

VELTIS®: INNOVATIVE ALBUMIN BASED TECHNOLOGY FOR HALF-LIFE EXTENSION AND OPTIMIZATION OF BIOTHERAPEUTICS

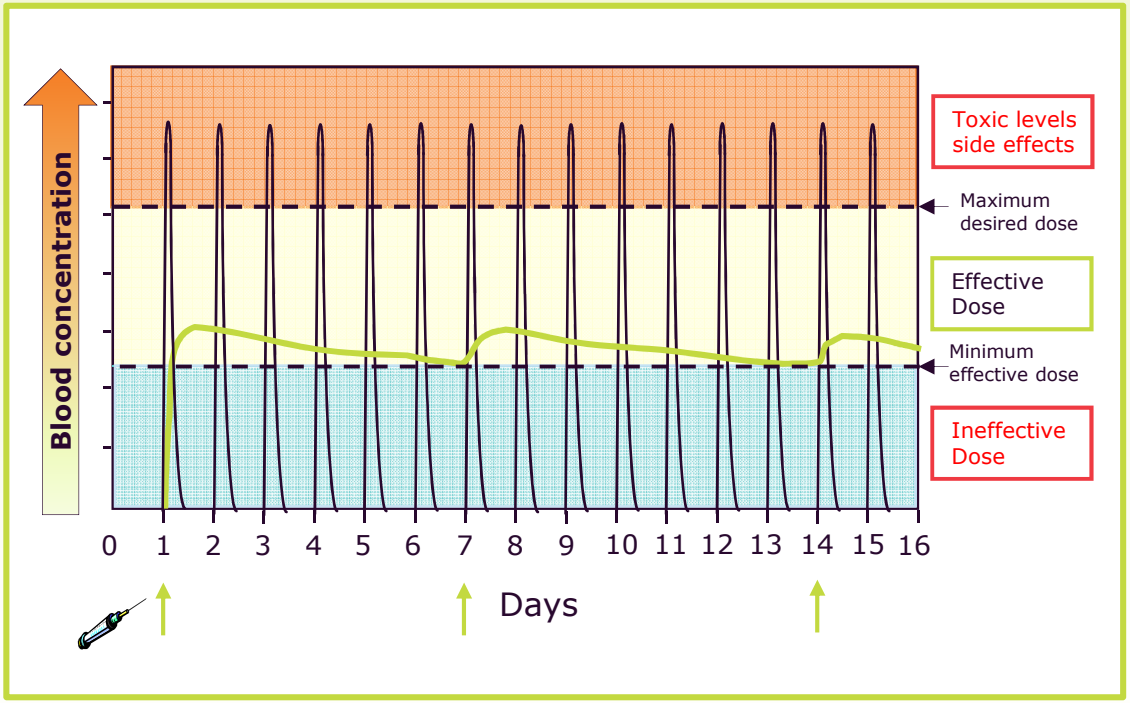
novozymes®
Re-Think Tomorrow

Dr Mikael Bjerg Caspersen
Industrial Biotechnology Conference – August 10th 2015

INNOVATIVE TECHNOLOGY ENABLING YOU TO RETHINK YOUR THERAPEUTIC WINDOW

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- Veltis® is an albumin-based drug delivery technology that improves drug efficacy and patient compliance based upon the natural transportation properties of albumin
- Control dose frequency and quantity to achieve optimal tolerability and efficacy using engineered human albumin
- Approved in GSK's Eperzan*/ Tanzeum™**
- Veltis® delivers outstanding performance from the albumin experts
  - Science & know-how
  - Regulatory & technical support
  - Credible route to commercial manufacture
  - Long life IPRs



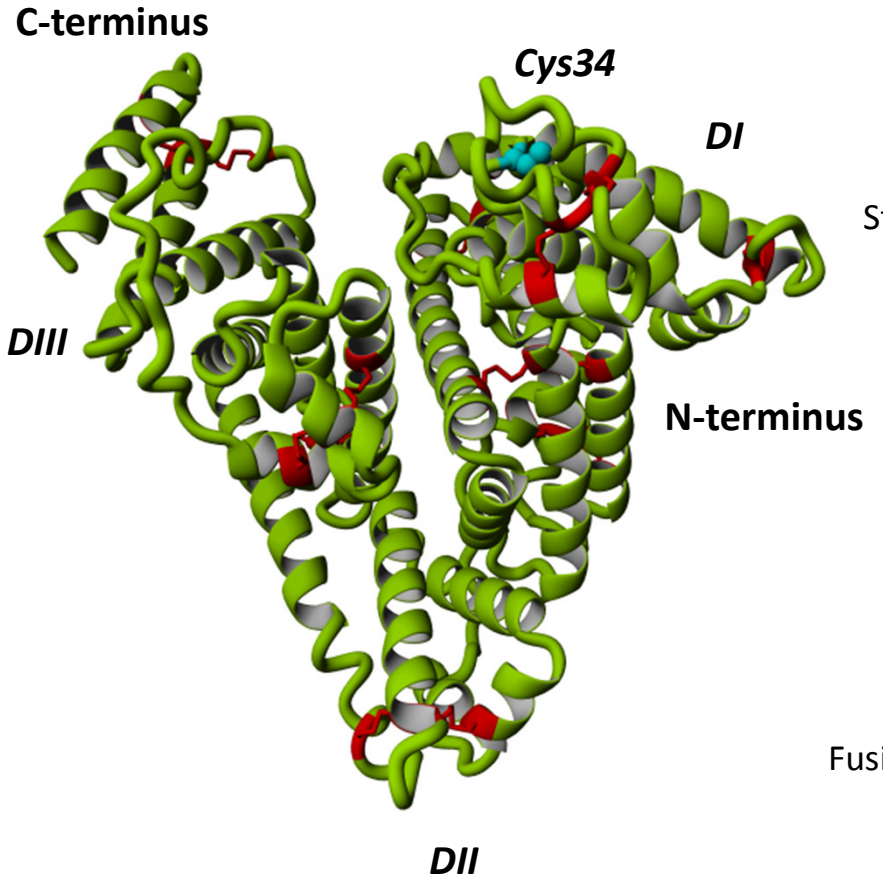
Clinically proven
Allows you to optimize your peptide or protein

- **Dose size**
- **Dose frequency**

*EU Approval in March 2014, **FDA Approval in April 2014

ALBUMIN: A NATURAL DRUG DELIVERY PLATFORM

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Physical properties

Single polypeptide chain
Very soluble
Flexible
Stable to adverse pH and temperature conditions

Biochemical properties

Very abundant
Highly disulphide bridged
Single free thiol
Long circulatory half-life

Biopharmaceutical properties

Long history of safe use
Low intrinsic activity
Recombinant versions available
Fusions and conjugates approved, safe and well tolerated
Low immunogenicity
Inherent tumour accumulation

Figure 1. Biochemical and biophysical properties of albumin for drug delivery. Albumin's inherent physical, biochemical and biopharmaceutical properties collectively ensure albumin is an excellent drug delivery platform. The 17 disulphide bonds are indicated in red while the free thiol at Cys34 within DI is shown in turquoise.

