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

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Overview

- Background
- Study Design
- Results
- Conclusion

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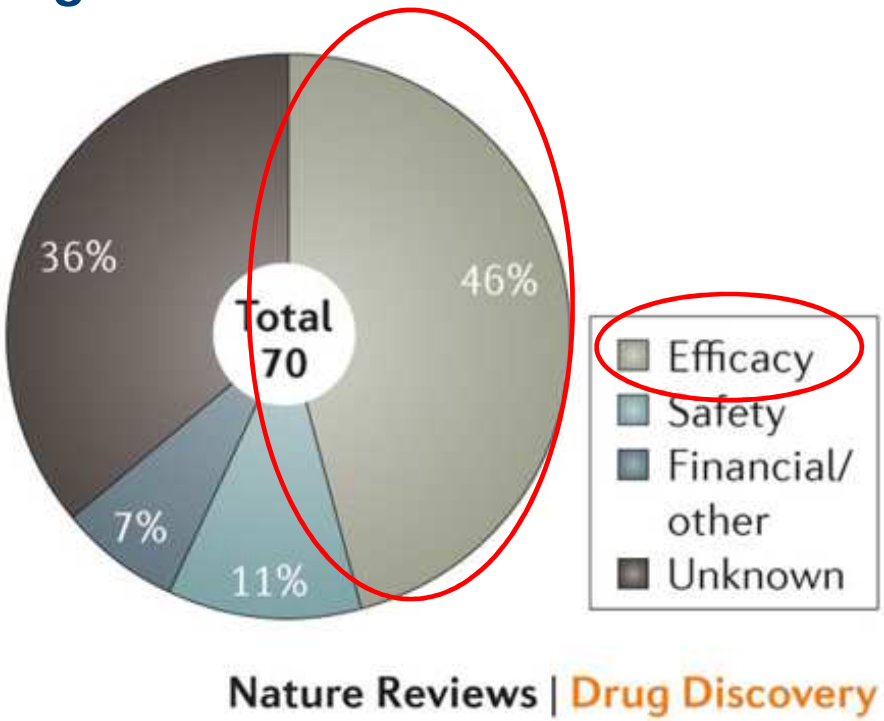
Background (1)

