Opportunity for Collaboration: AlbudAb™ Half-Life Extension Platform

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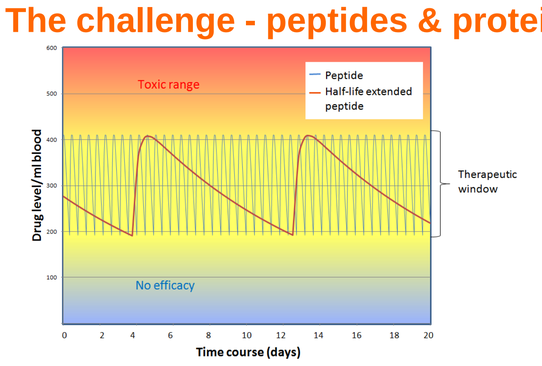
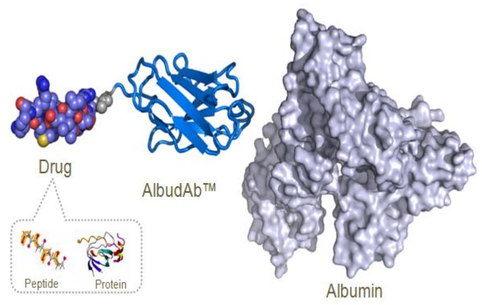
Introduction

The challenge - peptides & proteins with short half-life



Peptides and small proteins offer a differentiated therapeutic approach to monoclonal antibodies. Transforming such molecules into patient-friendly and safe medicines presents a challenge due to their short plasma half-life. Repeated high level dosing is required to achieve "therapeutic levels" of low molecular weight drugs in blood, which can lead to toxicity and unwanted side effects. Increasing the half-life of a peptide or protein prolongs the exposure of drug in the patient within the therapeutic window, improves patient compliance and reduces dosing frequency, side effects and cost.

A solution - AlbudAb™ half-life extension platform



GSK has developed the AlbudAb™, a half-life extension platform, to address the problem of low plasma exposure and harness the full therapeutic potential of peptides or proteins.

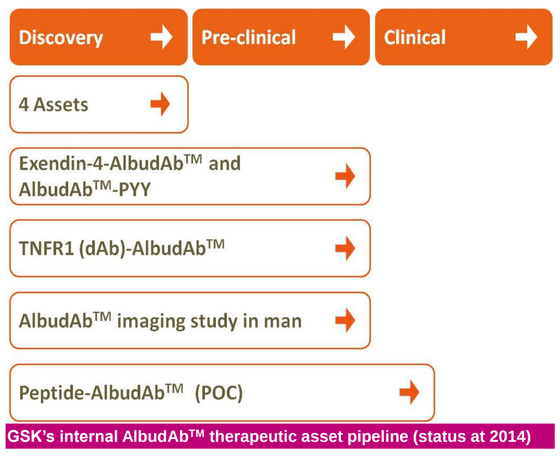
Using this versatile platform, payloads are covalently attached to an AlbudAb™, a human domain antibody (dAb) with high binding affinity for the ubiquitous serum albumin molecule thereby preventing renal clearance and conferring benefits of FcRn mediated recycling of albumin.

The AlbudAb™ platform

Key benefits

1. Pharmacokinetics support every other week dosing for suitable peptides and small proteins in man
2. Tailored species cross-reactivity (human, cyno, rat, mouse, not bovine)
3. Biological activity of payload retained
4. Payload attachment to the N- or C-terminus via genetic fusion or alternatively by chemical conjugation
5. No impact on albumin function or distribution
6. Compatible with bacterial and eukaryotic expression systems
7. Access to FcRn recycling without having a Fc function
8. Stability compatible with liquid formulation
9. Proven safety record in non–human primates and man
10. Demonstrated manufacturing processes for clinical grade AlbudAb™

GSK's Commitment

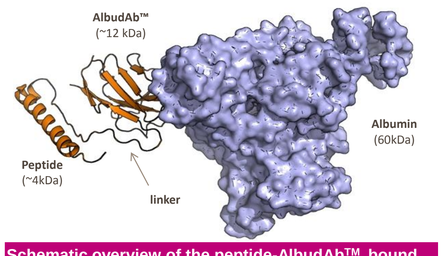


GSK's internal AlbudAb™ therapeutic asset pipeline (status at 2014)