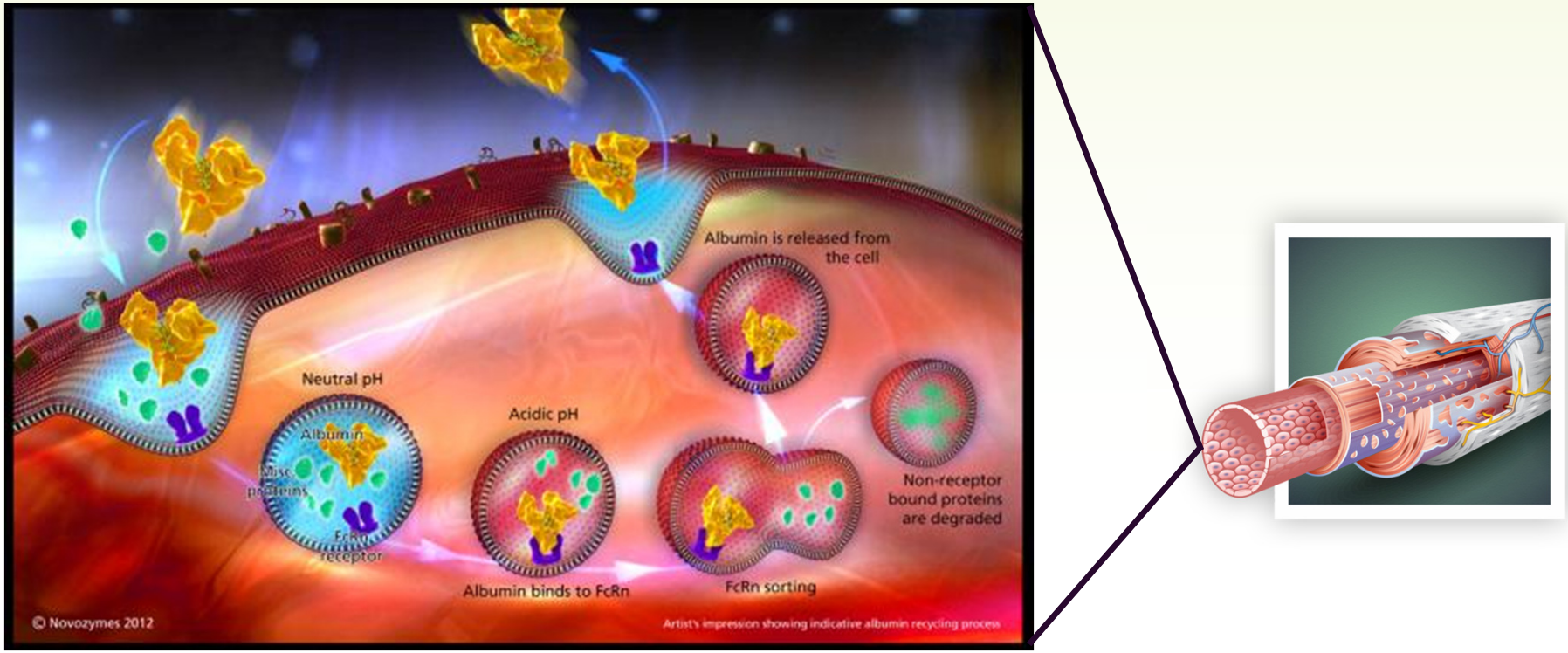
D. Sleep. Albumin and its application in drug delivery (2015) Expert Opin Drug Deliv. Vol. 12, Pages 793-812

ALBUMIN IS RESCUED FROM DEGRADATION BY THE FcRn RECEPTOR

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Human albumin has a naturally long plasma half-life ~19 days due to:

- Size - retained by kidney/glomerulus
- FcRn (neonatal Fc receptor) recycling: pH-dependent recycling "rescues" albumin from degradation and prolongs half-life



VELTIS® TECHNOLOGY PIPELINE

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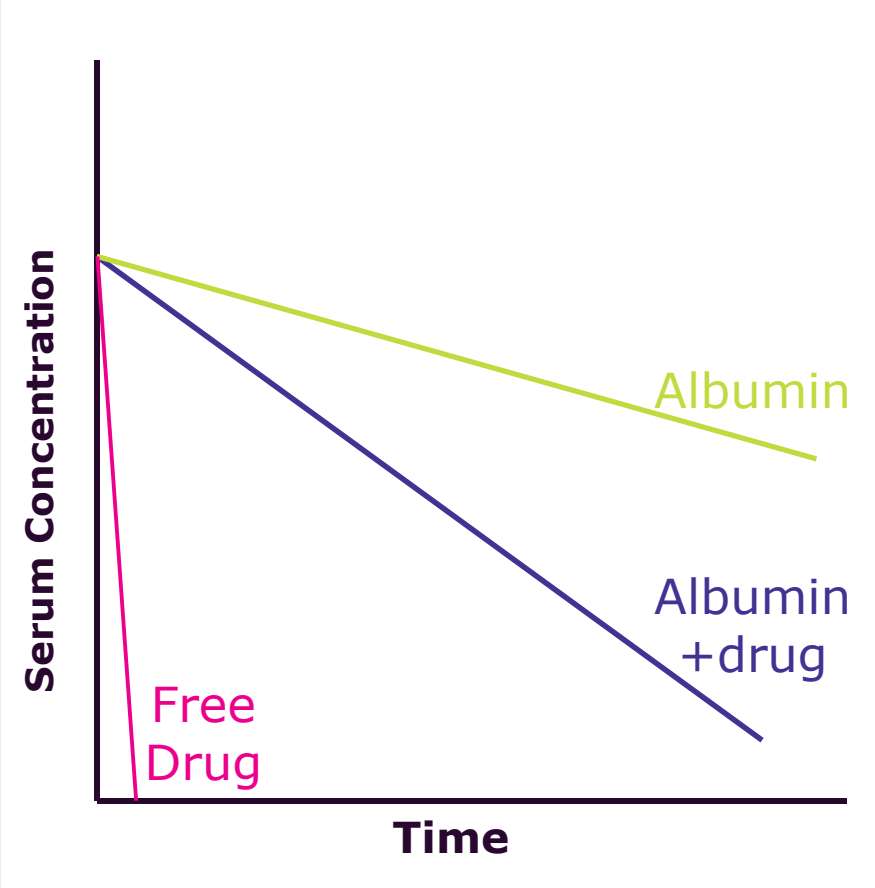
Drug	Pre-clinical	Phase I	Phase II	Phase III	BLA / MAA Submitted	Approved
Eperzan/ Tanzeum™	Diabetes					GlaxoSmithKline
CSL654	Hemophilia B					CSL Behring Biotherapies for Life™
TV-1106	Growth hormone deficiency			TEVA		
CSL689	Hemophilia A & B			CSL Behring Biotherapies for Life™		
Tregitopes	EpiVax, Inc.					
Not disclosed	Large Pharma					

Native sequence albumin

Engineered albumins

WHY ENGINEER HUMAN ALBUMIN?

