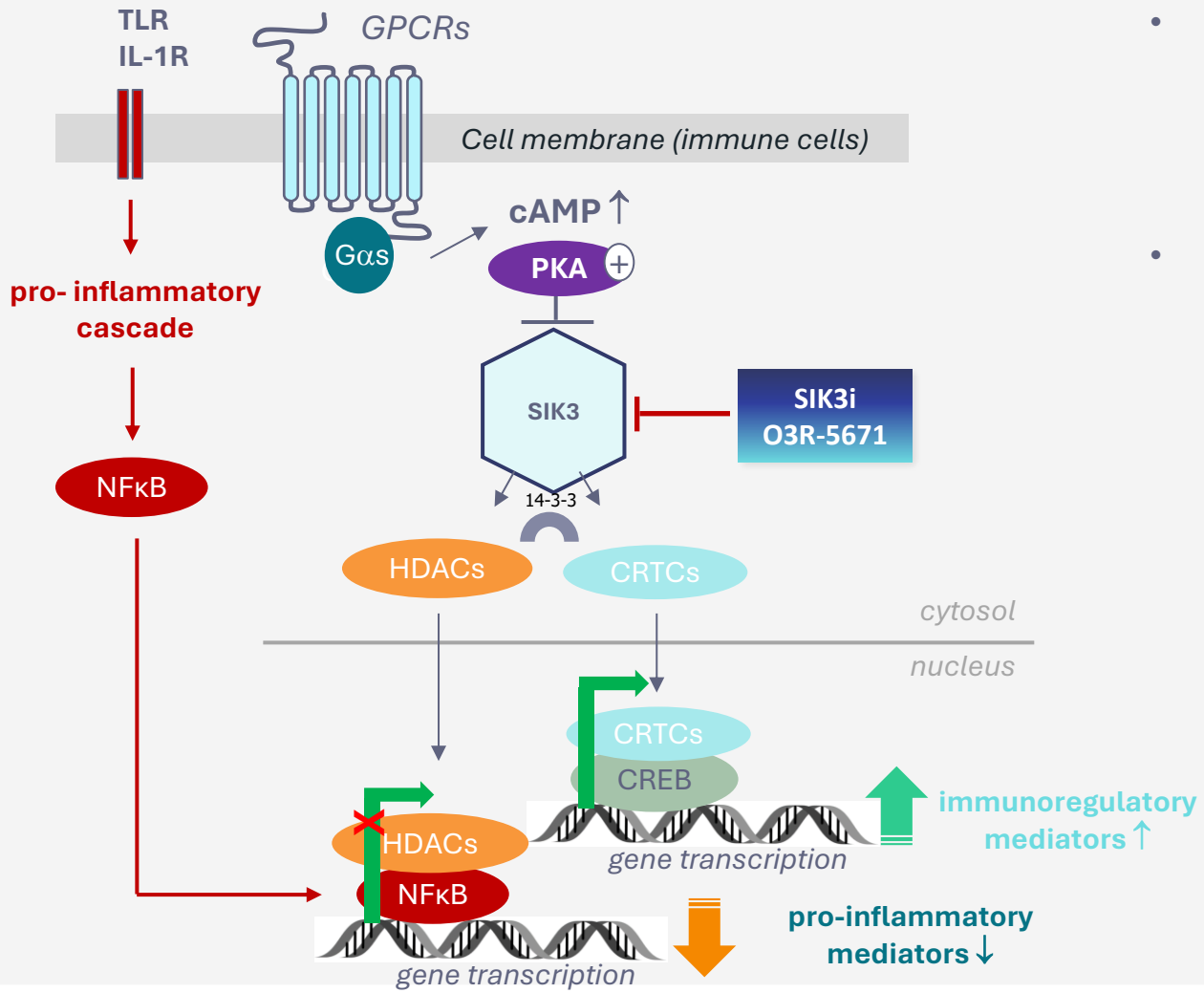
Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests, or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

