Activation of PAC1 by maxadilan: a new human target engagement biomarker

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Overview

- Background
- Study Design
- Results
- Conclusion
Background (1)

Drugs in clinical trials for central nervous system disorders (1990–2012)

46% of phase III trials discontinued due to lack of efficacy!

Need for in vivo in human target engagement biomarkers to strengthen GO/NO GO decisions

Nature Reviews | Drug Discovery
Background (2)

Focus on migraine: PAC1 receptor
Background (3)

Focus on migraine: PAC1 receptor
PART I: Dose Finding in healthy subjects (n=10)

- Intradermal injection of 3 different doses of maxadilan and placebo on one arm
- Dose escalation over 3 periods with at least 14 days wash-out between periods
PART II: Reproducibility in healthy subjects (n=10)

- Intradermal injection of 1 dose of maxadilan and placebo on both arms
- Reproducibility over time with 14 days wash-out between periods

Prestudy: screening

Period 1: Dose based on part I

Period 2: Dose based on part I

Post-study

3 weeks maximum

14 days

7-14 days
Study Design (3)
Results (1)

PART I: Dose Finding

Dermal Blood Flow (PU) (n=10)

- 0.9ng maxadilan
- 3ng maxadilan
- 10ng maxadilan

- placebo period 1
- placebo period 2
- placebo period 3
PART II: Reproducibility

Area under the curve $0\text{–}180\text{min}$ for DBF in ROI (PU$\times$min) (n=10)

Dermal Blood Flow in ROI (PU) at timepoint 60 min (n=10)

Data are presented as mean ± SEM

CCC = concordance correlation coefficient, AUC = area under the curve, SSC = sample size calculation
### Results (3)

**PART II: Reproducibility and sample size**

<table>
<thead>
<tr>
<th>Inter-arm $\text{AUC}_{0-180}$</th>
<th>Concordance correlation coefficient</th>
<th>Sample size calculation 30% shift</th>
<th>Sample size calculation 50% shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>0.88</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Visit 2</td>
<td>0.75</td>
<td>14</td>
<td>6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inter-period $\text{AUC}_{0-180}$</th>
<th>Concordance correlation coefficient</th>
<th>Sample size calculation 30% shift</th>
<th>Sample size calculation 50% shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left arm</td>
<td>0.77</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Right arm</td>
<td>0.71</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-180\min}$ = area under the curve from 0-180 minutes post maxadilan injection.
Results (4)

PART II: Duration

DBF (PU) duration: Follow-up until 5 days post-dosing (n=10*)

*Timepoints 6, 8 and 12 hours post-dose were only measured in 5 subjects
Conclusions

- ID maxadilan is safe and well tolerated in healthy male subjects.
- The dose of 0.9 ng was selected as the most appropriate dose for PART II based on the robust increase in DBF.
- DBF response to 0.9 ng maxadilan is reproducible between arms and between periods.
- A sample size of 10-15 subjects is needed to detect a 30-50% shift between 2 independent groups.

This biomarker can be used to evaluate target-engagement of PAC1 antagonists.
Special thanks to...
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