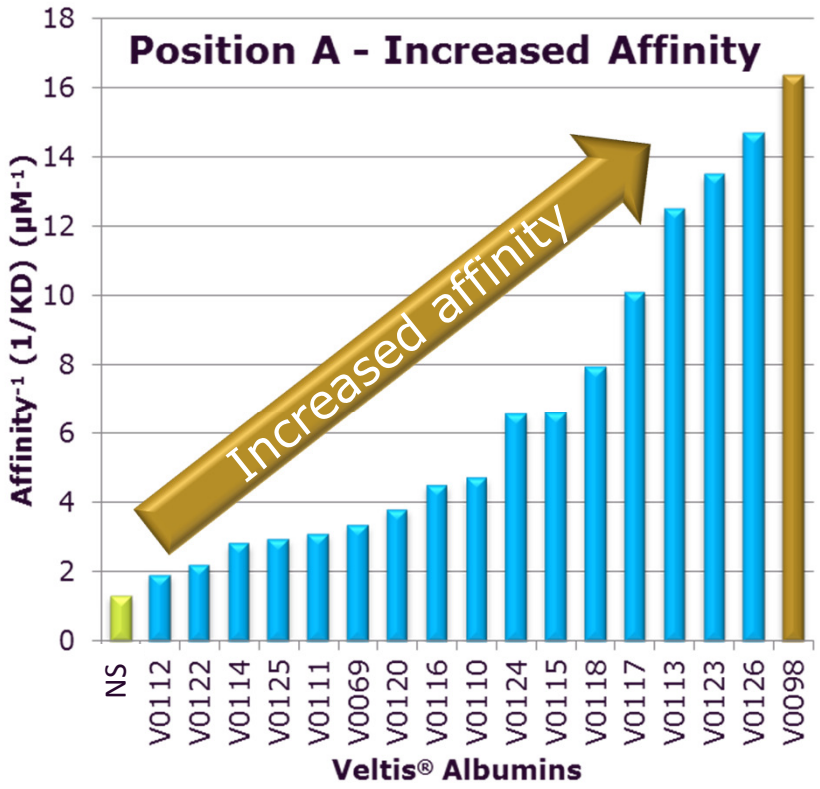
Illustrative PK curves

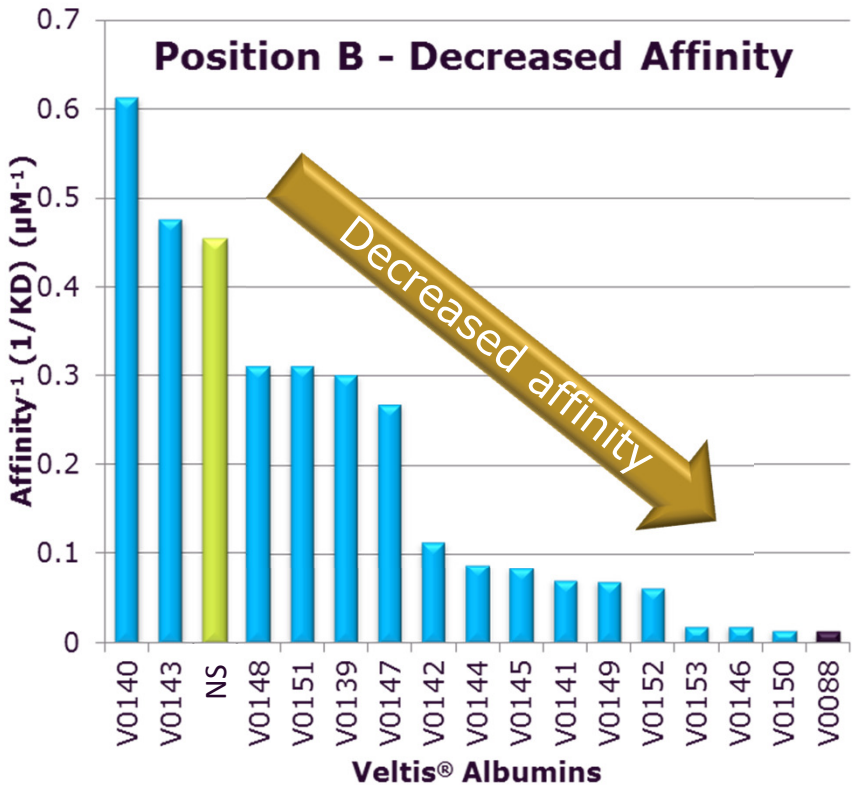


- The half-life of albumin fusions and conjugates are typically lower than that of albumin alone
- Final drug product can be cleared through either the albumin or the drug component
- Improved control over the final half-life of albumin fusion or conjugate to achieve once-weekly, once two-weekly or once-monthly peptide or protein drug dosing
- Define therapeutic dosing window by balancing dose size and frequency to achieve optimum efficacy and tolerability

