Dasiglucagon
A novel glucagon analog
Phase II Update.

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TIDES, San Diego 2nd May 2017

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Zealand in brief

- Founded in 1998 in Denmark
- Listed on Nasdaq Copenhagen: ZEAL
- Market Cap (14 March 2017): DKK 3.1 bn / $ 440 m
- 122 employees, mainly in R&D

Marketed products: Two in U.S and one ex-U.S.

Four product candidates in Phase 2

>18 years' track record with peptides

>10 Zealand invented medicines advanced to the clinic

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Two products based on Zealand inventions marketed in the U.S.

Adlyxin® (Lyxumia® in EU) - a GLP-1 receptor agonist

- Marketed in the U.S. as of January 2017
- Marketed as Lyxumia® in over 40 countries

Soliqua™ 100/33 - a combination of GLP-1 and insulin

- Marketed in the U.S. as of January 2017
- Formulary coverage continuously improving with United coverage from 1 July 2017

Suliqua™ - a combination of GLP-1 and insulin

- Approved in the EU in January 2017
- First launches expected in Q2 2017

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Our main focus is on specialty gastrointestinal and metabolic diseases

Speciality medicines

We use our peptide-based research capabilities to discover specialty medicines

- **Over 1,000 rare diseases and disorders**
- **Affecting more than 300 million people**
- **Many are life threatening, with no available therapy**

Gastrointestinal diseases

Glepaglutide is our front runner in building a gastronintestinal (GI) portfolio.

We have a number of pre-clinical GI projects where we exploit our peptide platform to develop therapies addressing patient needs.

- >180 GI diseases affect millions of people.

60 million
people in the U.S. suffer from GI diseases[1]

Metabolic diseases

Metabolic diseases have been the focus since our early days. We have a strong track record in this area

- Two products on the market with our partner Sanofi
- Two Phase 2 programs
- Two partnered programs approaching Phase 1

- Hundreds of metabolic diseases, many of which are rare with no therapy available.

36.5%
of U.S. adults are obese[2]

1 National Institutes of Health, U.S. Department of Health and Human Services. Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases. Bethesda, MD: National Institutes of Health; 2009. NIH Publication 08–6514.
2 https://www.cdc.gov/nchs/data/databriefs/db219.pdf

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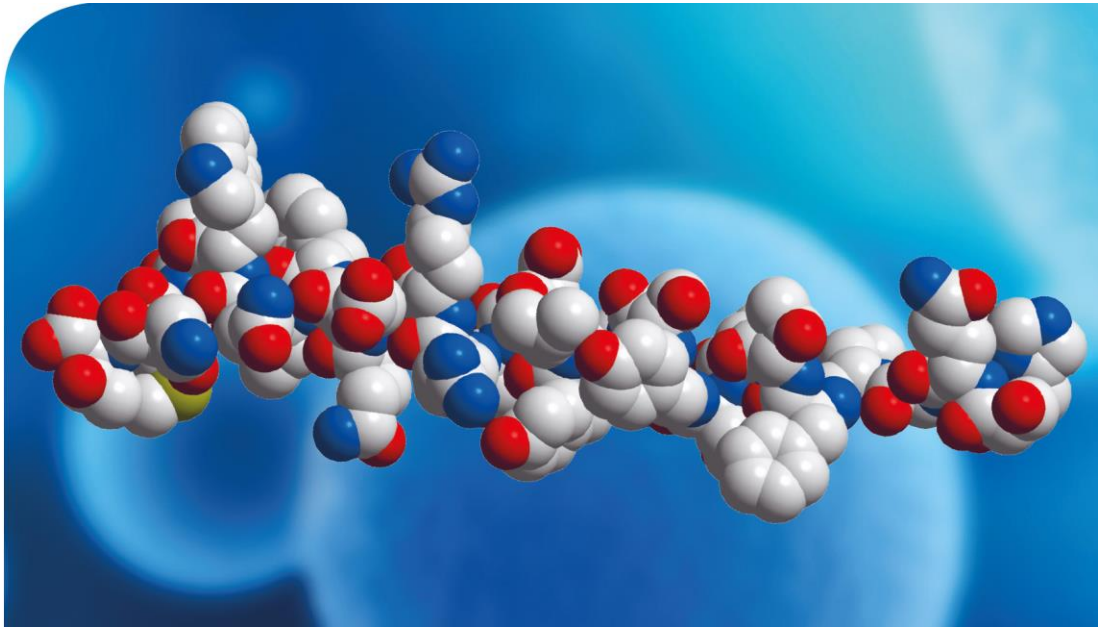
Platform of scientific expertise in peptide therapeutics