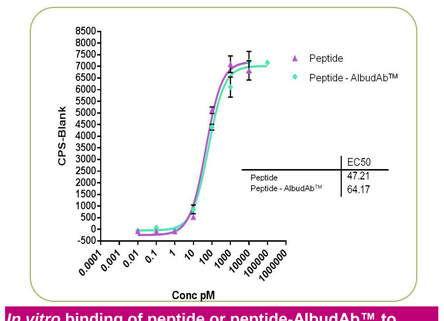
- GSK has invested significantly in the research and development of the AlbudAb™ – a next generation half-life extension platform
- Completed a FTIH study
- Three assets in pre-clinical development
- Extensive pre-clinical toxicity packages
- GMP manufacturing processes developed for three assets
- An imaging study in man will start in 2014
- We have also published on three additional assets

An exemplar peptide-AlbudAb™ molecule

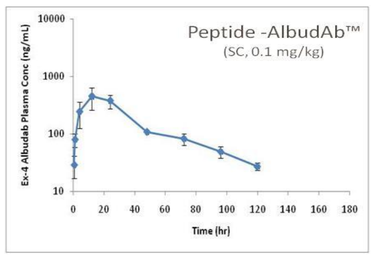
Pre-clinical data



Schematic overview of the peptide-AlbudAb™ bound to serum albumin

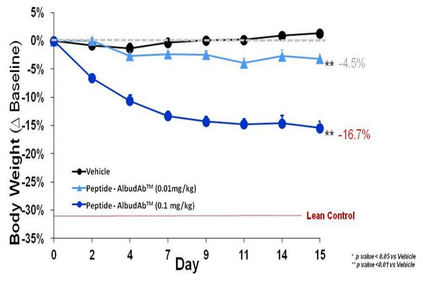


In vitro binding of peptide or peptide-AlbudAb™ to GLP1R showing similar potency



Molecule	T1/2 (hrs) Mouse
Peptide-AlbudAb™	29.8
Peptide	0.5

Long half-life for the peptide-AlbudAb™ shown in a mouse pK study.

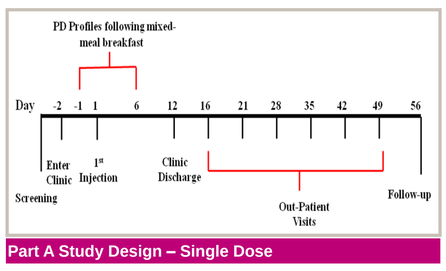


Peptide-AlbudAb™ gives significant weight loss in Diet-induced obesity (DIO) C57BL/6 mice chronic efficacy study

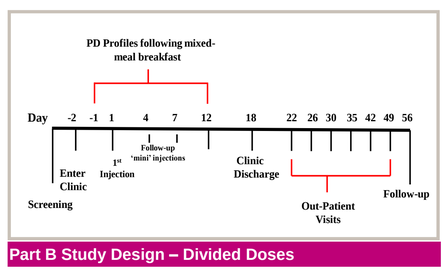
Clinical data

Study design

The pharmacokinetics, pharmacodynamics, and safety/tolerability of a peptide-AlbudAb™ was assessed in normal and obese healthy volunteers, in the first evaluation of an AlbudAb™ in humans. In this double-blind (sponsor unblinded), randomized, placebo-controlled study (Figures below), 82 subjects (18 placebo, 64 peptide-AlbudAb™), received escalating single doses of a peptide-AlbudAb™ or placebo (subcutaneous injections into the abdomen) in sequential cohorts from 0.1mg to 4mg, Divided doses on Days 1, 4, and 7: 4.0mg as 1mg + 1mg + 2mg, 6.0mg as 2mg + 2mg + 2mg.