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

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Nature drug discovery; 2015

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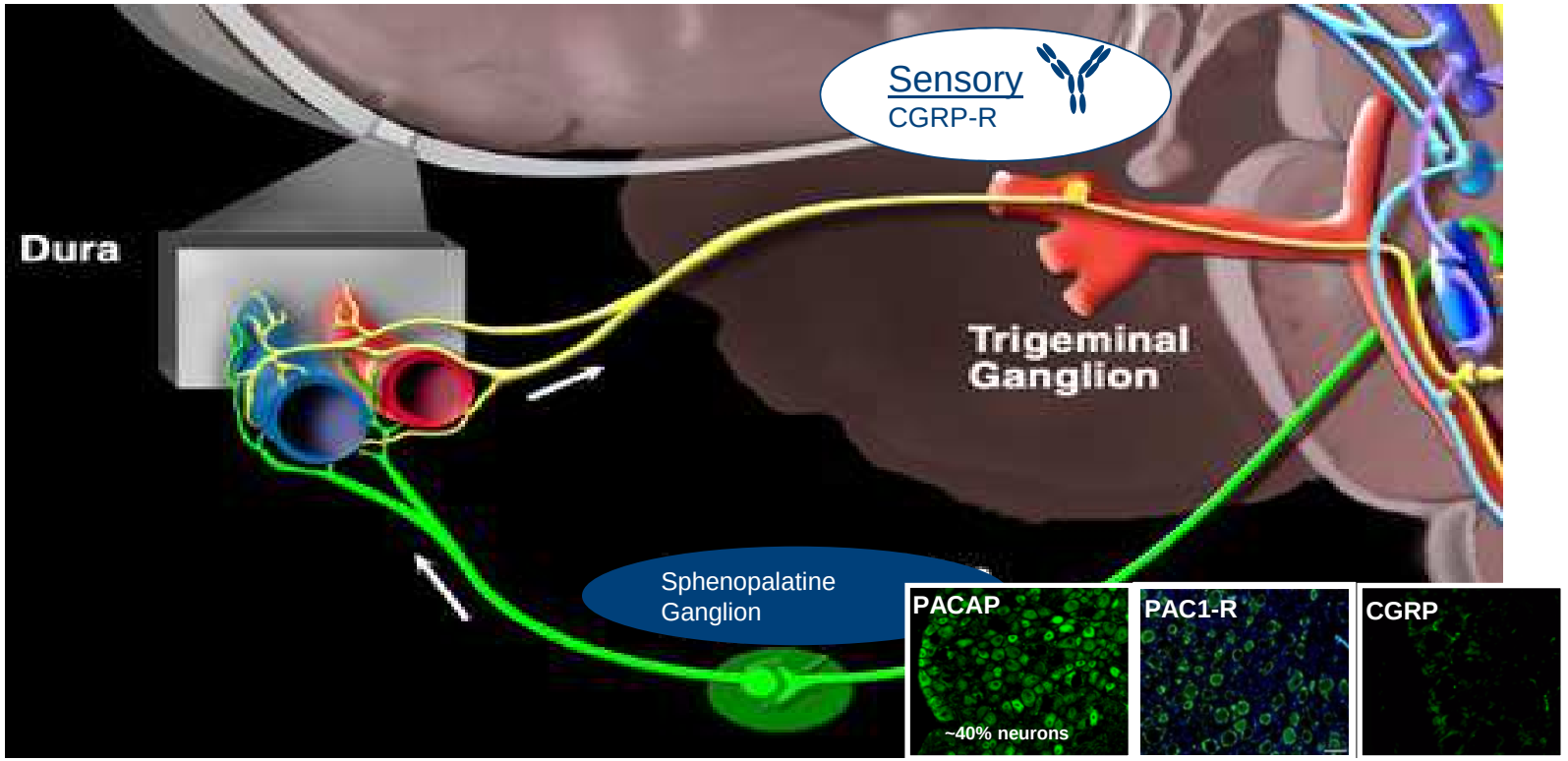
Background (2)

Focus on migraine: PAC1 receptor



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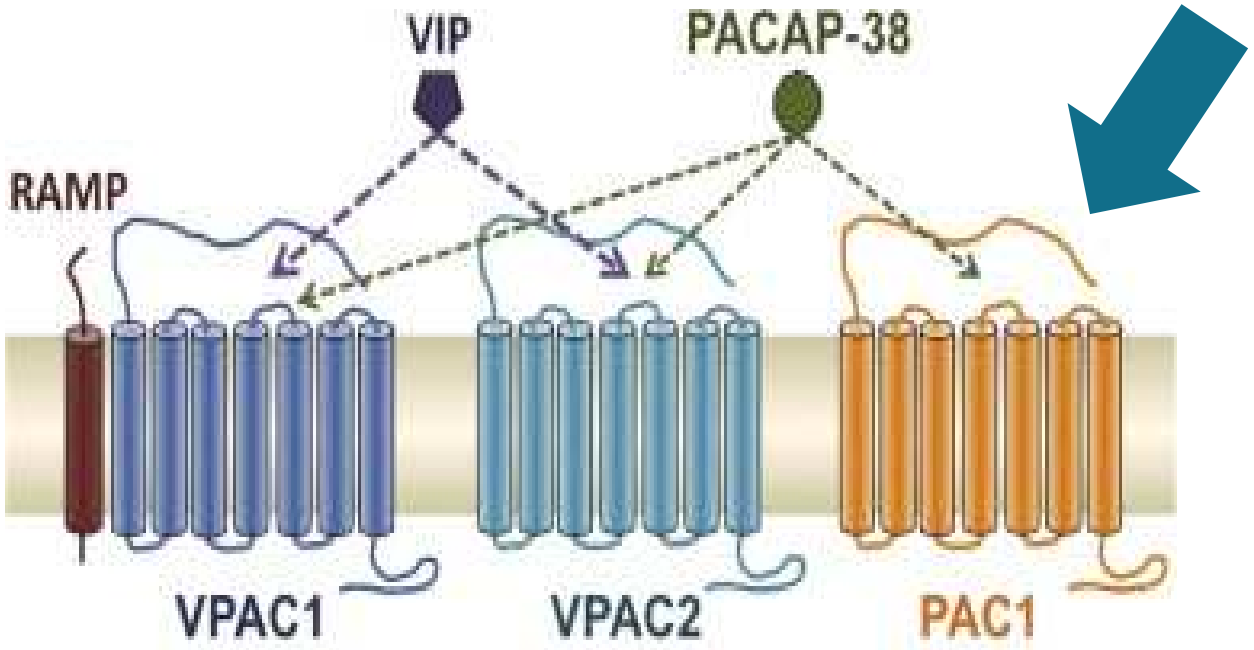
Background (3)

