Congenital Hyperinsulinism and Dasiglucagon

Clinical Development Program

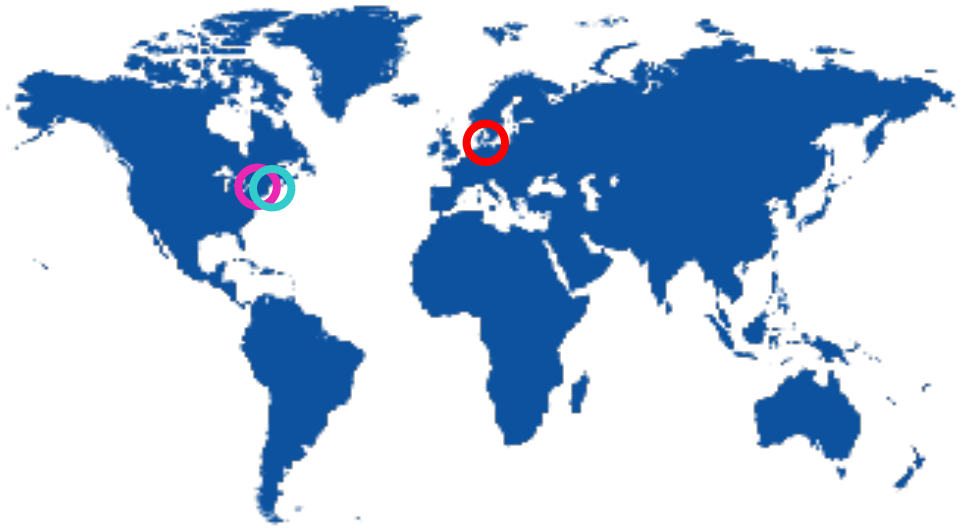
Sep 2022

Table of Contents

Who Are We? And What Do We Do?

Global Organization

- **Founded in 1998 in Denmark**
- **R&D focused, biotechnology company**
- **Multiple approved assets worldwide**



Copenhagen, Denmark

Boston, MA

Marlborough, MA – now Mannkind

Peptide-based Therapies:

Modifying Peptides to Optimize Treatment

Rational peptide design = create peptides that improve on the characteristics of naturally occurring hormones/ proteins

- **Structural optimization**
- **May confer one or more therapeutic advantages:**
  1. **Selectivity** for intended target
  2. **Improved physical-chemical properties** such as solubility and half-life
  3. **Potency** at low concentrations
  4. **Favorable safety profile** in terms of side effects and drug interactions

Our mission is to change lives with next generation peptide therapeutics

>1 B USD market opportunity[1]

>1 B USD market opportunity[2]

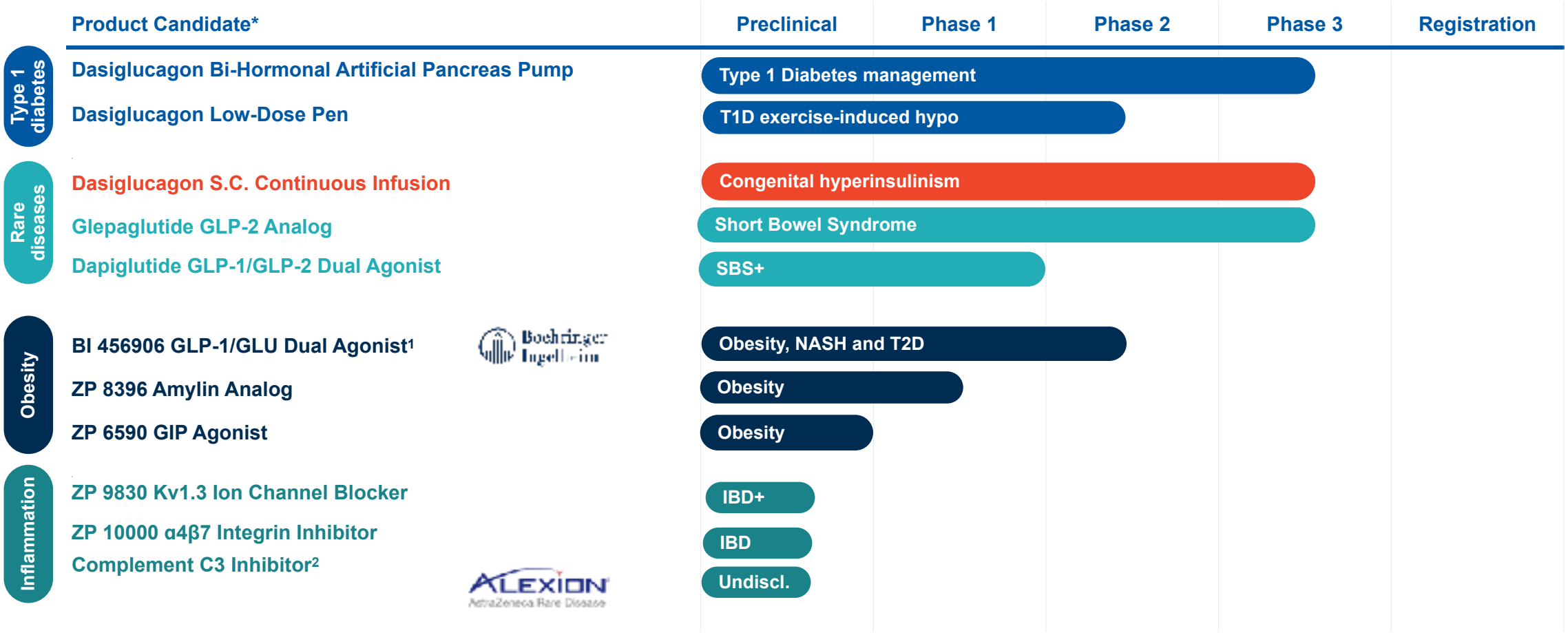
>10 B USD market opportunity[3]