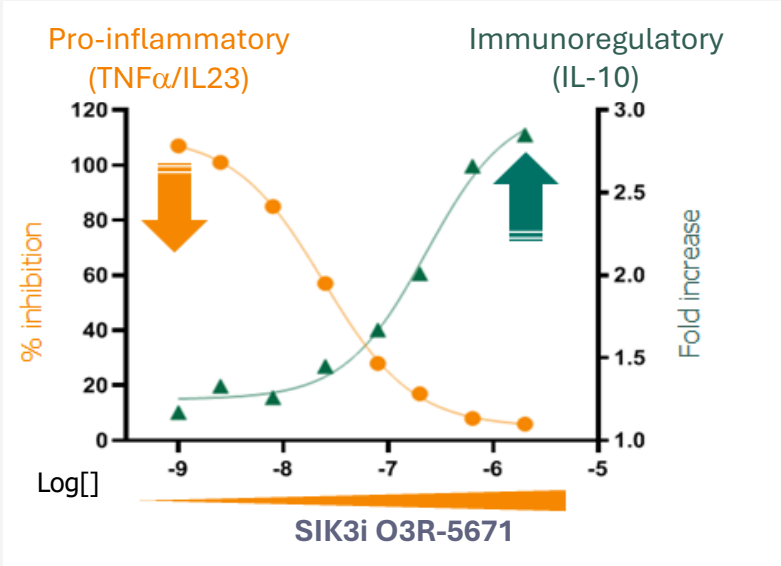
Fabrice Kolb was a Galapagos GmbH employee from 2019 to 2025 and is now a full-time employee of Onco3R Therapeutics BV

Discovery of the SIK3 inhibitor O3R-5671

SIK3 inhibition directly impacts pro- and anti-inflammatory pathways



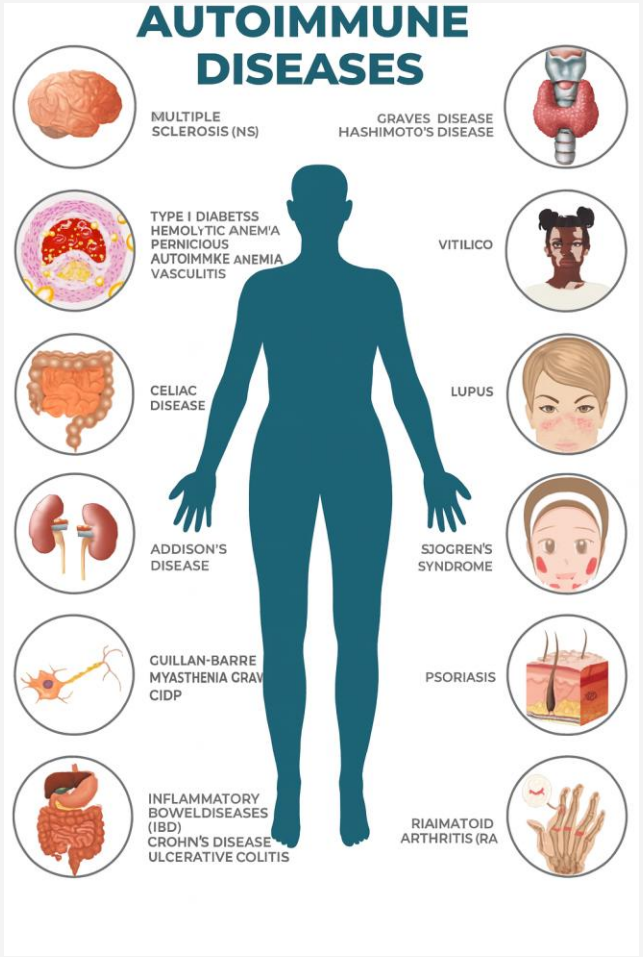
- A family of 3 salt-inducible kinases (SIKs): SIK1, SIK2, SIK3
  - **activated** by liver kinase B1 (LKB1)
  - **suppressed** by cAMP/PKA
- SIK3 inhibition controls NFκB and CREB regulated gene expression in inflammatory conditions (HDACs / CRTCs substrates)