HOW TO ACHIEVE CONTROL

Receptor affinity can be tuned up or down





ENGINEERING THE ALBUMIN-FcRn INTERACTION FOR ENHANCED PHARMACOKINETICS

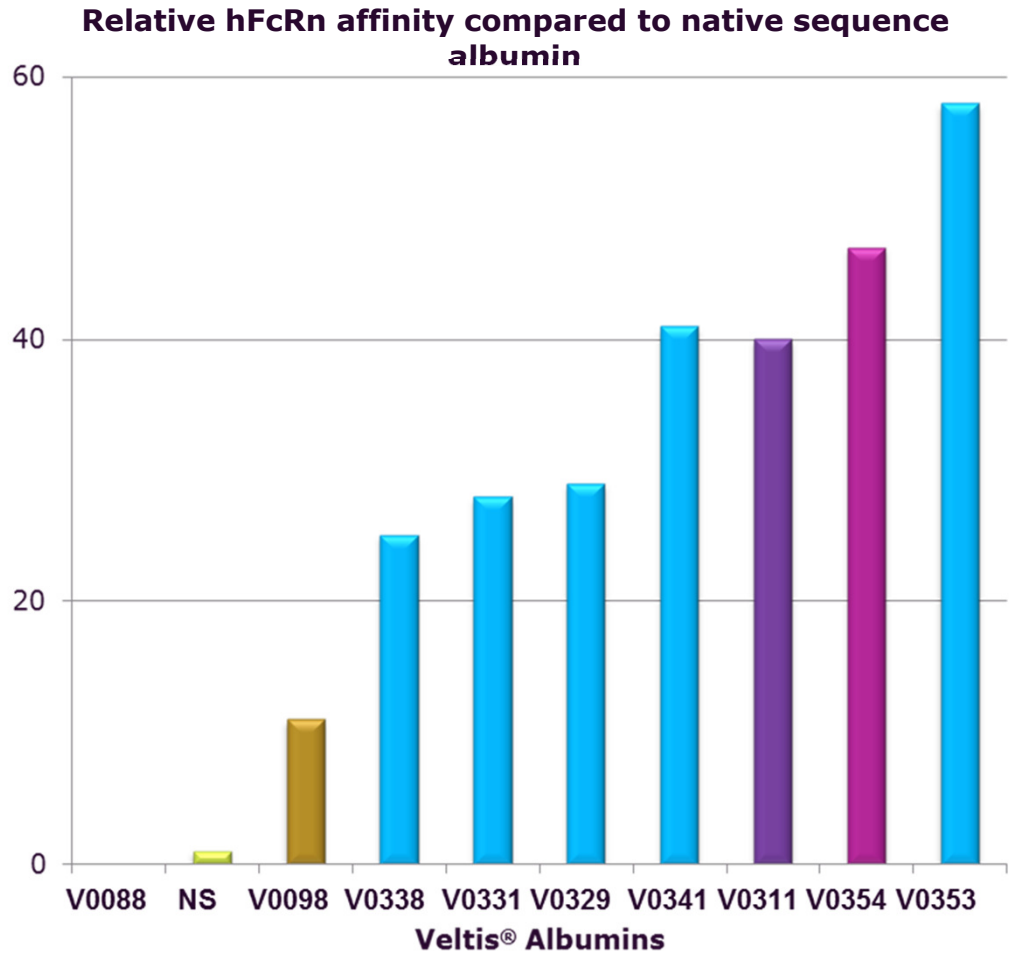
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Albumins have been engineered for increased and decreased binding affinity to the human FcRn receptor

- Variants selected for enhanced binding at endosomal pH and no significant binding at neutral pH

FcRn binding affinity can be both increased and decreased in a pH dependent manner

Variants contain between 1-5 amino acid substitutions



TRANSLATING FcRn BINDING TO *IN VIVO* PHARMACOKINETICS

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How does Veltis® technology behave in common animal species?

Primate

Closest to humans



Macaque

Double transgenic mice

Human FcRn /Human albumin



WT Mice and Tg Mice

Rodents

Cross species binding difference





Endothelial cell-based rescue assay

***In vitro* receptor binding (SPR/Biacore)**

RODENT PK STUDIES – NOT AS SIMPLE AS YOU MIGHT THINK

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Human albumin has a short half-life in rats

Albumin	Model	$T_{1/2}$(h)
Human	Rat	15
Rat	Rat	49

- **Explained by cross-species FcRn binding properties**
- **Human albumin binds very poorly to FcRn from rodents**

Animal FcRn affinities

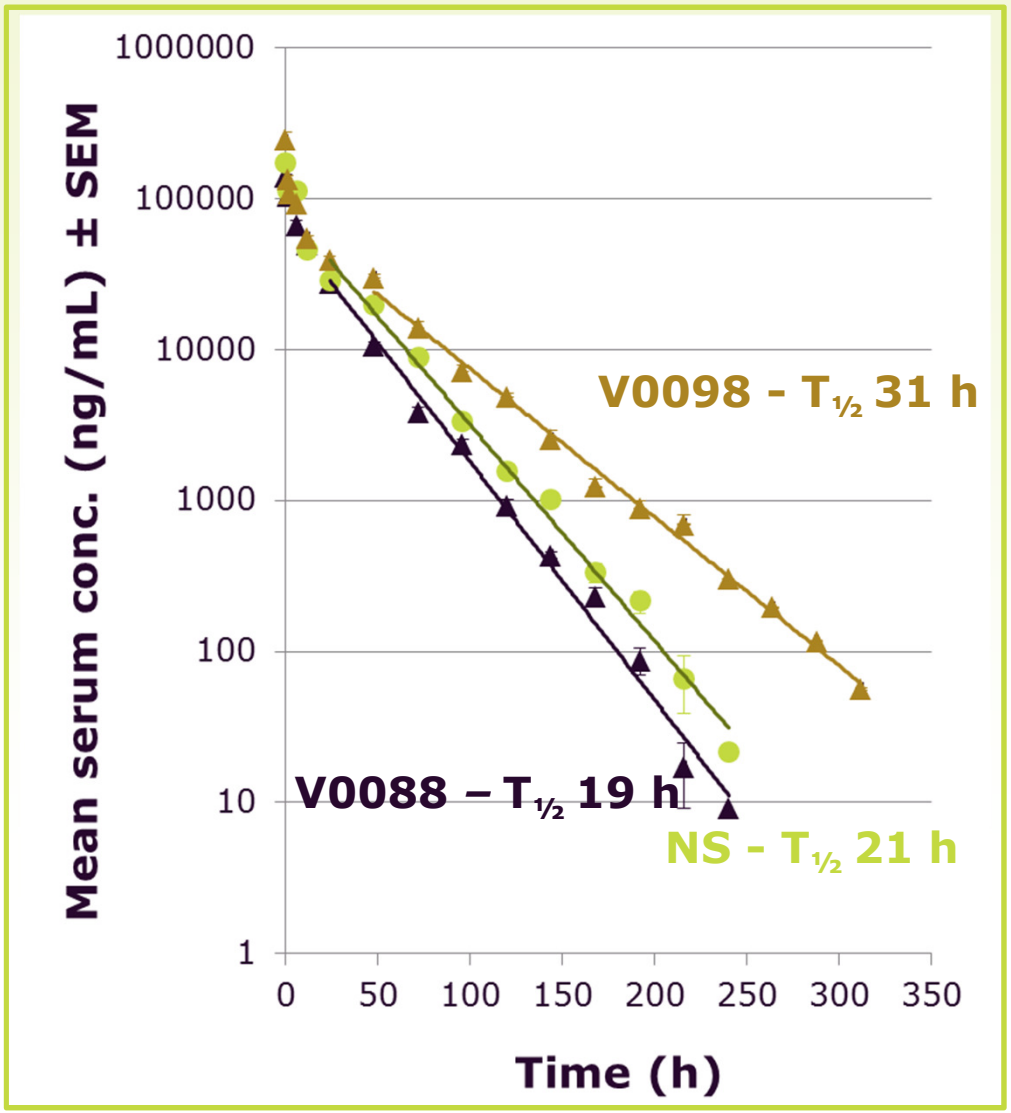
Implications for PK and transgenic animals

