#D1.240 ATH-409, a selective and covalent ITK inhibitor, protects against atopic dermatitis in preclinical models

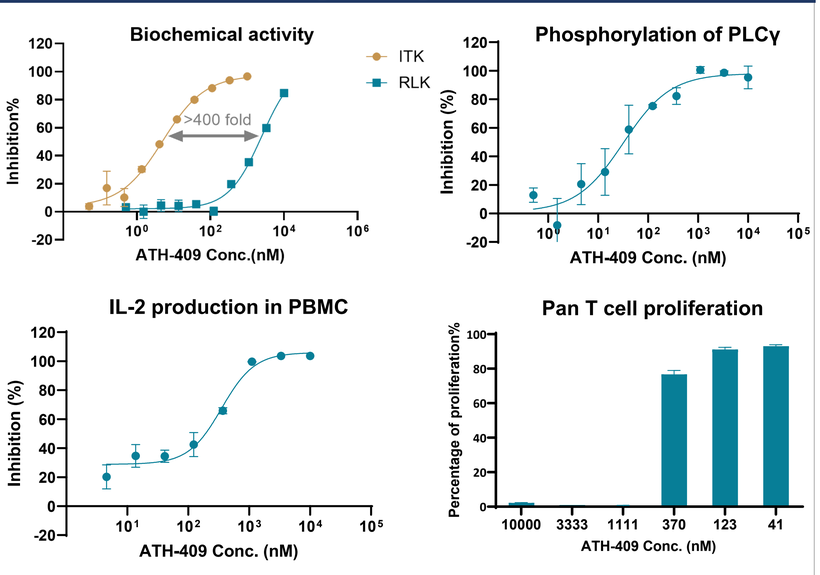
Lei Jiang, Baoying Cheng, Xin Cheng, Yuyao Zhang, Youxi Chen, Wenwen Zhao, Feng Zhou

Atheron Therapeutics (Shanghai), Ltd

Introduction

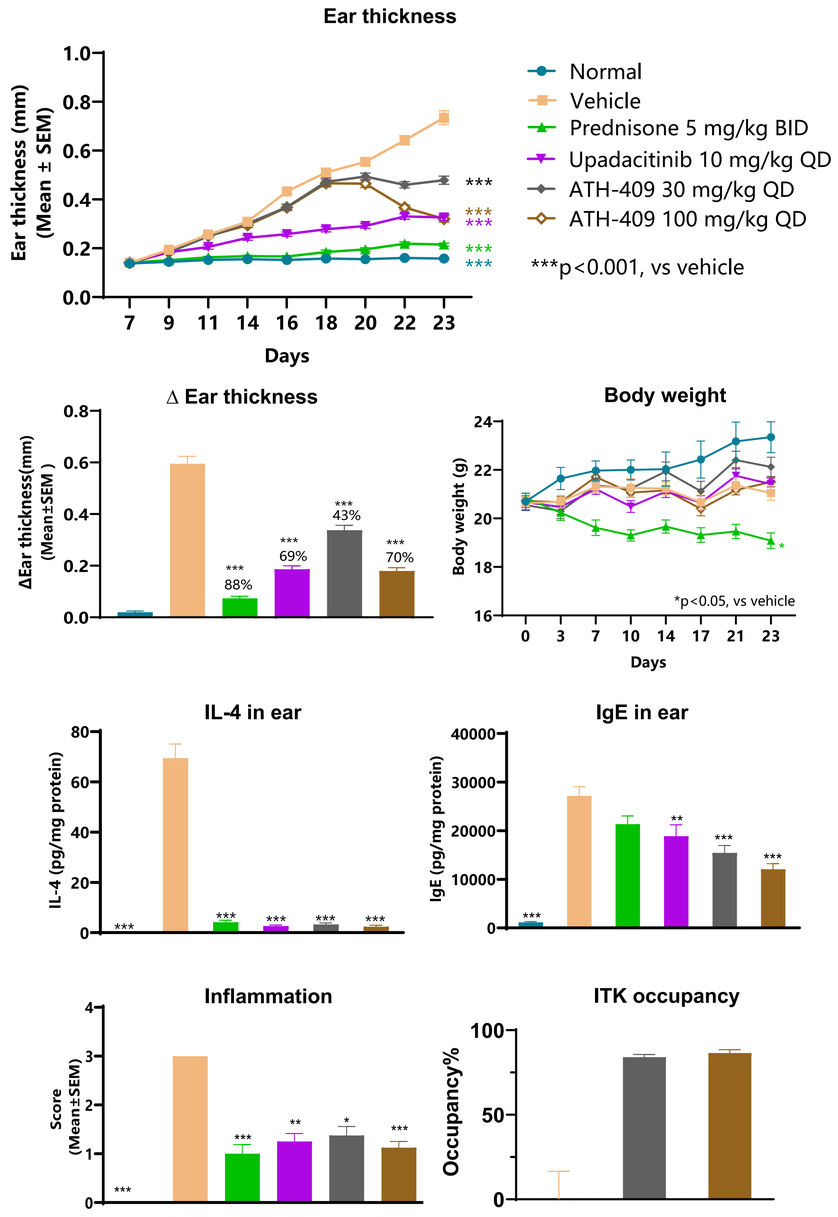
- Atopic dermatitis (AD) is the most common chronic inflammatory skin disease characterized by dysregulated Th2-driven inflammation. There still remain unmet medical needs for exploring novel therapy strategies, due to inefficient efficacy and adverse effects of current typical and systemic drugs.
- IL-2-inducible T-cell kinase (ITK), a member of the TEC family, plays a critical role in T cell signal transduction and T cell differentiation. ITK knockout mice show defects in Th2 differentiation, while retaining the ability to differentiate into Th1 cells because Resting lymphocyte kinase (RLK) is more dominant in Th1 differentiation. These findings suggest that developing ITK inhibitors sparing RLK activity could serve as a potential target for Th2-related diseases, such as AD.
- ATH-409, a highly selective covalent ITK inhibitor, robustly suppresses ITK activity and inhibits the phosphorylation of PLCγ1, leading to blockage of TCR activation-induced IL-2 release. It demonstrates inhibitory effects on the proliferation of human pan-T cells and Th2 differentiation, but displays a weak effect on Th1 differentiation. It shows good selectivity against 430 kinases, including 10 cysteine-containing kinases.