18 year track record

5,000 peptides synthesized

10 projects advanced to clinical development

400 patents



Patent portfolio of 40 families including peptide half-life extension technologies

- **Enhanced biological activity**
- **Increased potency**
- **Longer duration of action**
- **Extended shelf life**
- **Increased liquid stability**

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Zealand's pipeline of product candidates

Product	Indication	Development stage	2017 milestones	Commercial rights
Glepaglutide[1]	Short Bowel Syndrome	Phase 2	Phase 2 results	ZEAL&
Dasiglucagon[1]	Acute, Severe Hypoglycemia Diabetes	Phase 2	Phase 3 initiation	ZEAL&
	Dual Hormone Artificial Pancreas Pump-based diabetes management	Phase 2a	Phase 2a results	ZEAL&
Elsiglutide[2]	Chemotherapy Induced Diarrhea	Phase 2	New Phase 2 trials	HELSINN
GLP1-GLU[3]	Obesity/ Type 2 Diabetes	Pre-IND	Phase 1 initiation	Boehringer Ingelheim
Undisclosed[3]	Obesity/ Type 2 Diabetes	Pre-IND	Phase 1 initiation	Boehringer Ingelheim

[1] Glepaglutide and dasiglucagon are proposed International Non-proprietary Names (pINN)

[2] Zealand is entitled to mid to high single-digit percent royalties on global sales. Total milestones: Up to €m 140 (€m 124 remaining).

[3] Zealand is entitled to high single to low double-digit percent royalties on global sales. Total milestones: Up to €m 681 (€m 652 remaining).

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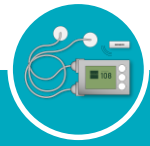
Zealand's internal pipeline of product candidates

	Glepaglutide[1]	Dasiglucagon[1]	
Product	 GLP-2 analog	 Glucagon analog Single-dose version	 Glucagon analog Multiple-dose version
Status	Phase II	Phase II	Phase II in preparation
Indication	Short bowel syndrome	Acute, severe hypoglycaemia, or "Insulin shock"	Pump-based diabetes management
Intended offering	Repeat use injection pen	Ready-to-use rescue pen	Component of a dual-hormone artificial pancreas
Unmet needs to address	• Lessen/avoid parenteral nutrition support • Reduce diarrhea/stoma output • Improve patient health and quality of life	• Easy-to-use rescue treatment • Faster recovery from severe hypoglycemia • Less fear associated with insulin treatment	• More patients to reach glycaemic target with lower risk of hypoglycaemia • Easier and automated diabetes management

[1] Glepaglutide and dasiglucagon are proposed International Non-proprietary Names (pINN)