Focus on migraine: PAC1 receptor



Kaiser *et al.* Neuropeptides 2013

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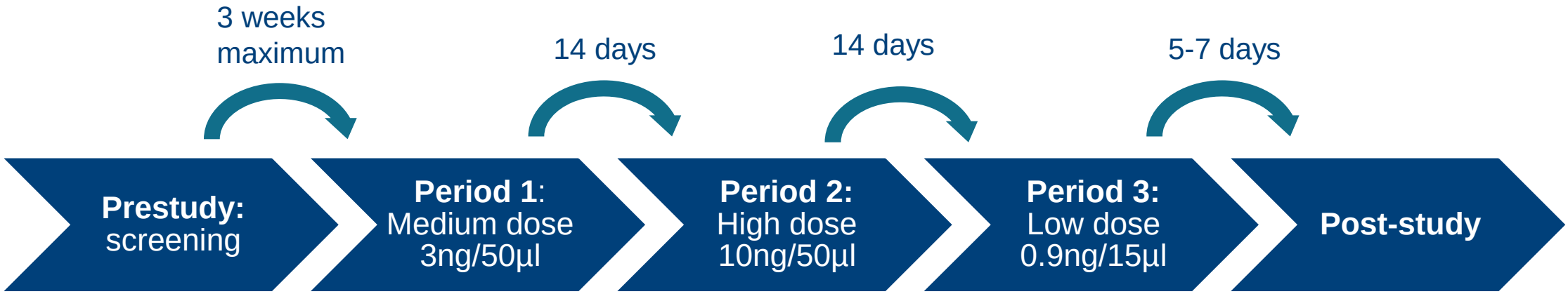
Study Design (1)

PART I: Dose Finding in healthy subjects (n=10)

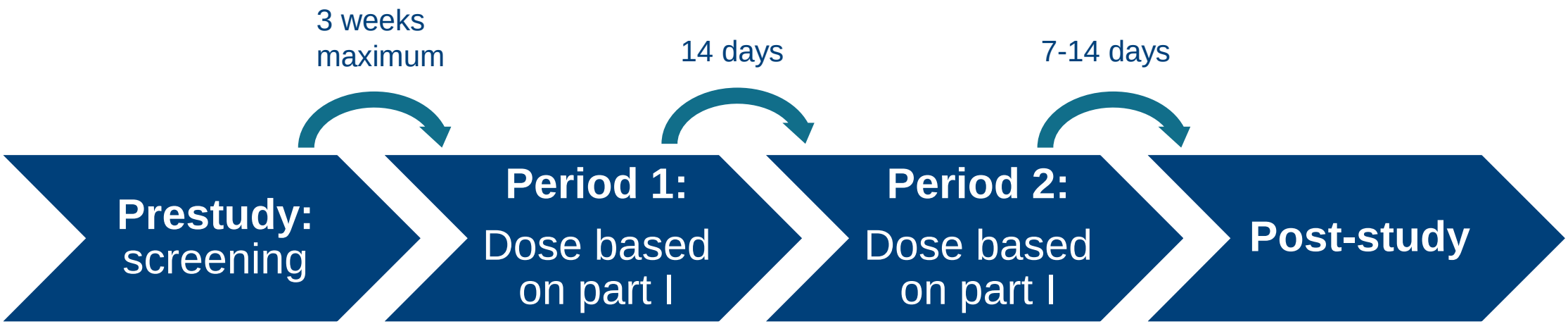
- Intradermal injection of 3 different doses of maxadilan and placebo on one arm
- Dose escalation over 3 periods with at least 14 days wash-out between periods



