1. Abstract

Effector memory T cells (T\textsuperscript{EM}) of both CD4 and CD8 lineages are key drivers of autoimmunity and are pathogenic in several autoimmune diseases including psoriasis, type 1 diabetes, lupus nephritis, and inflammatory bowel disease, among others, by both human clinical and animal experimental data. T\textsuperscript{EM} cells are a potent, highly specific, first-in-class peptide blocker of Kv1.3 and effector memory T cells. Here we report on the safety, tolerability, pharmacodynamics and immunomodulating proof-of-concept data for dalazatide from a phase Ib study in patients with active plaque psoriasis.

Methods:
A double blind trial was conducted in patients with active mild to moderate plaque psoriasis. Cohorts received either 30 mg (n=10), 60 mg (n=10) or placebo (n=4) twice weekly subcutaneous injections for 8 weeks with 4 weeks of follow up. Skin lesion biopsies were collected at baseline and at week 4 post treatment for gene expression and immunohistological analyses. Plasma, serum and peripheral blood mononuclear cells were collected at baseline and at several times during the study. Target lesions were evaluated at baseline and at day 32.

Results:
The treatment was well tolerated by all subjects completing the study and reporting only mild adverse events. 50% of subjects in 60 mcg cohort achieved clinical improvement in target lesion. Improvements were observed as early as day 15 and up to 4 weeks following last dose (day 57, end-of-study). Ongoing improvement continued during follow-up period in some subjects. 90% of subjects in 60 mcg group had reduction in PASI score.

Conclusion:
These results demonstrate that twice weekly subcutaneous dosing of Kv1.3 blocker dalazetide is safe and well tolerated in psoriasis patients. Improvement in clinical disease endpoints provides proof-of-concept data for the immunomodulating mechanism of action of dalazatide in a prototypical T cell mediated autoimmune disease.

2. Kv1.3 as a Target for Autoimmune Disease

- Effector memory T cells (T\textsuperscript{EM}) cause autoimmune disease
- T\textsuperscript{EM} cells depends on the Kv1.3 K+ channel for function
- Kv1.3\textsuperscript{39} autoreactive T\textsuperscript{EM} cells identified in multiple autoimmune diseases
- Blockade of Kv1.3 suppresses inflammation
- Kv1.3\textsuperscript{39} autoreactive T\textsuperscript{EM} cells identified in multiple autoimmune diseases
- Dalazatide is a highly specific and potent peptide inhibitor of Kv1.3

Kv1.3 channel expression in T cells (Wulff et al., 2003)

<table>
<thead>
<tr>
<th>Species Channel</th>
<th>Naïve CCR7+CD45RA+</th>
<th>TCM CD27+CD45RA+</th>
<th>EM CD27− CD45RA+</th>
<th>Resting Activated</th>
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<tbody>
<tr>
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<td>250</td>
</tr>
<tr>
<td>Human (CD8+)</td>
<td>~250</td>
<td>300</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>Mouse (CD4+)</td>
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<td>250</td>
<td>250</td>
<td>1800</td>
</tr>
<tr>
<td>Mouse (CD8+)</td>
<td>5</td>
<td>500</td>
<td>35</td>
<td>50</td>
</tr>
</tbody>
</table>

3. Dalazatide is well tolerated in clinical studies

Initial Phase I Studies Demonstrate Dalazatide Safety in Healthy Volunteers

Results from SAD and MAD studies:
- Drug well tolerated in both studies
- No significant findings in labs, vitals, ECGs, physical exams, neurological exams
- All AEs were considered to be mild
- Maximum tolerated dose not determined
- No subject developed anti-drug antibody

4. Dose Rationale, Safety, Tolerability

PK/PD Model
Dose and dose frequency for clinical trials were based on preclinical models of efficacy, PK, and PD data

5. 186-03 Phase Ib Trial: Active Plaque Psoriasis

A 4 Week Study of the Safety, Tolerability and Pharmacodynamics of Dalazatide in Active Plaque Psoriasis

Study Design: Phase Ib
- Placebo controlled
- Mild to moderate psoriasis
- Primary endpoints: safety, tolerability, and immunogenicity of repeat doses
- Secondary endpoints: exposure, % BSA, PASI, IGA, DLQI, PDL, and biomarkers (not powered to evaluate clinical efficacy)
- Active psoriasis patients with ≥3% BSA and multiple target lesions

Results
Safety & Tolerability
- Drug was well tolerated: all subjects completed all scheduled doses
- Most common AEs were Grade 1 and mild
- No subjects withdrew, reduced dose or missed a dose
- No laboratory-associated adverse events identified

Clinical Activity:
- 50% of subjects in 60 mcg cohort achieved clinical improvement in target lesion
- Significant improvement in target lesions following 4 weeks of treatment, that lasts beyond the last dose (day 29)
- 90% of subjects in 60 mcg cohort had reduction in PASI score
- Patients in the 60 mcg cohort classified as ‘Responders’ (R) had at least a one step reduction in target lesion score in clinical assessment
- 60 mcg cohort experience PASI reductions which correlate with reductions in circulating T\textsuperscript{EM} and cytokine biomarkers

6. Dalazatide Does Not Alter Major T cell Subset Frequencies

7. Reductions in T\textsuperscript{EM}, Cell Activation Markers and Key Cytokines

8. Dalazatide Appropriately Engages the Target

- Clinical efficacy demonstrated
- Four T\textsuperscript{EM} cell subpopulations identified that are responsive to drug treatment
- Five cytokine biomarkers identified that correlate with clinical activity
- Subset of biomarkers directly relevant to systemic autoimmune diseases like Lupus
- Efficacy, exposure and biomarkers confirm PK/PD Model