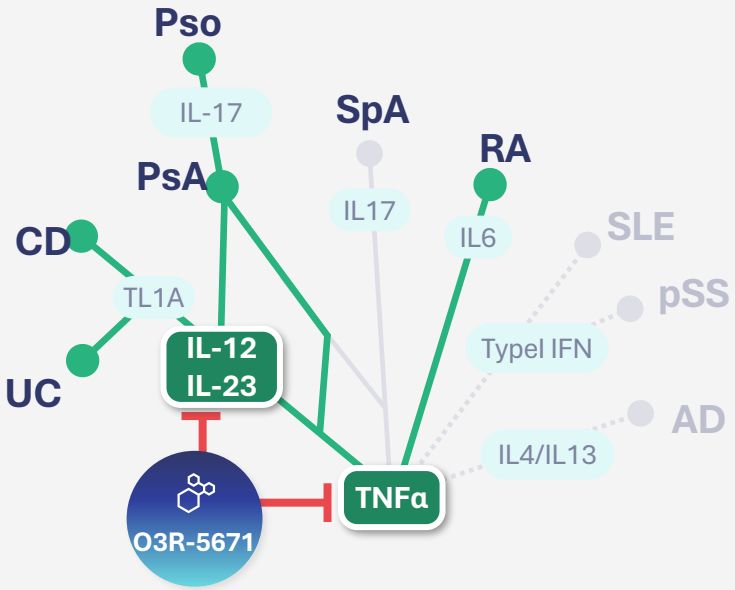


O3R-5671 SIK3i targets key pathogenic cytokines

A potential solution for multiple auto-immune diseases

>500,000,000 Autoimmune Patients Worldwide





O3R-5671

Inhibits Multiple Cytokines

➡ **Expected increased response**

Oral

➡ **Convenience**

Avoids Anti-drug Antibodies

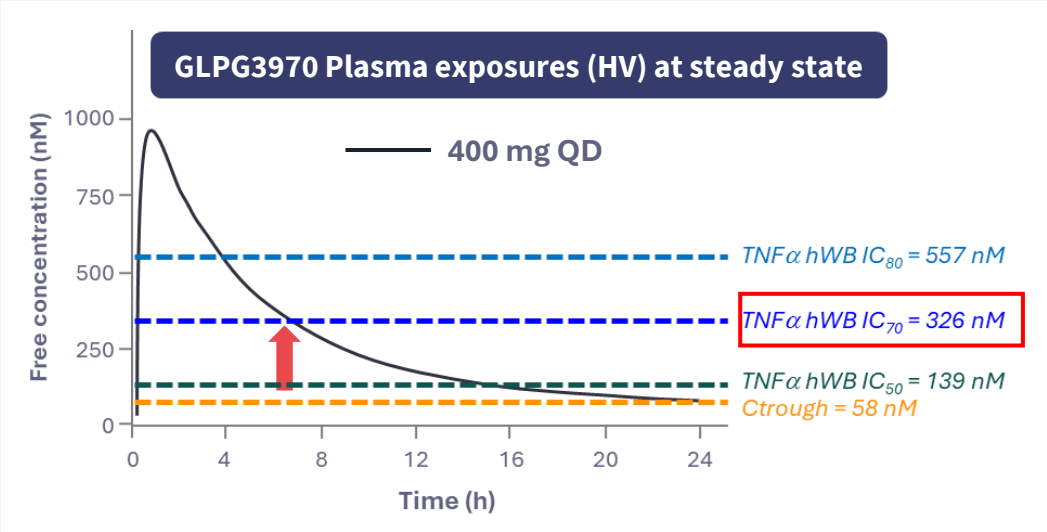
➡ **No loss of response expected**

Encouraging Pre-clinical Safety

➡ **Good tolerability expected vs existing drugs**

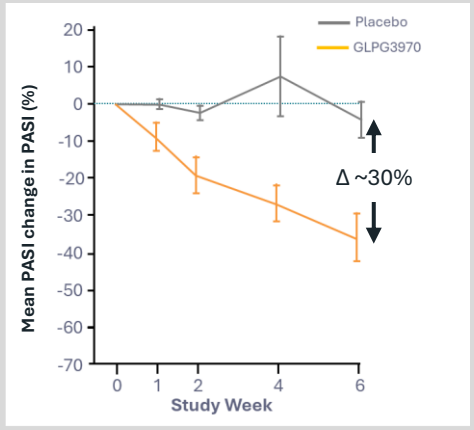
Learnings from former SIK2/SIK3 inhibitor GLPG3970

GLPG3970	
Selectivity	SIK2/SIK3 inh. (SIK2-related toxicities)
Cellular activity	100-300 nM on activated myeloid cells
Off-targets	hERG inhibition leading to QTc prolongation
Human dose	400 mg QD: suboptimal target coverage
Safety window	Limited (1.5 x)

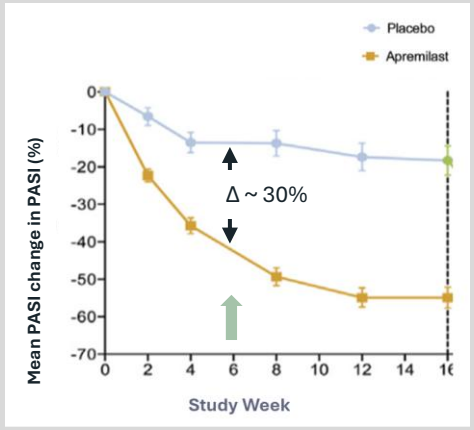


Despite partial drug pressure, GLPG3970 showed activity in Pso Ph1b and Proof of mechanism in UC