Study Design (2)

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



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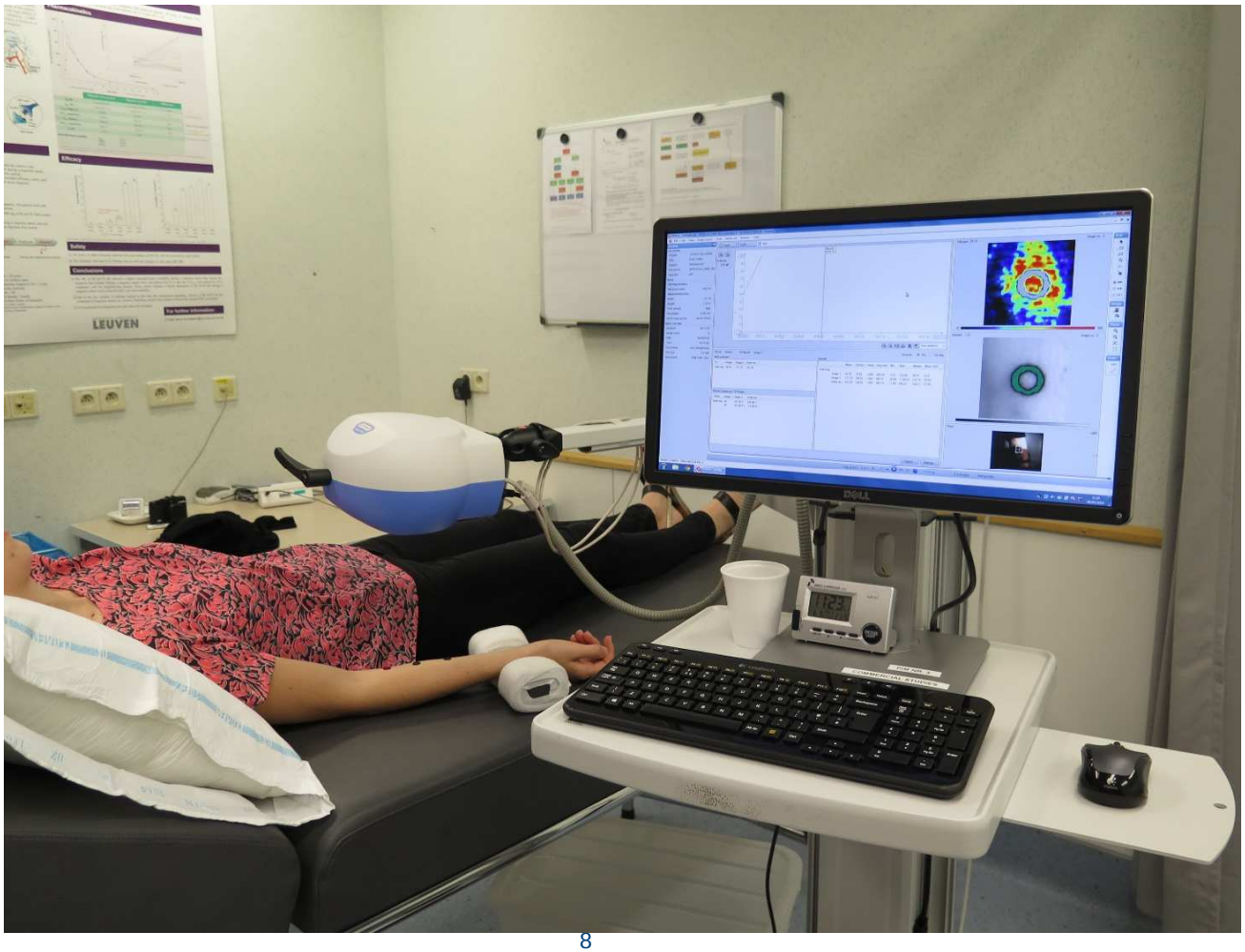
Study Design (3)