KD (µM)	HSA	MSA
Human FcRn	4.5	0.8
Mouse FcRn	86	9.3

Human albumin compounds will be out-competed by MSA in WT mice and hFcRn transgenic mice (Roopenian)

Andersen *et al*. (2010) J. Biol. Chem. 285(7):4826-36

FcRn BINDING TRANSLATES TO PK MODIFICATION IN ***WILD TYPE MICE***



V0098 - Improved FcRn binding variant

- Half-life extension (31 h)
- Increase in AUC
- Reduced clearance
- Increased FcRn rescue

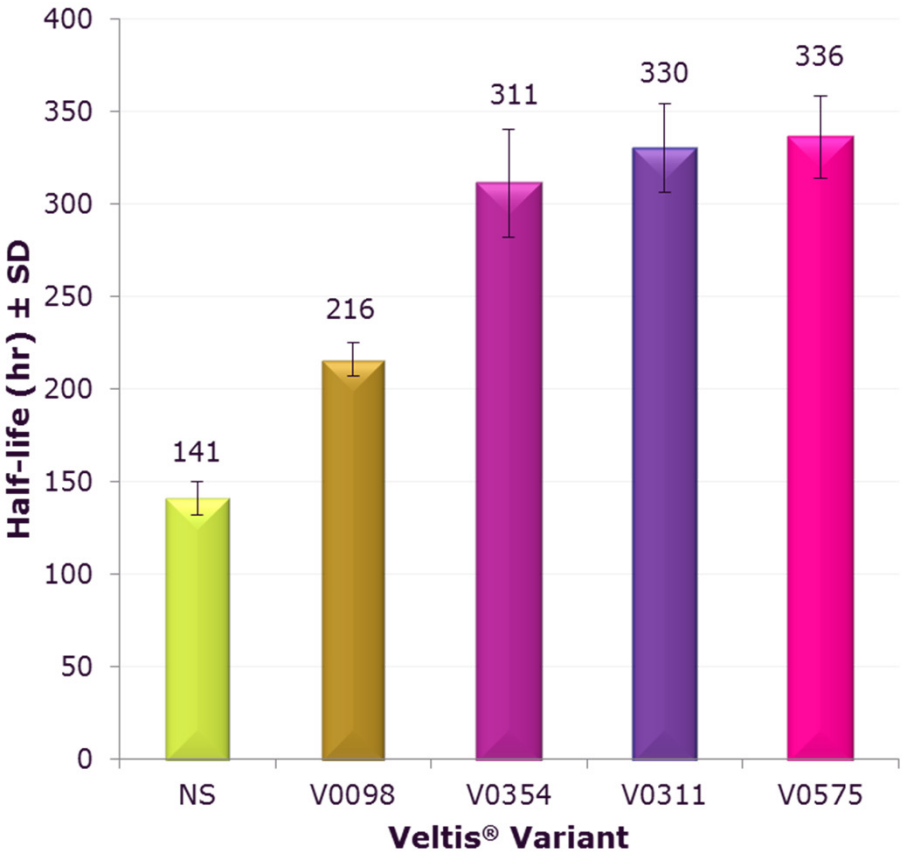
V0088 -Reduced FcRn binding variant

- Shorter half-life (19 h)
- Decrease in AUC
- Increased clearance
- Reduced FcRn rescue

Animal model: WT NMRI mice; single bolus intravenous administration; 10mg/kg

ENGINEERED ALBUMINS ACHIEVE MORE THAN A ***DOUBLING*** OF HALF-LIFE IN A PRIMATE MODEL

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The prolongation in half-life is a result of a reduced clearance, increased mean residence time (MRT) and increased AUC

Doubling of half-life in primates opens the door to **monthly** dosing of therapeutic peptides and proteins in humans

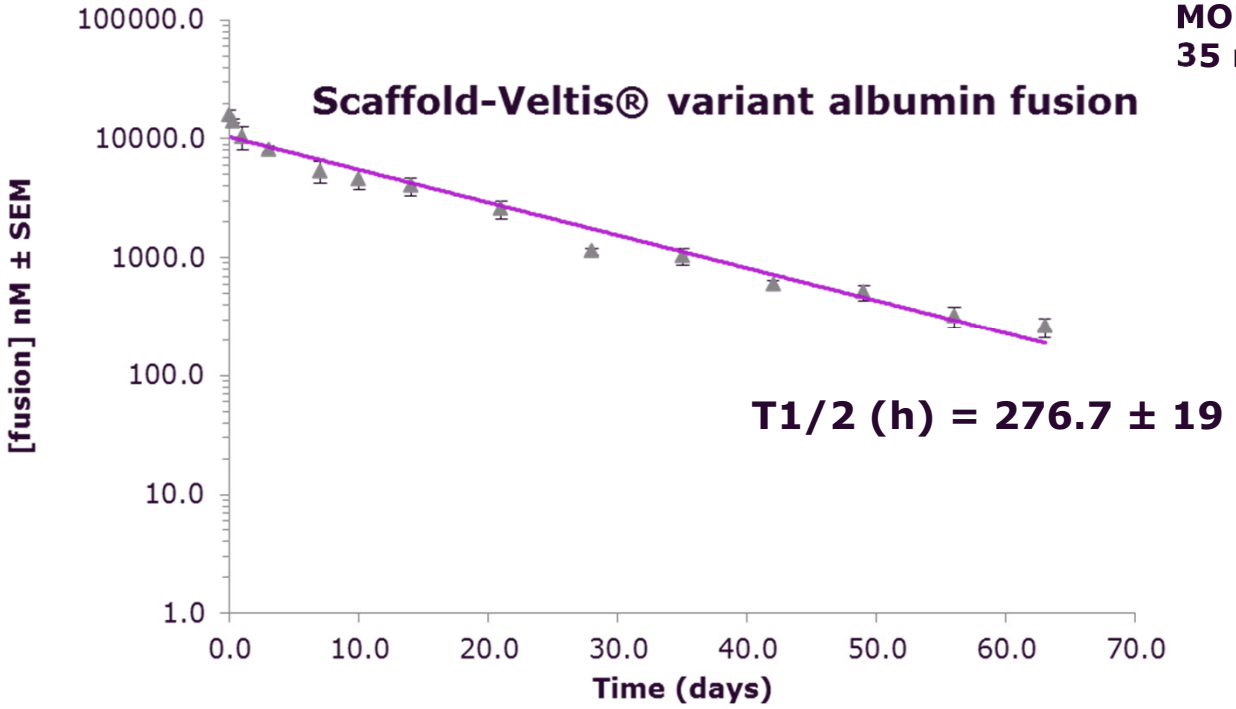
Cynomolgus PK study with a model API demonstrated a half-life of more than 270 hours