Effect on ITK signaling and T cell function



- ATH-409, a selective ITK inhibitor, sparing RLK activity, potently inhibited the phosphorylation of PLCγ1 and further blocked TCR-induced IL-2 production and proliferation.

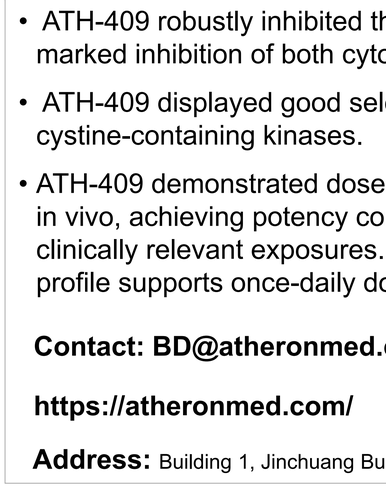
In vivo efficacy



- ATH-409 ameliorated ear skin swelling in oxazolone-induced AD model, accompanied by robust reductions in cytokine release and histopathology. It achieved nearly complete occupancy at 2h post single dose in mouse spleens.
- ATH-409 at 100 mg/kg showed efficacy comparable to that of upadacitinib at a clinically relevant exposure.

Kinase selectivity

ATH-409 kinase selectivity
(3 μM, 430 kinases)



Cystine containing kinases	ATH-409	Selectivity fold
ITK	4.9	1.0
BLK	3023.4	617.0
BMX	>10000	>2040
BTK	2441.5	498.3
EGFR	>10000	>2040
ErbB2	>10000	>2040
ErbB4	>10000	>2040
JAK3	7586.2	1548.2
MKK7	>10000	>2040
TEC	625.2	127.6
RLK	2132.7	435.2

- ATH-409 exhibited off-target potency against 5 of 430 kinases with inhibitory rates greater than 90% at 3 μM. Further studies suggest a good selectivity profile of ATH-409.
- ATH-409 displayed at least 100-fold selectivity against the 10 cysteine-containing kinases.

Summary

- ATH-409 is a potent and selective ITK inhibitor with over 400-fold selectivity against RLK.
- ATH-409 robustly inhibited the signaling pathway, leading to marked inhibition of both cytokine secretion and T-cell proliferation.
- ATH-409 displayed good selectivity against kinases, including cystine-containing kinases.
- ATH-409 demonstrated dose-dependent anti-inflammatory efficacy in vivo, achieving potency comparable to that of upadacitinib at clinically relevant exposures. Furthermore, its pharmacokinetic profile supports once-daily dosing.

Contact: BD@atheronmed.com

https://atheronmed.com/

Address: Building 1, Jinchuang Building, 4560 Jinke Road, Pudong, Shanghai