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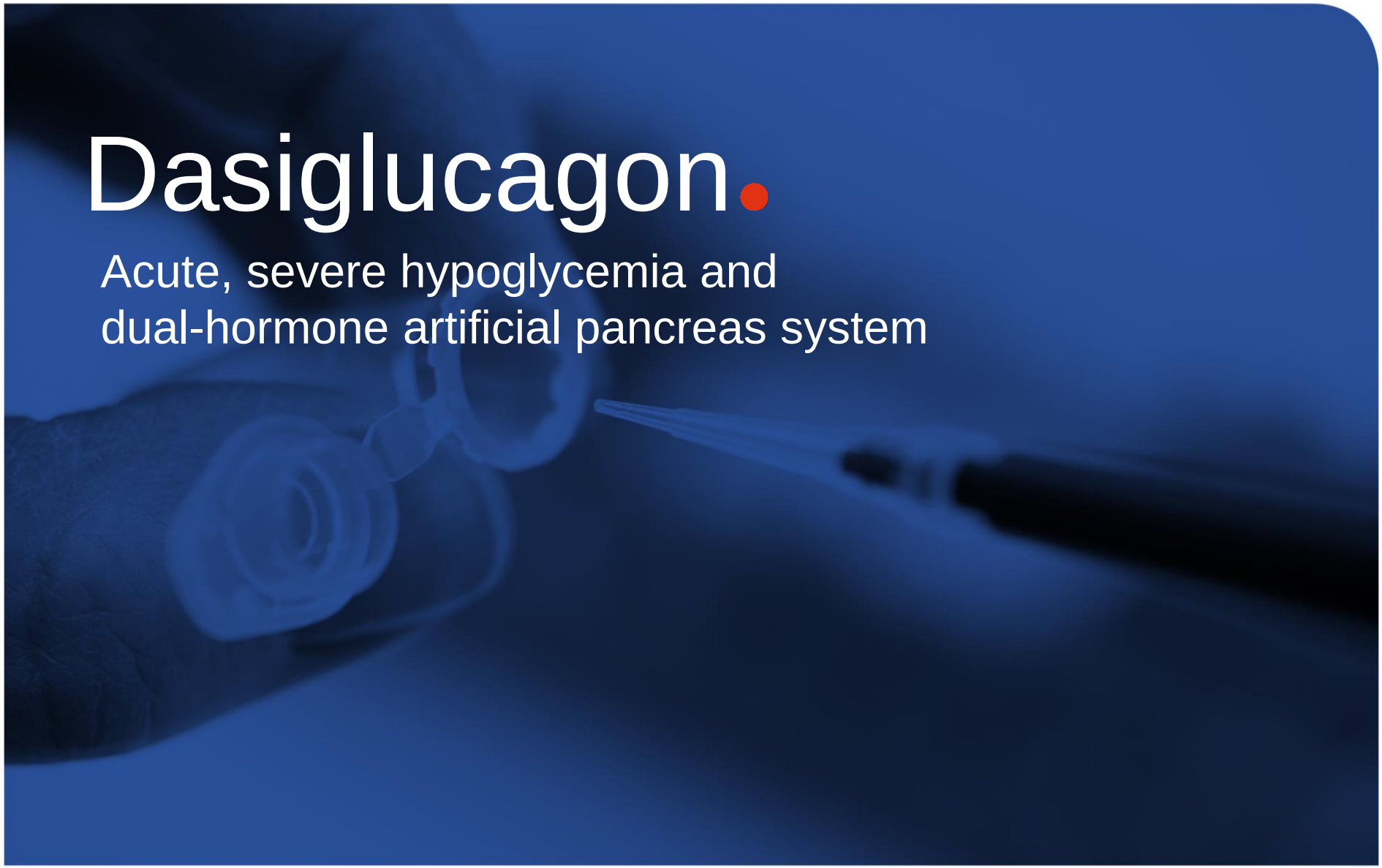
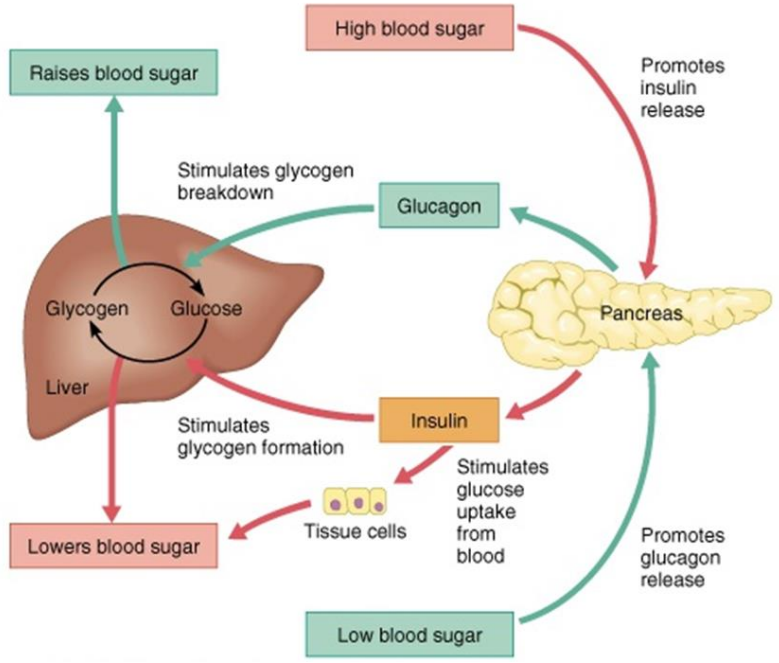
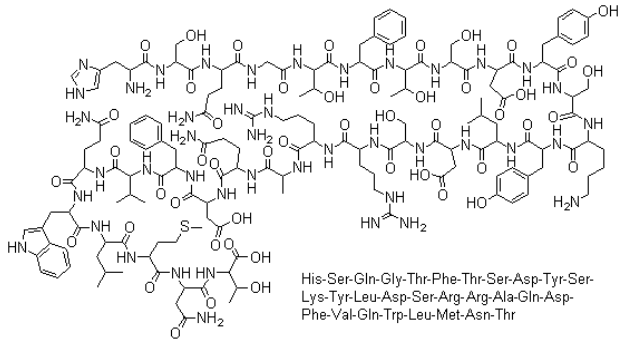
Dasiglucagon.