ONCE-MONTHLY DOSING: REASONS TO BELIEVE

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Veltis® variant albumin fusion to a scaffold molecule delivered a half-life of *over 11 days*

PHARMACOKINETIC PROFILE IN CYNOMOLGUS MONKEY (n=3, IV BOLUS 35 mg/kg)

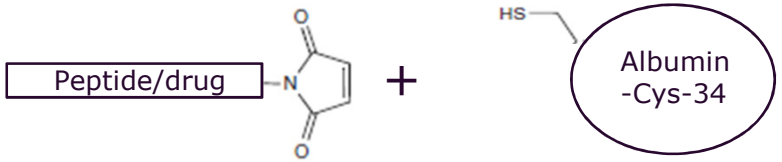


ATTACHMENT TO VELTIS® CAN BE THROUGH EITHER CONJUGATION OR FUSION

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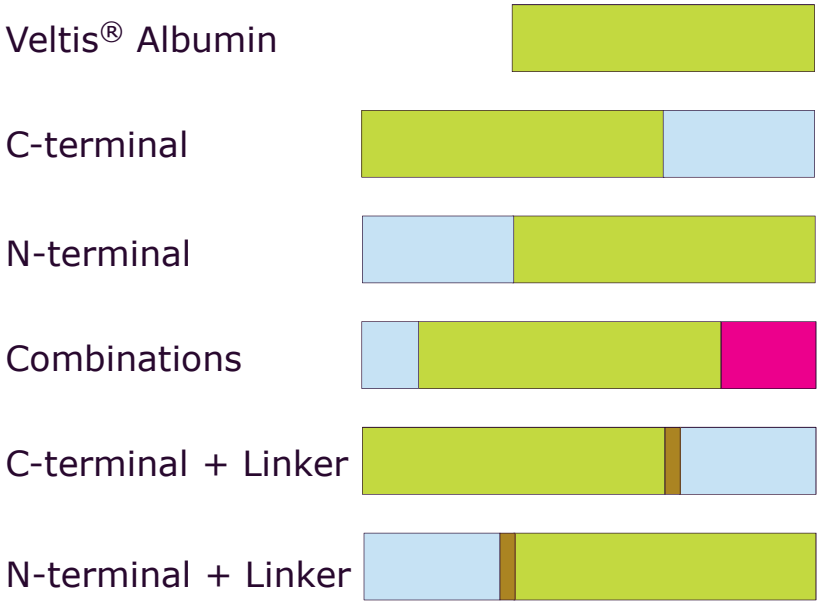
Conjugation to Veltis®

- Chemically modify peptide or drug to allow covalent attachment to Veltis® albumin molecule:
  - Lysine
  - Tyrosine
  - Free thiol (SH)
- Free thiol is the most widely used conjugation route:
  - Specifically reactive with maleimide groups
  - 1:1 Stoichiometric peptide loading



Fusion to Veltis®

- Veltis® albumin fusion proteins are produced as a single polypeptide



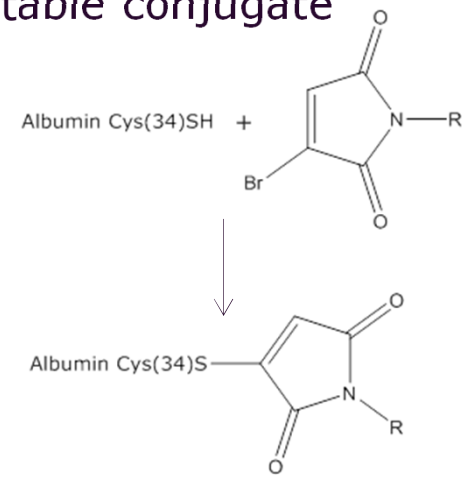
PARTNERING FOR SUCCESS IN CHEMICAL CONJUGATION

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ThioLogics

Next generation maleimide conjugation technology for site-specific protein conjugation

Link target molecule to Veltis® albumin at high reaction yield for serum-stable conjugate



ALMAC

Complete service range

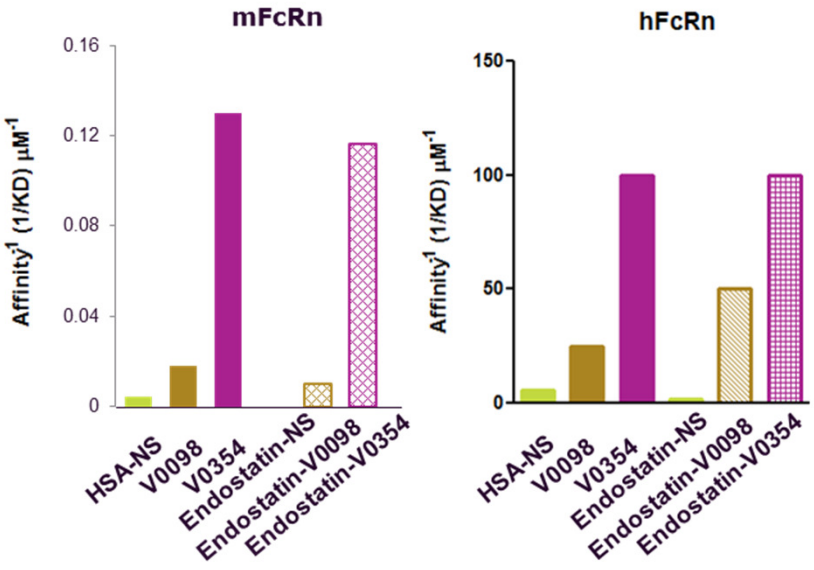
- Non-GMP custom synthesis
- Conjugation
- GMP manufacture
- >9000 peptides manufactured
- Expertise in challenging peptides