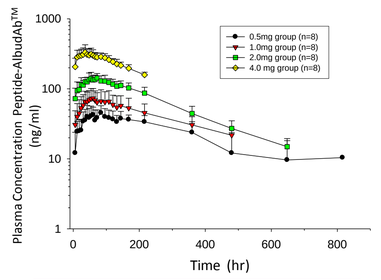


Part A Study Design – Single Dose

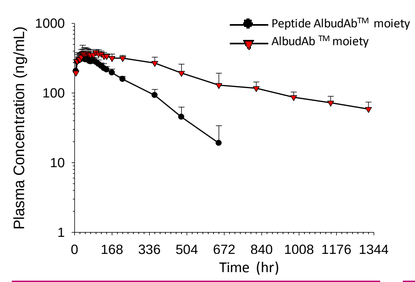


Part B Study Design – Divided Doses

Pharmacokinetics



Part A : Pharmacokinetics



Pharmacokinetics of the peptide and AlbudAb™ moiety at a 4mg dose

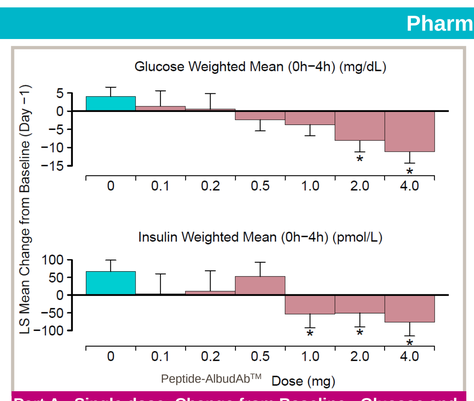
Half-life	$T_{1/2}$ (days) Human
Peptide *	0.02
Peptide moiety	6.3
AlbudAb™ moiety	15
Albumin *	19

* Published data

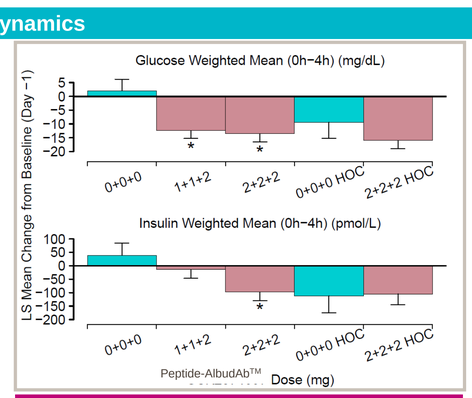
An overview comparing the half-life of a peptide, a peptide-AlbudAb™ and Albumin

In Part A – Single doses of peptide-AlbudAb™ AUC(0-∞) and C_{max} were slightly less than dose proportional with increasing dose. The median $T_{1/2}$ was 6.3 days ranging from 4-22 days and independent of dose. The median time to maximum plasma concentrations was prolonged (T_{max}=57 hours) and independent of dose.
In Part B – Plasma concentrations after multiple doses of peptide-AlbudAb™ were given over 1 week were additive, predictable, and provided smoothed-out ascending plasma concentrations. There was not a strong relationship between AUC(0-∞) and body weight suggesting dose may not need to be adjusted based on weight.

Pharmacodynamics



Part A - Single dose: Change from Baseline - Glucose and Insulin



Part B – Divided dose: Change from Baseline-Glucose and Insulin

Glucose: Following a mixed meal, plasma GLUCOSE was decreased following both single and divided doses. The decrease was dose-dependent with single doses and with statistical significance (ANCOVA) observed at the 2mg, 4mg, 1+1+2mg and 2+2+2mg dose levels.
Insulin: Following a mixed meal, plasma INSULIN was decreased following both single and divided doses. Statistical significance (ANCOVA) was observed at the 1mg, 2mg, 4mg, and 2+2+2mg dose levels.

Safety and Tolerability

Pharmacodynamic effects, safety issues and tolerability were as expected for this class of drug. No other safety issues were identified during the course of the study.

Conclusion

The AlbudAb™ platform provided long duration and exposure of the peptide. Pharmacokinetics of the peptide-AlbudAb™ support weekly dosing in man.

Summary

- We have produced half-life extended peptides that are efficacious in mouse models of obesity and diabetes
- We have shown that fusion of a peptide to an AlbudAb™ provided long duration and exposure of the peptide in man
- Glucose and insulin levels in man were consistent with those seen in healthy volunteers when peptide (without AlbudAb™) administered alone, indicating PD effects preserved with AlbudAb™ attached
- Parmacokinetics of the peptide-AlbudAb™ in man support weekly dosing
- AlbudAb™ is a flexible, robust, well-characterised half-life extension platform that has been clinically evaluated
- AlbudAb™ pharmacokinetics support every other week dosing in humans for suitable stable peptides and small proteins

Open Innovation – The vision

The AlbudAb™ platform is available to external partners:

- To bring together platform technology with target biology knowledge
- To enable collaboration with academia or industry through providing an AlbudAb™ manual, tool molecules and scientific support
- To develop medicines that transform the lives of patients

If you have a potential therapeutic peptide or small protein that could benefit from the AlbudAb™ platform contact us:

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Acknowledgements

The Biopharm Innovation AlbudAb™ externalisation team gratefully acknowledges the full project team and project leader Rebecca Hodge, GSK EE-DPU colleagues Mark Paulik, Robin O'Connor-Semmes, Jiang Lin, Shane Roller, Andrew Carpenter and team and Jim Meyers and GSK Biopharma R&D colleagues Christopher Herring and Lucy Holt, the Biopharm Innovation Unit, Biopharm Process Research and Biopharm Process Development.

All studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed. The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents.

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