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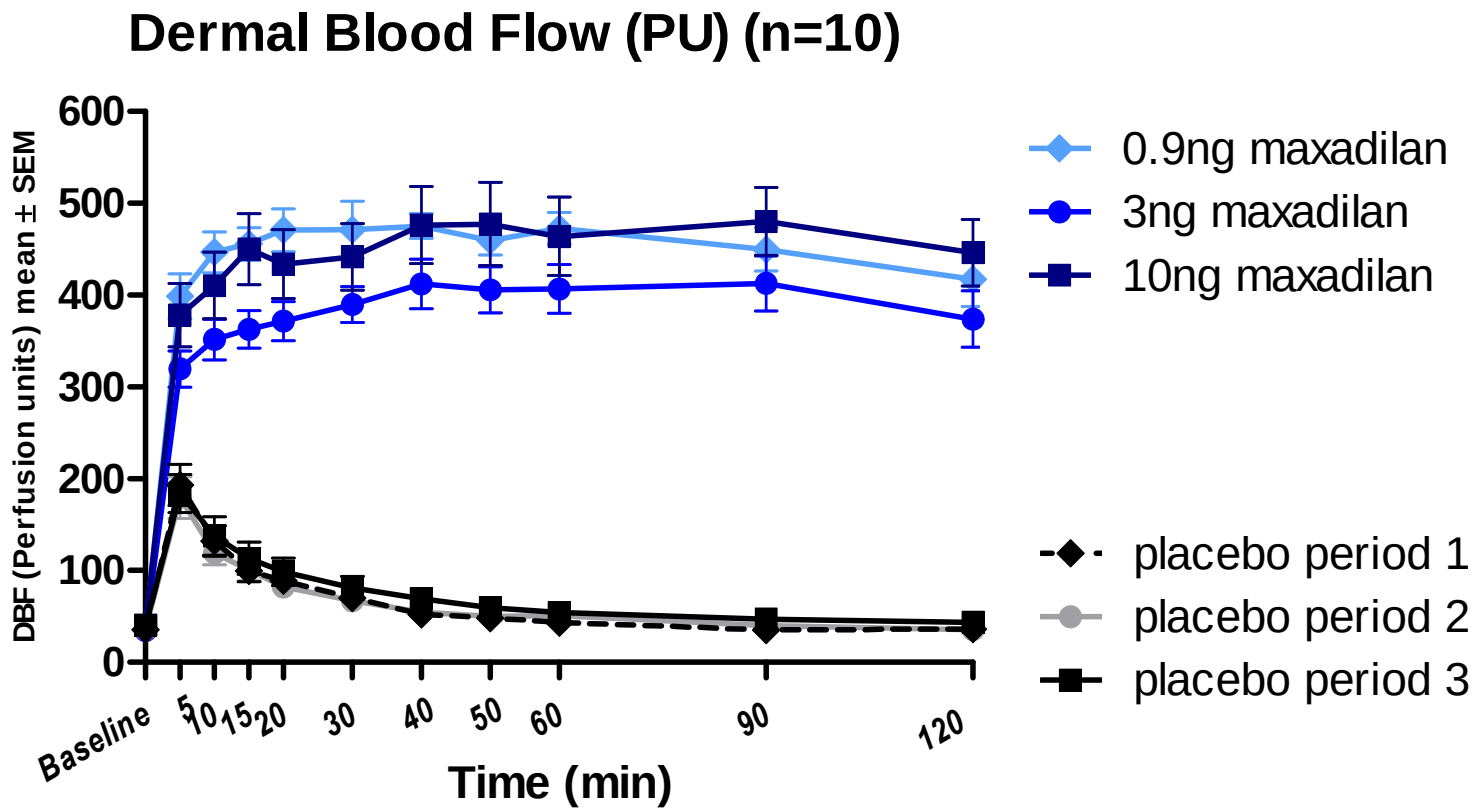
Results (1)