>>10 B USD market opportunity[4]

Proprietary peptide platform

[1] Rescue market alone ~300m USD in 2020 (Source: Symphony); [2] SBS market alone expected to grow by 5.8% CAGR (Source: Research&Markets), bringing GLP-2s above 1 B USD by 2030 (based on Gattex 2020/2021sales ~600 mUSD);
[3] Assuming continued growth rate of ~15% CAGR from current level of >1B USD (Source: EvaluatePharma), market exceeds 10B by 2035; [4] Current market for Crohn's disease alone ~13B USD and growing (Source: EvaluatePharma);
[5] V-Go part of current diabetes management focus, but not relevant in T1 diabetes - long-term strategic fit will need to be assessed; [2] Licensed to Bohringer Ingelheim, [3] Licensed to Astra Zeneca

Our pipeline addresses significant unmet medical needs across several diseases and provides near-term value triggers



* investigational compounds whose safety and efficacy have not been evaluated or approved by the FDA or any other regulatory authority

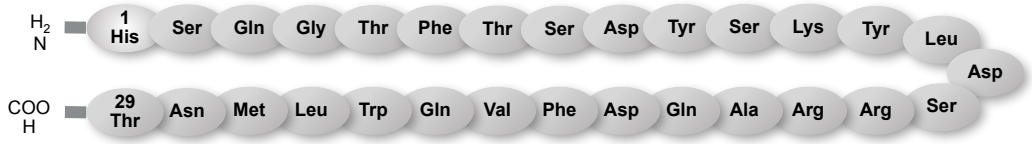
[1] Licensed to Boehringer Ingelheim: EUR 345 million outstanding potential development, regulatory and commercial milestones + high single to low double digit % royalties on global sales

[2] Licensed to Alexion: USD 610 million potential development, regulatory and commercial milestones + high single to low double digits % royalties on net sales