➢ Similar activity to Apremilast at 6 wks



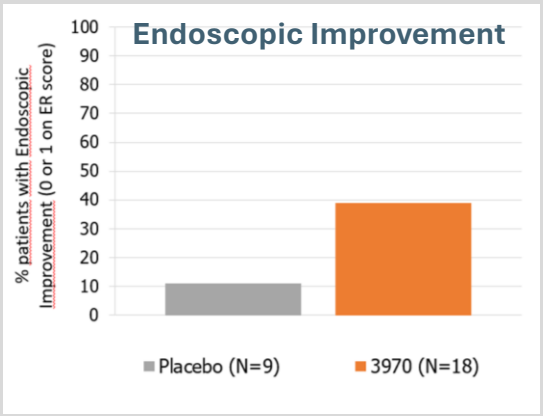
Psoriasis, GLPG3970 350 mg QD



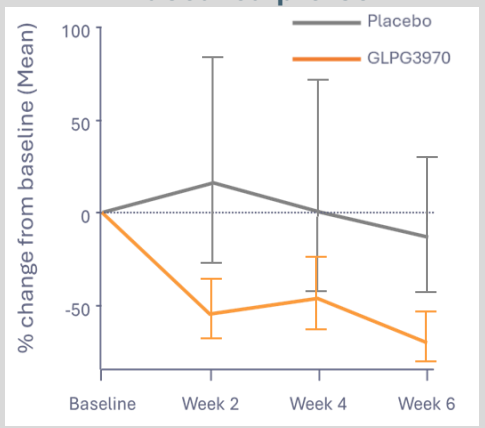
Apremilast 30 mg BID

➢ Signal of biological activity on endoscopic improvement, RHI, FCP, TNFα

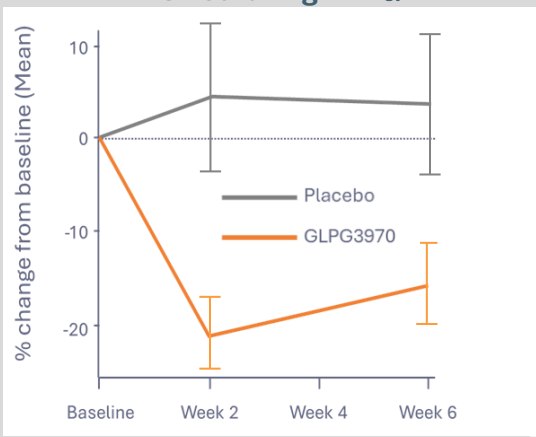
