ShK-186, a Kv1.3 Channel Inhibitor that Targets Effector Memory T cells: Safety and Tolerability in Humans and its Evaluation in a Model of Anterior Uveitis
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INTRODUCTION
ShK-186 is a peptide drug that broadly blocks pathogenic effector memory T cells implicated in a wide array of autoimmune diseases including chronic uveitis and dry eye disease (Siegler et al.). ShK-186 selectively and potently inhibits Kv1.3 (IC50 < 100 pM), a potassium channel required for sustained intracellular calcium influx during activation of effector memory T cells including Th1 and Th17 cells. ShK-186 is effective in preventing disease in models of psoriasis, rheumatoid arthritis, multiple sclerosis, delayed type hypersensitivity and autoimmune uveoretinitis and it is the first Kv.3 blocker to enter clinical trials.

SUMMARY
Safety and tolerability phase 1 Trial: ShK-186 was well tolerated with no serious adverse events reported in single ascending dose and multiple ascending dose double blind, placebo-controlled phase 1 trials in healthy volunteers of up to 28 days duration. The dose and regimen evaluated provided drug exposure surpassing the predicted therapeutic dose range. Target Expression and effect of ShK-186 in autoimmune uveitis model: ShK-186 was able to penetrate the eye when administered topically. ShK-186 caused no observable or histologically adverse effects when administered at relatively high doses for up to 7 days. In a rat model of anterior uveitis where infiltrating mononuclear cells are primarily activated T cells, topical ShK-186 treatment reduced disease parameters, inflammatory cell infiltration and histopathological changes. Characterization of infiltrating inflammatory cells indicated they were Kv.3 positive CD3+ T cells. Their infiltration was blocked by topical ShK-186 treatment.

CONCLUSIONS
ShK-186 was well tolerated in phase 1 trials in healthy volunteers. Our results in a model of anterior uveitis warrant further investigation into extending the therapeutic scope of ShK-186 into autoimmune eye indications including uveitis and dry eye.

1. ShK-186 Targets Kv1.3 Channels on Autoreactive Effector Memory T cells
By selectively targeting T cells that cause autoimmune attack, ShK-186’s MOA is more broad than cytokine-targeting therapies but safer than immunosuppressive drugs.

Key differentiators:
• Novel MOA
• Immune sparing
• Targets major autoimmune disease markets
• Potent, stable small molecule
• Excellent safety profile
• Broad intellectual property

2. Kv1.3 in Human Disease
Kv1.3 and KCa1.1 are K+ channels needed to maintain membrane potential (by allowing K+ efflux) during T cell activation and the requisite increase in intracellular Ca++. While KCa1.1 is important in activation of naive and central memory T cells, Kv1.3 is only highly expressed in activated effector memory T cells.

3. Preclinical Safety and Phase I Trial Results

Safety Pharmacology: Favorable Profile

Biodistribution:

4. Pathogenic T cells in Autoimmune Eye Diseases

5. Topical ShK-186 peptide drug penetrates the eye

6. ShK-186 Reduces Disease in Model of Autoimmune Anterior Uveitis

7. Immunohistochemistry and Histopathology

8. Current Status and Future Plans

For questions about Kineta’s ShK-186 program contact Liz Whalley, Ph.D. liz.whalley@kinetabio.com