Dasiglucagon Development Program

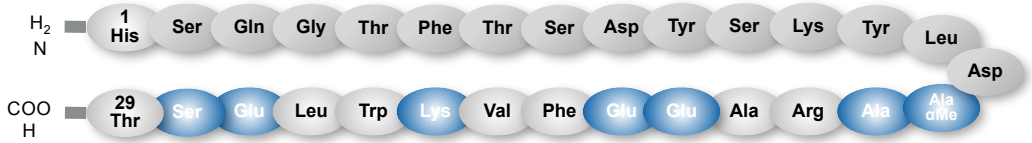
Dasiglucagon: A Novel Glucagon Analog

Native Human Glucagon

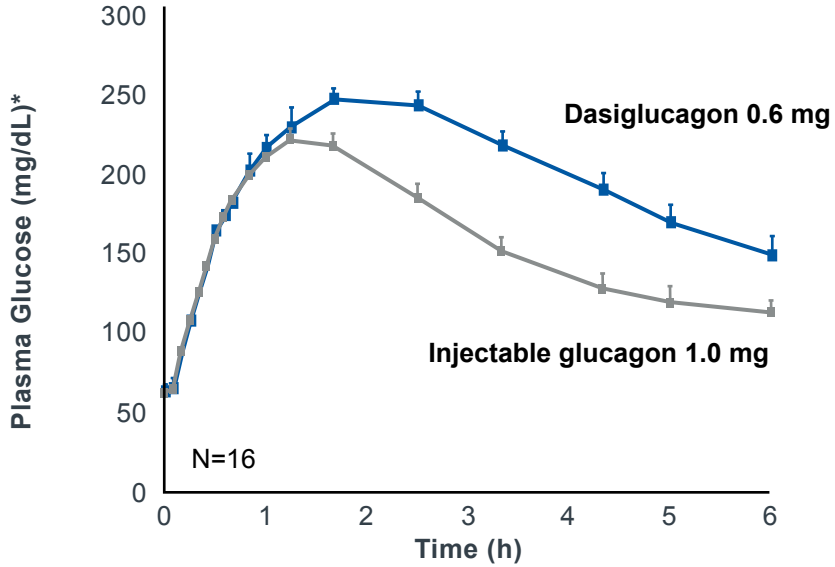


Dasiglucagon (A Novel Glucagon Analog)

Amino acid substitution



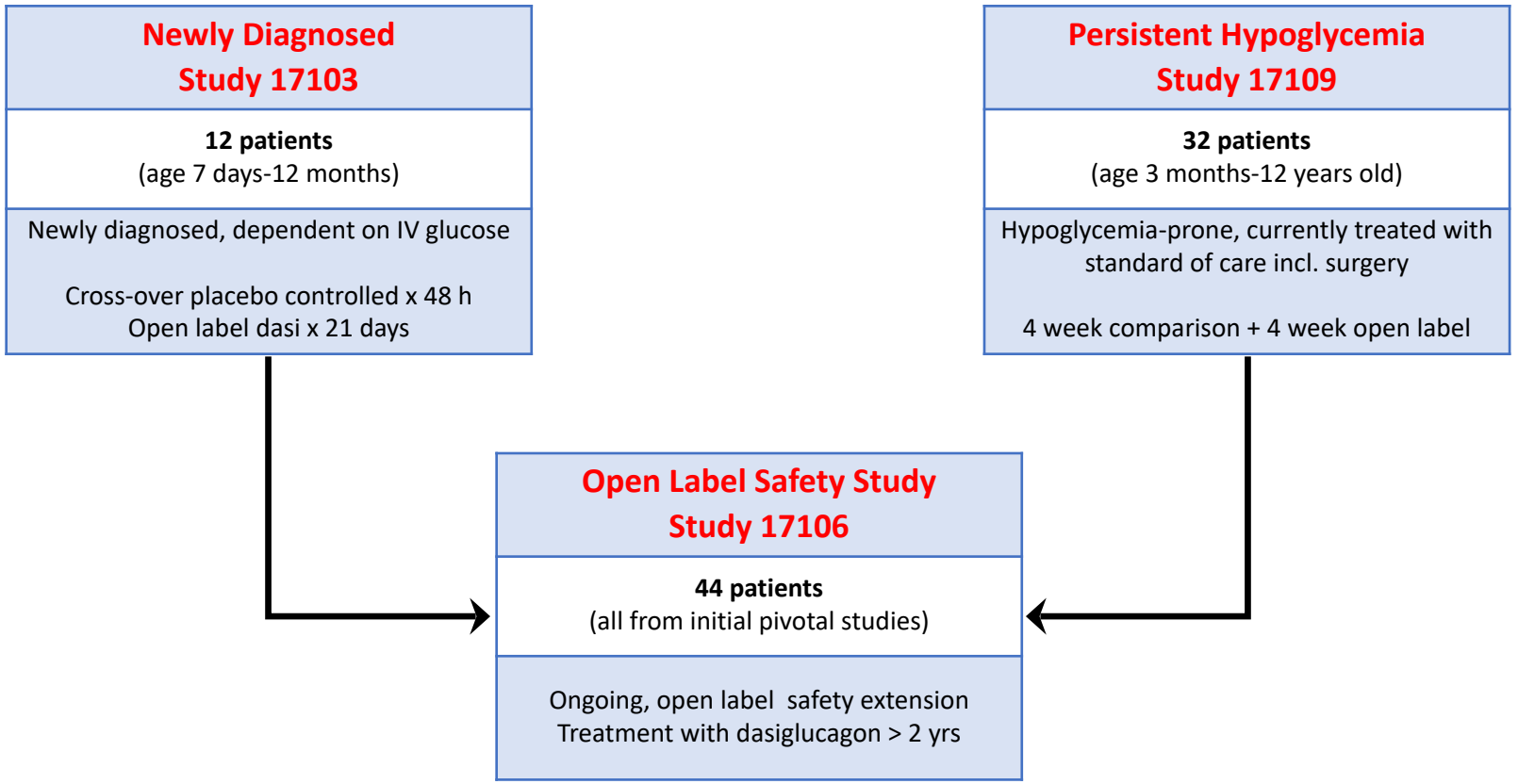
- **Native human glucagon is effective as an anti-hypoglycemic agent,**
  - Lacks stability, fibillates in aqueous solutions; limits clinical utility
- **Dasiglucagon = glucagon analog with 7 amino acid substitutions improving**
  - Improves aqueous solubility and enhanced physical stability
  - Suitable for longer term continuous or intermittent infusion