Acute, severe hypoglycemia and dual-hormone artificial pancreas system



Glucagon Biology





His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr

Glucagon

- A 29 amino acid peptide
- Member of the secretin family of hormones
- Secreted by α-cells of the islets of Langerhans in the pancreas when the concentration of glucose in the bloodstream falls too low.
- Glucagon causes the liver to convert stored glycogen into glucose, which is released into the bloodstream.
- Conversely, high blood-glucose levels stimulate the release of insulin.
- Insulin allows glucose to be taken up and used by insulin-dependent tissues.
- Thus, glucagon and insulin are part of a feedback system that keeps blood glucose levels stable.
- Native glucagon has a very short half life and is intrinsically unstable in aqueous liquid solution

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Acute, severe hypoglycemia (insulin shock) – A major concern for diabetes patients on insulin

Severe hypoglycaemia = diabetic emergency

- Patients experience **anxiety, tremors, palpitations, nausea and confusion**
- Can lead to **unconsciousness, seizures and death**

In the U.S.:
~280,000 visits to the emergency ward after a hypoglycemic event (2013)[1]

Glucagon is an effective treatment

- A native peptide that increases blood sugar
- Native glucagon is inherently unstable in liquid formulation

Current glucagon rescue kits are complex to use

- Based on native glucagon and only available as powder
- Require multi-step preparation before injection
- High risk of administration failure[3]

".. the complexity of the kit is a problem .." [2]

[1] Center for Disease Control and Prevention.cdc.org
[2] Research Commissioned by Zealand Pharma n = 11.373 posts on hypoglycemia in diabetes fora
[3] Results from human factor studies published by Locemia and Xeris

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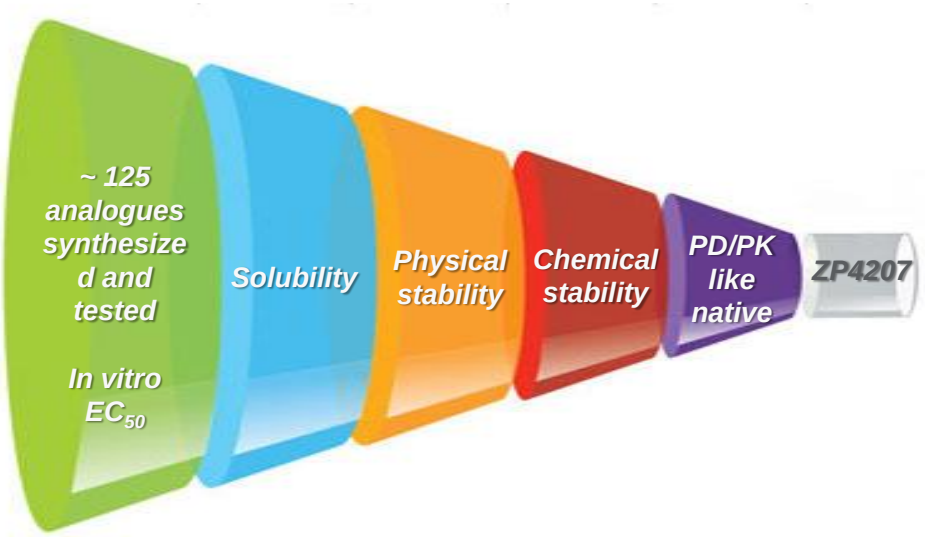
The route to Dasiglucagon[1]

Goals

- Maintain potency at the glucagon receptor
- Solve disadvantages of native glucagon
  - Improve solubility
  - Improve chemical stability
  - Improve physical stability
- Enable formulation in aqueous media at neutral pH
- Maintain PK and PD equivalent to native glucagon



[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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Dasiglucagon[1] – improved chemical stability