Ulcerative colitis, GLPG3970 400 mg QD



Faecal calprotectin



Circulating TNFα

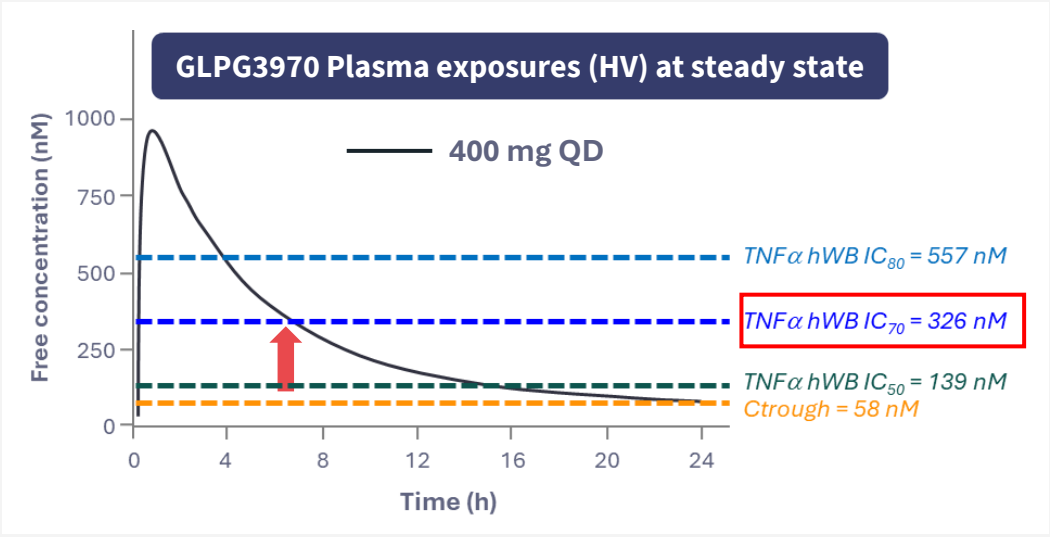


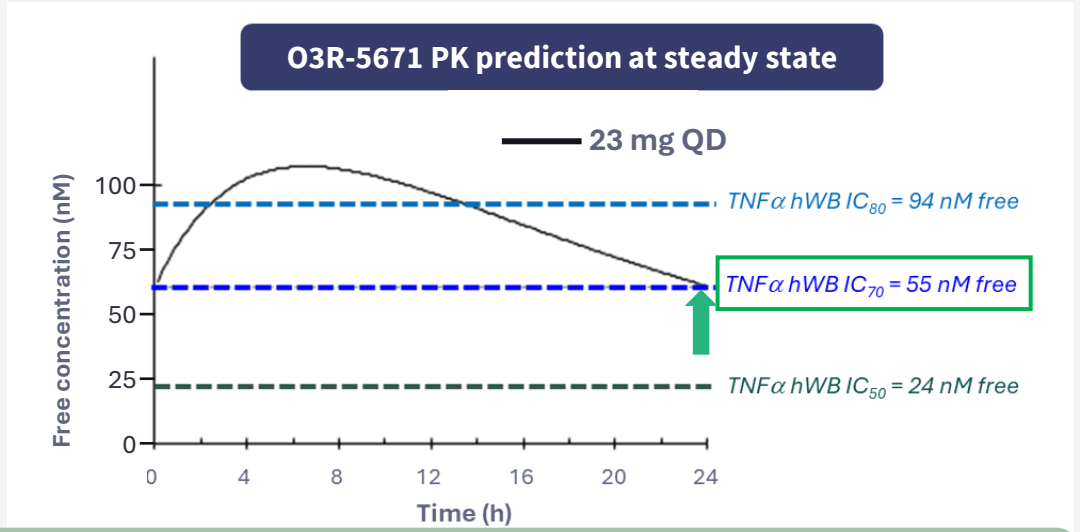
Safety-limited dosing leads to insufficient signals to move forward : need for a more selective and potent SIK3 inhibitor