Hovelmann et al. *Diabetes Care*. 2018;41:531-537.

Dasiglucagon for the Management of CHI:

Clinical Trials



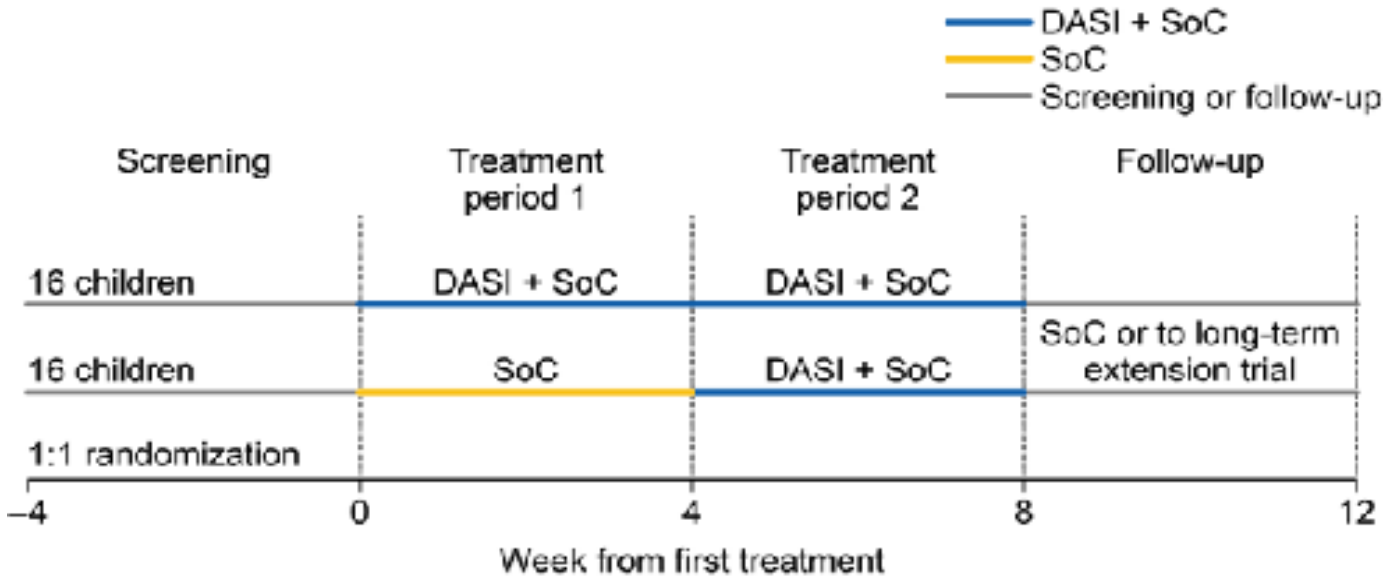
Clinical Trials Register (EU)- Study 17103 (Jan 2022) https://clinicaltrialsregister.eu/ctr-search/trial/2017-004545-24/DE
ClinicalTrials.gov- Study 17106 (Jan 2022) https://clinicaltrials.gov/ct2/show/NCT03941236?term=NCT03941236&draw=2&rank=1
ClinicalTrials.gov-Study 17109 (Jan 2022) https://clinicaltrials.gov/ct2/show/NCT03777176
Clinical Trials Register (EU)-Study 17109 (Jan 2022) https://clinicaltrialsregister.eu/ctr-search/trial/2017-004547-21/DE
ClinicalTrials.gov-Study 17109 (Jan 2022) https://clinicaltrials.gov/ct2/show/NCT04172441?term=NCT04172441&draw=2&rank=1