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		27	28	29
H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	R	A	Q	D	F	V	Q	W	L	M	N	T
H	**S**	**Q**	**G**	**T**	**F**	**T**	**S**	**D**	**Y**	**S**	**K**	**Y**	**L**	**D**	**Aib**	**A**	**R**	**A**	**E**	**E**	**F**	**V**	**K**	**W**	**L**	**E**	**S**	**T**

Aib16

- Reduces cleavage of the peptide bond between amino acid 15 and 16

Glu20

- Eliminates hydrolysis of the side chain amide function of Gln

Glu21

- Reduces cleavage of the peptide bond between amino acid 21 and 22
- Eliminates the formation of isoAsp21 and D-isoAsp21

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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Dasiglucagon[1] – improved chemical stability

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		27	28	29
H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	R	A	Q	D	F	V	Q	W	L	M	N	T
H	**S**	**Q**	**G**	**T**	**F**	**T**	**S**	**D**	**Y**	**S**	**K**	**Y**	**L**	**D**	**Aib**	**A**	**R**	**A**	**E**	**E**	**F**	**V**	**K**	**W**	**L**	**E**	**S**	**T**

Lys24

- Eliminates hydrolysis of the side chain amide function of Gln

Glu27

- Eliminates the oxidation of Met
  - Pedersen, J.S., Dikov, D., Otzen, D.E., Biochemistry (2006), 45, 14503.

Ser28

- Eliminates hydrolysis of the side chain amide function of Asn

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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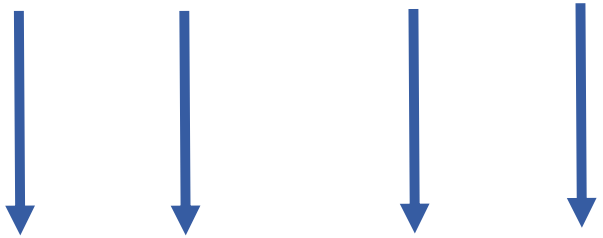
Dasiglucagon[1] – improved solubility & physical stability

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		27	28	29
H	S	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	R	A	Q	D	F	V	Q	W	L	M	N	T
H	**S**	**Q**	**G**	**T**	**F**	**T**	**S**	**D**	**Y**	**S**	**K**	**Y**	**L**	**D**	**Aib**	**A**	**R**	**A**	**E**	**E**	**F**	**V**	**K**	**W**	**L**	**E**	**S**	**T**



The substitutions Ala17, Glu20, Lys24 and Glu27 results in the addition of two acidic amino acids to the peptide which lowers the pI by approximately two units from ~7 to 4.7

This leads to a significant improvement in the aqueous solubility at neutral pH

The presence of multiple charges at physiologically relevant pH values increases the electrostatic repulsions between peptide molecules, reducing the tendancy towards self-association and aggregation

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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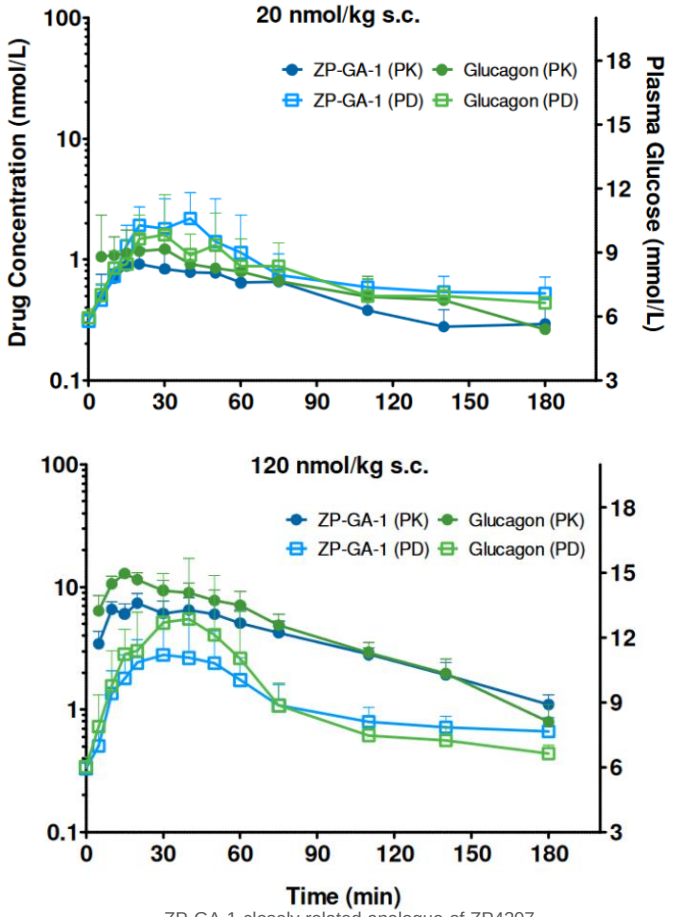
Dasiglucagon[1] Pre-Clinical Summary