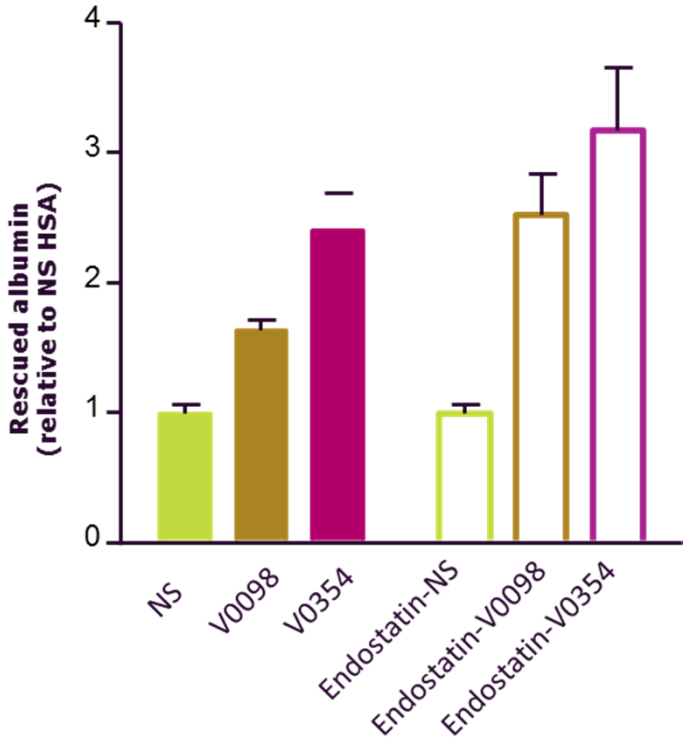
VELTIS® VARIANTS FOR GENETIC FUSION PROOF OF CONCEPT: ENDOSTATIN

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Receptor affinity maintained when Endostatin is fused to Veltis®

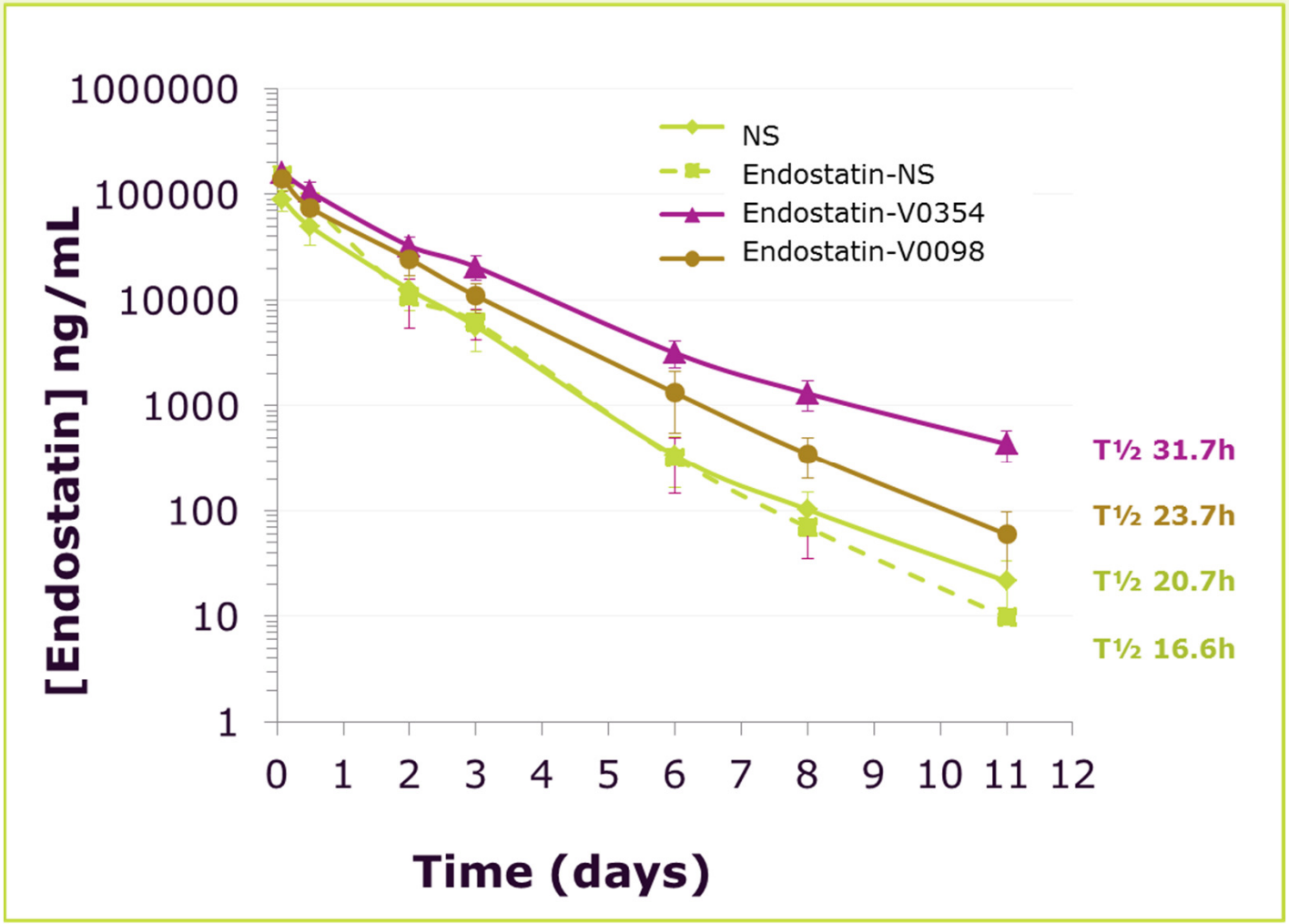


Endothelial cell-based rescue assay



ENDOSTATIN FUSED TO VELTIS® VARIANTS SIGNIFICANTLY PROLONGS HALF-LIFE

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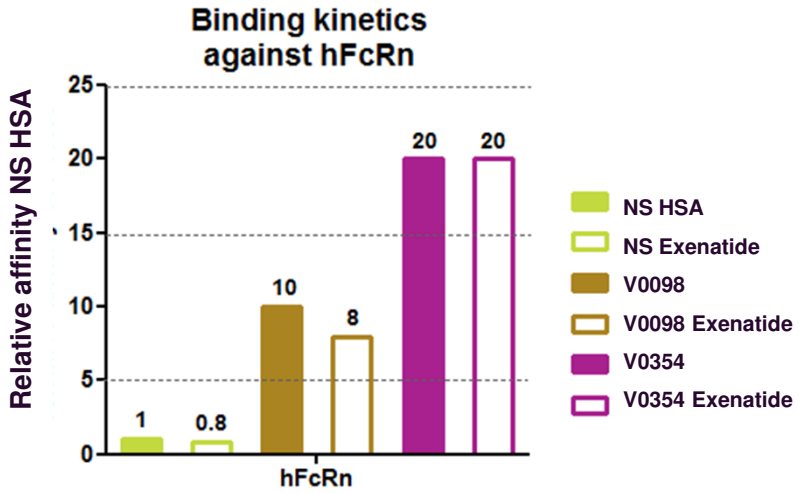
Endostatin genetically fused to Veltis® albumins**V0098** and **V0354** shows a 1.4- and 1.9- fold longer half-life, respectively, compared to fusion to NS human albumin