PART I: Dose Finding



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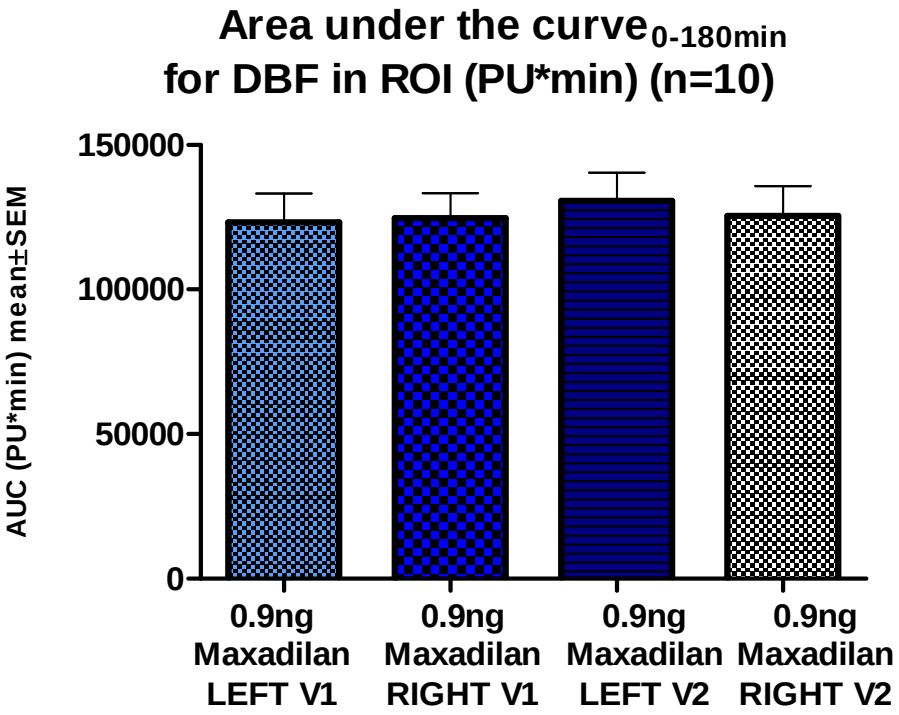
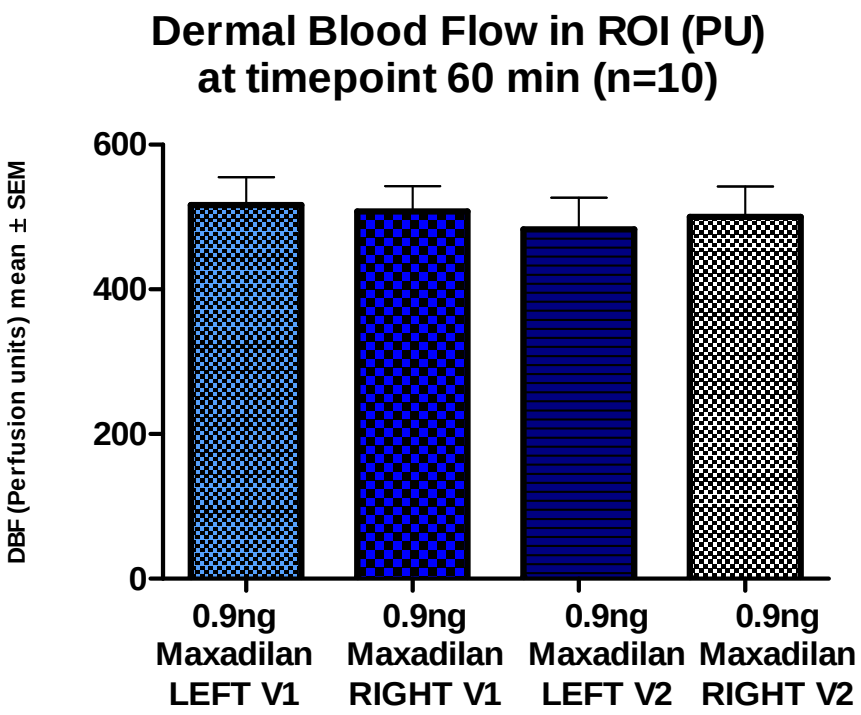
Results (2)