Dasiglucagon represents a major improvement over native glucagon

- The chemical stability at physiological pH has been improved by eliminating the chemically labile amino acids in glucagon
- The solubility at physiological pH (7.4) has been improved by lowering the pI
- The physical stability has been improved by a combination of altering the electrostatic repulsions together with the removal of amino acids critical for the aggregation propensity (position 27 and 16)
- Potency has been maintained at the glucagon receptor
- PK/PD profiles are maintained in both dogs and rats

PK/PD in dogs



ZP-GA-1 closely related analogue of ZP4207

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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Dasiglucagon[1] – Phase I

Dasiglucagon – A glucagon peptide analog

For illustration only

- Shown to be stable in liquid solution
- Potential for use in an auto-injector pen
- Intended to provide an easy and convenient rescue from severe hypoglycaemia
- Potential to offer faster rescue than existing rescue treatment options

Phase I Summary

- A single-dose Phase I trial was concluded in 2015.
- A two-part study to evaluate safety and tolerability in both healthy volunteers and Type 1 diabetes patients as well as PK/PD, as compared to native glucagon.
- 64 healthy volunteers were treated with single-ascending doses of dasiglucagon.
- 20 patients with Type 1 diabetes were made hypoglycemic before treatment to get an indication of the efficacy of dasiglucagon in a cross-over design with native glucagon as active comparator.
- Dose-proportionality following single and multiple dosing in the range from 0.1 to 2.0 mg dasiglucagon

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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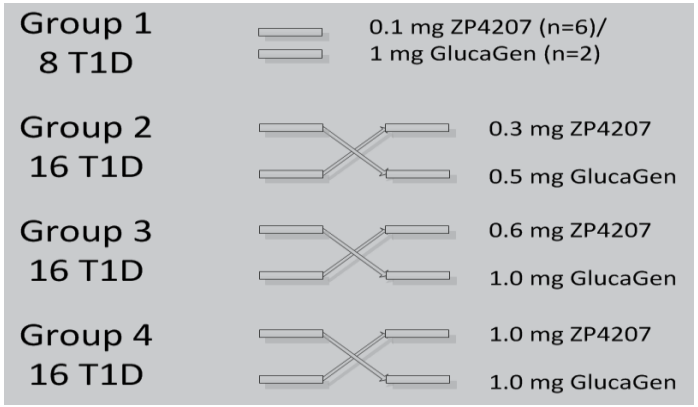
Dasiglucagon[1] for single-dose rescue treatment – Phase II results support potential as ready-to-use pen

Phase II – Design

Primary objective:
Characterize the pharmacological profile of single-dose dasiglucagon compared to existing treatment (GlucaGen[2])



- n = 58 adults with type 1 diabetes (single-center)
- Insulin challenge trial
- Cross-over design in 3 dose groups

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)
[2] Approved glucagon rescue treatment marketed by Novo Nordisk

Phase II – Results

Single-dose dasiglucagon

- **Induced a clinically relevant blood glucose response as fast and effective as existing treatment**
- **Observed to be well-tolerated with a safety profile similar to marketed glucagon**

All patients in dose groups 2-4

- Reached blood glucose concentrations of >70 mg/dL within 30 minutes of dosing
- Achieved glucose increases of >20 mg/dL within a median time of 9-10 mins

Guidance from FDA on process for initiating the next development step in Q1 2017
Full Phase II data to be presented at ADA 2017

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Dual-hormone artificial pancreas devices may significantly reduce burden of living with Type 1 diabetes

Dual hormone pancreas vs usual care (n = 39 adults with type 1 diabetes)[1]