Identification of O3R-5671, a Best-in-Class SIK3 Inhibitor addressing all limitations of GLPG3970

GLPG3970	
Selectivity	SIK2/SIK3 inh. (SIK2-related toxicities)
Cellular activity	100-300 nM on activated myeloid cells
Off-targets	hERG inhibition leading to QTc prolongation
Human dose	400 mg QD: suboptimal target coverage
Safety window	Limited (1.5 x)

Onco3R O3R-5671	
Selectivity	SIK3 selective and kinome selective
Cellular activity	50-100 nM on activated myeloid cells
Off-targets	No hERG
Human dose	Low projected dose allowing optimal target coverage
Safety window	Large (210 x at similar drug pressure)





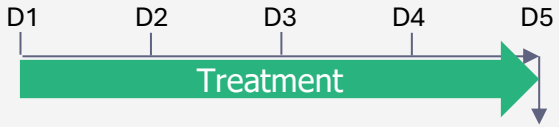
1 mg of O3R-5671 leads to equivalent drug pressure than 400 mg GLPG3970 and a much larger safety margin

O3R-5671 shows strong activity in a mouse Psoriasis model, comparable to TYK2i

PsoCyt model (IL-23-induced)

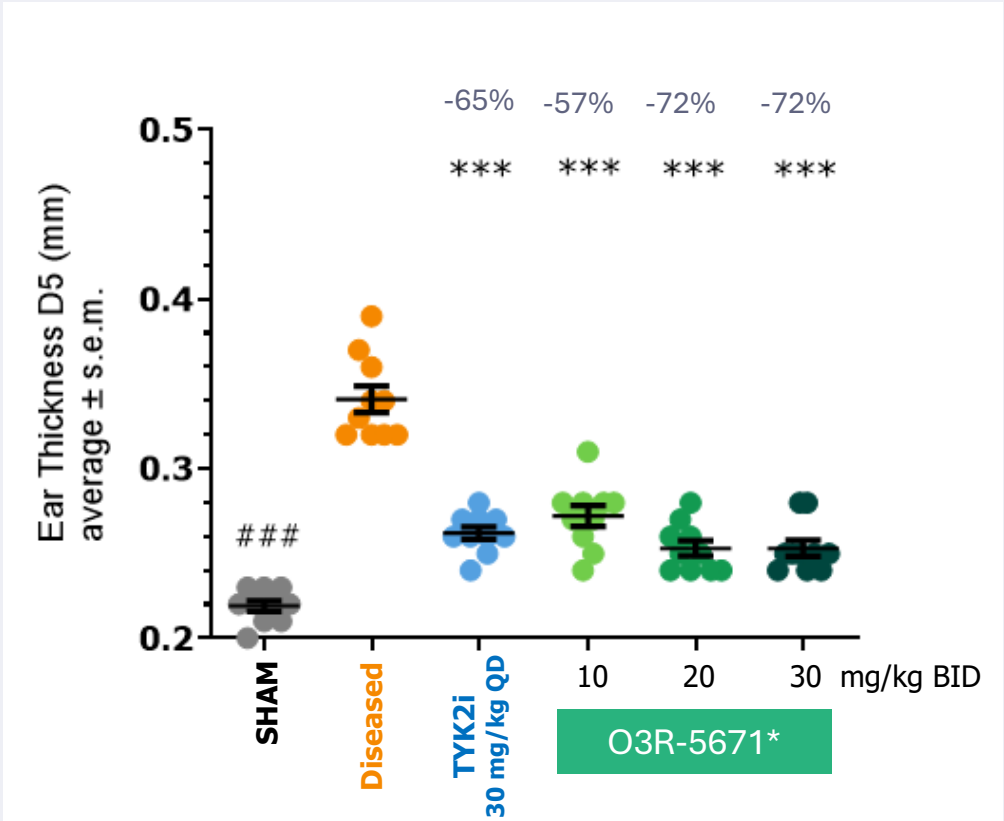
Daily intradermal IL-23 injections in the ear for 4 days