5 subjects/compound, IV Bolus (10 mg/kg) male NMRI mice

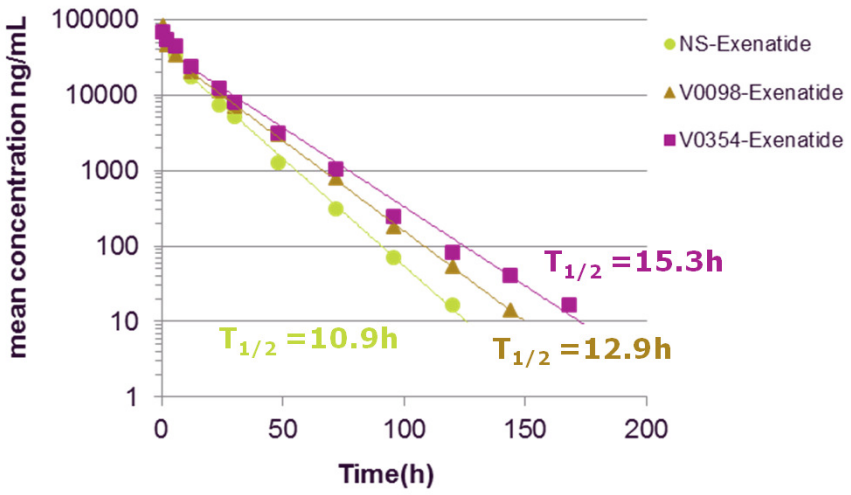
VELTIS® VARIANTS FOR CONJUGATION PROOF OF CONCEPT: EXENATIDE

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Receptor affinity maintained when Exenatide is conjugated to Veltis®



Pharmacokinetic profiles of albumin exenatide conjugates in WT mice

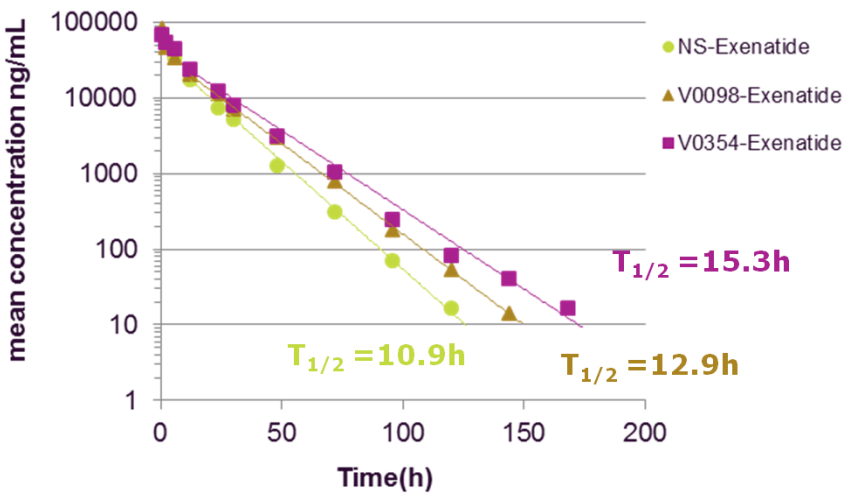


WT mice IV Bolus (5mg/Kg)

VELTIS® VARIANTS FOR IMPROVED PK/PD PROOF OF CONCEPT: EXENATIDE

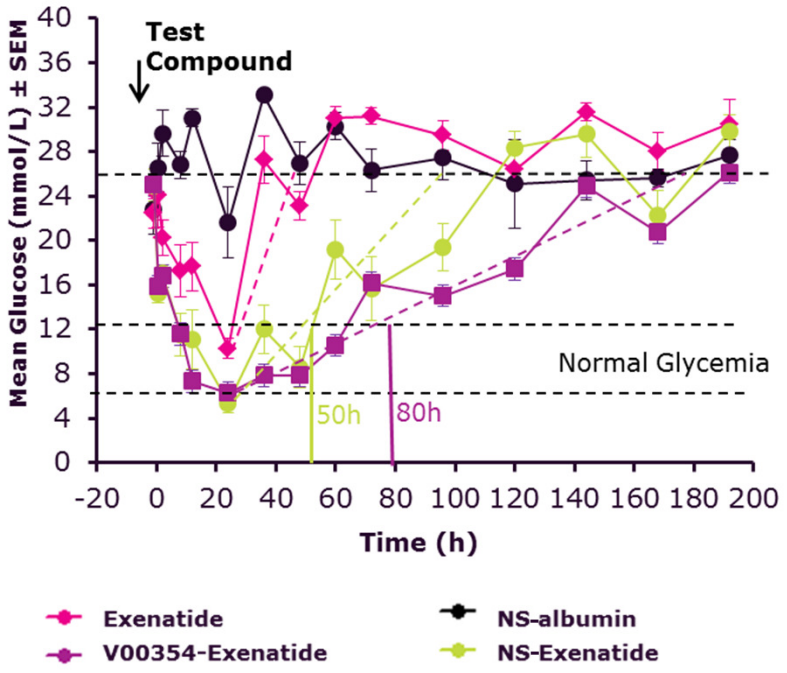
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Pharmacokinetic profiles of albumin exenatide conjugates in WT mice



WT mice IV Bolus (5mg/Kg)

Pharmacodynamic profiles in diabetic mice



Diabetic mice SC (500nmol/Kg)

Veltis® exenatide conjugates retain therapeutic effect and prolong efficacy

COMPLETE SUPPORT PACKAGE FROM THE ALBUMIN EXPERTS

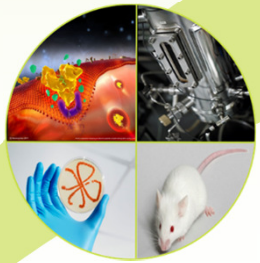
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Clinical Development
- Phase I-II supply through Novozymes or partners
- Tech transfer to CMO
- cGMP supply of Veltis® albumins



Veltis® Tool Box
- FcRn and cell assays
- Yeast expression
- Conjugation technology
- 2xKOKI mouse





Pre-clinical Development
- Fermentation optimization
- Process development
- Provision of materials for toxicology and *in vivo* studies from Novozymes or partner



Rapid Proof of Concept
- Fusion and conjugate design
- Research licences
- Veltis® albumin samples

THANK YOU

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POSTER A55

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