Articles

Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial

Firas H El-Khatib, Courtney Balliro, Mallory A Hillard, Kendra L Magyar, Lapo F Ekhlaspour, Manasi Sinha, Debbie Mondesir, Aryan Esmaeili, Celia Hartigan, Michael J Thompson, Sarosh Malkani, J Paul Murphy, David M Maahs, Paula Clinton, Eliana Frank, Darrell M Wilson, Daniel DeSalvo, Lisa Norlander, Trang Ly, Bruce A Buckingham, Jennie Diner, Milana Dezube, Laura A Young, April Goley, M'Sue Kirkman, John H Shaw, Hui Zheng, Rajendrasinh K Setoguchi-Iwata, Edward R Damiano, Steven J Russell

Summary

Background The safety and effectiveness of a continuous, day-and-night automated glycaemic control system using insulin and glucagon has not been shown in a free-living, home-use setting. We aimed to assess whether bihormonal bionic pancreas (initialised only with body mass) can safely reduce mean glycaemia and hypoglycaemia in adults with type 1 diabetes who were living at home and participating in their normal daily routines without restrictions on diet or physical activity.

Methods We did a random-order crossover study in volunteers at least 18 years old who had type 1 diabetes and lived within a 30 min drive of four sites in the USA. Participants were randomly assigned (1:1) in blocks of two using sequentially numbered sealed envelopes to glycaemic regulation with a bihormonal bionic pancreas or usual care (conventional or sensor-augmented insulin pump therapy) first, followed by the opposite intervention. Both study periods were 11 days in length, during which time participants continued all normal activities, including athletics and driving. The bionic pancreas was initialised with only the participant's body mass. Autonomously adaptive dosing algorithms used data from a continuous glucose monitor to control subcutaneous delivery of insulin and glucagon. The coprimary outcomes were the mean glucose concentration and time with continuous glucose monitoring (CGM) glucose concentration less than 3·3 mmol/L, analysed over days 2–11 in participants who completed both periods of the study. This trial is registered with ClinicalTrials.gov, number NCT02092220.

Findings We randomly assigned 43 participants between May 6, 2014, and July 3, 2015, 39 of whom completed the study: 20 who were assigned to bionic pancreas first and 19 who were assigned to the comparator first. The mean CGM glucose concentration was 7·8 mmol/L (SD 0·6) in the bionic pancreas period versus 9·0 mmol/L (1·6) in the comparator period (difference 1·1 mmol/L, 95% CI 0·7–1·6; p<0·0001), and the mean time with CGM glucose concentration less than 3·3 mmol/L was 6·6% (0·4) in the bionic pancreas period versus 1·9% (1·7) in the comparator period (difference 1·3%, 95% CI 0·8–1·8; p<0·0001). The mean nausea score on the Visual Analogue Scale (score 0–10) was greater during the bionic pancreas period (0·52 [SD 0·83]) than in the comparator period (0·05 [0·17]; difference 0·47, 95% CI 0·21–0·73; p=0·0024). Body mass and laboratory parameters did not differ between periods. There were no serious or unexpected adverse events in the bionic pancreas period of the study.

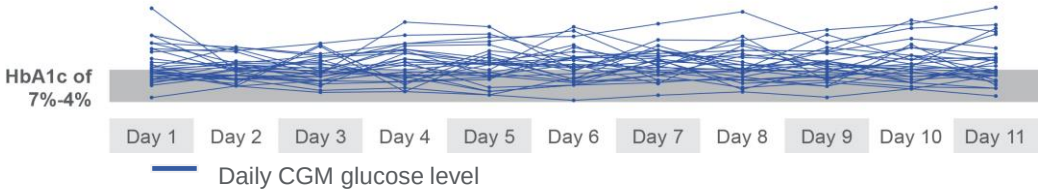
Interpretation Relative to conventional and sensor-augmented insulin pump therapy, the bihormonal bionic pancreas, initialised only with participant weight, was able to achieve superior glycaemic regulation without the need for carbohydrate counting. Larger and longer studies are needed to establish the long-term benefits and risks of automated glycaemic management with a bihormonal bionic pancreas.

Funding National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, and National Center for Advancing Translational Sciences.