BALB/c mice



Readout:
Ear Thickness

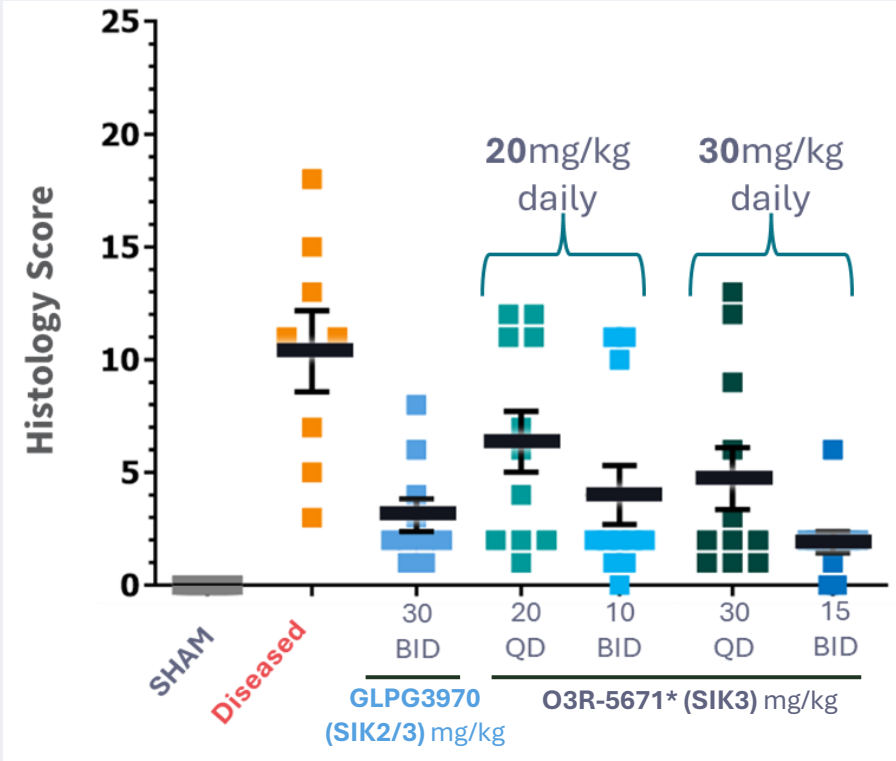
Ear thickness on Day 5



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

Statistical Analysis: One-way ANOVA + Dunnett's post-test vs IL23-Disease group; ns: p>0.05; *p<0.05; **p<0.01; ***p<0.001

O3R-5671 dose-dependently reduces disease score in a T-cell transfer mouse colitis model



- **SIK3 inhibition is sufficient for *in vivo* pharmacological effect**
- **Same activity as IL-23 biologics in same model**

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

O3R-5671 Summary and next steps

- SIK inhibition has been clinically validated by the SIK2/3 inhibitor GLPG3970
- O3R-5671 is a potential best-in-class selective SIK3 inhibitor
  - Optimal target coverage
  - SIK-specificity
  - No safety flags identified
- O3R-5671 entered the clinic in September
  - SAD/MAD with extensive biomarker plan
  - First dose cohort completed, flat PK profile confirmed, second cohort ongoing

Novel mode of action with potential to change treatment paradigm in multiple auto-immune diseases, including UC and CD

ueg week

Onco3R Therapeutics

Thank you

Follow us

www.onco3R.com

Onco3R Therapeutics

Presentation download link

UNITED EUROPEAN
GASTROENTEROLOGY

ueg week