PART II: Reproducibility





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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

Inter-arm $AUC_{0\text{-}180}$	Concordance correlation coefficient	Sample size calculation 30% shift	Sample size calculation 50% shift
Visit 1	0.88	7	4
Visit 2	0.75	14	6

Inter-period $AUC_{0\text{-}180}$	Concordance correlation coefficient	Sample size calculation 30% shift	Sample size calculation 50% shift
Left arm	0.77	13	6
Right arm	0.71	15	7

$AUC_{0\text{-}180min}$ = area under the curve from 0-180 minutes post maxadilan injection

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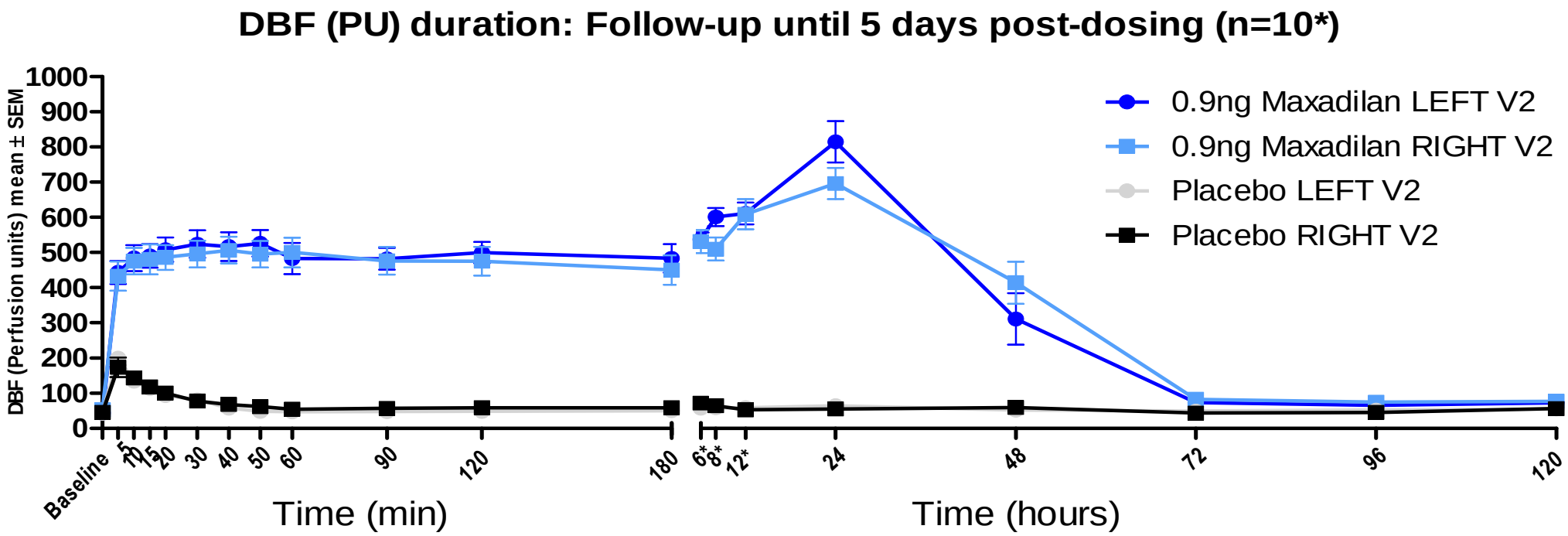
Results (4)

PART II: Duration



*timepoints 6, 8 and 12 hours post-dose w ere only measured in 5 subjects

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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

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Special thanks to…

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