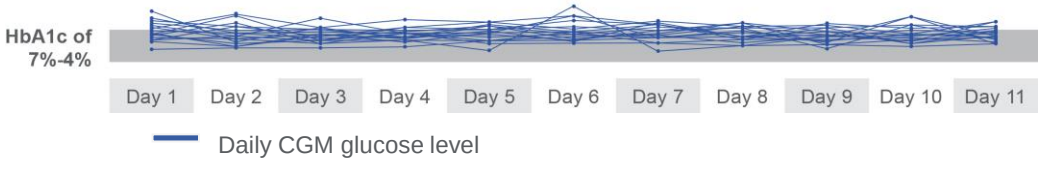
Introduction

People with type 1 diabetes are at risk of life-threatening acute and chronic complications. Maintaining mean blood glucose concentrations near the non-diabetic range prevents complications of type 1 diabetes and reduces mortality.[1–3] However, most people with type 1 diabetes are not able to maintain mean blood glucose in this range,[4–6] and intensifying treatment to achieve therapeutic goals increases the risk of both symptomatic and life-threatening hypoglycaemia.[7–9] Current treatments need painstaking effort by patients to count carbohydrates, closely monitor blood glucose, and make dosing decisions for insulin, a drug with a narrow therapeutic range and a low margin for error. An unmet need exists for better methods to manage glycaemia. We have investigated a strategy to automate glycaemic management with a bihormonal bionic pancreas that uses continuous glucose monitoring (CGM) and mathematical algorithms to automatically administer both insulin and glucagon.[10–13]

Treatment with insulin only pump – All day (24 hrs)



Treatment with dual-hormone pancreas system – All day (24 hrs)



[1] The Lancet, December 2016: S0140-6736(16)32567-3 and Elkhatib F, Buckingham BA, Buse JB, et al. Abstract 77-OR. at: ADA 76th Scientific Sessions; June 10-14, 2016; New Orleans, LA. Association

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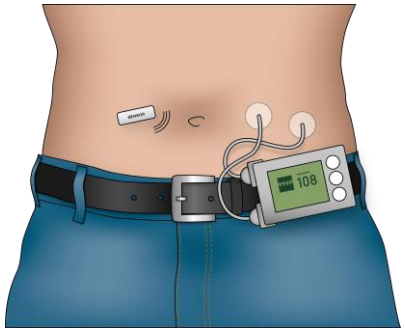
In 2016 Zealand and Beta Bionics initiated a collaboration to advance clinical trials with the iLet

The iLet being developed by Beta Bionics is a potential first-in-class dual-hormonal (bionic) artificial pancreas[1]

- Sensor guided automatic injection of insulin when blood glucose is high and glucagon when blood glucose is low
- Holds potential to allow more patients to obtain recommended mean blood glucose targets with very low risk of hypoglycemia[1]
- Dual-hormone artificial pancreas devices have been tested in five out-patient, short-term trials[1]

Need glucagon in liquid formulation

- Current glucagon formulations are only available as powder and are inherently unstable in liquid formulations



[1] www.BetaBionics.com
[2] The Lancet, December 2016: S0140-6736(16)32567-3

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Dasiglucagon[1] is believed to be the most advanced glucagon product in development for liquid delivery in a pump

Phase Ib with positive results reported in 2015 √

- A randomized, double-blind, placebo-controlled, multiple ascending dose trial in 24 health subjects with dosing over 5 consecutive days
- Dasiglucagon provided a clinically relevant glucose response and was well tolerated with a good safety profile in the trial

Two Phase IIa trials initiated in 2016 √

Phase IIa trial testing dasiglucagon in the Beta Bionic dual-hormone artificial pancreas system

- Aim is to assess the safety, efficacy and tolerability of dasiglucagon in adults with type 1 diabetes, compared to Glucagon marketed by Lilly

Phase IIa trial testing the multiple-dose formulation of dasiglucagon in adults with type 1 diabetes

- Aim is to assess pharmacokinetic and pharmacodynamic properties of dasiglucagon micro-doses compared to Glucagon marketed by Lilly

Phase IIa results expected in H1 2017

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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Dasiglucagon – the story so far....

- Dasiglucagon[1] is a novel analogue of glucagon with significantly improved physicochemical properties

Dasiglucagon[1] for single dose rescue treatment

- Successfully completed a Phase II clinical study in 2016
- All patients achieved a clinically relevant blood glucose response which was as fast and effective as existing treatment
- Confirmed safety and tolerability observed
- Will initiate a Phase III study in 2017

Dasiglucagon[1] for use in a dual hormone artificial pancreas

- Initiated two Phase IIa clinical studies in 2016
- Results expected in 2017

[1] Dasiglucagon is a proposed International Non-proprietary Name (pINN)

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Acknowledgements

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