***Dasiglucagon for CHI is currently under investigation and is not approved by the FDA**

Trial 17109

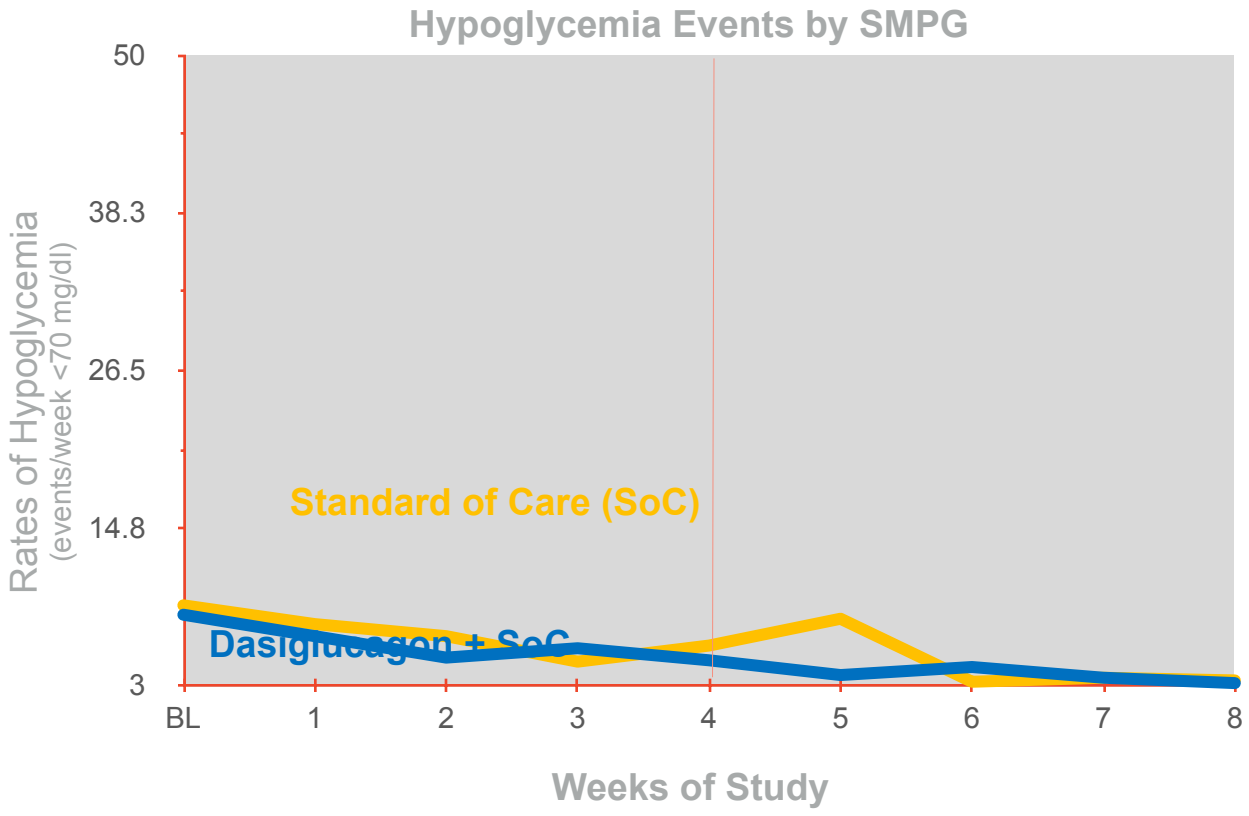
Study 109 – Trial Design

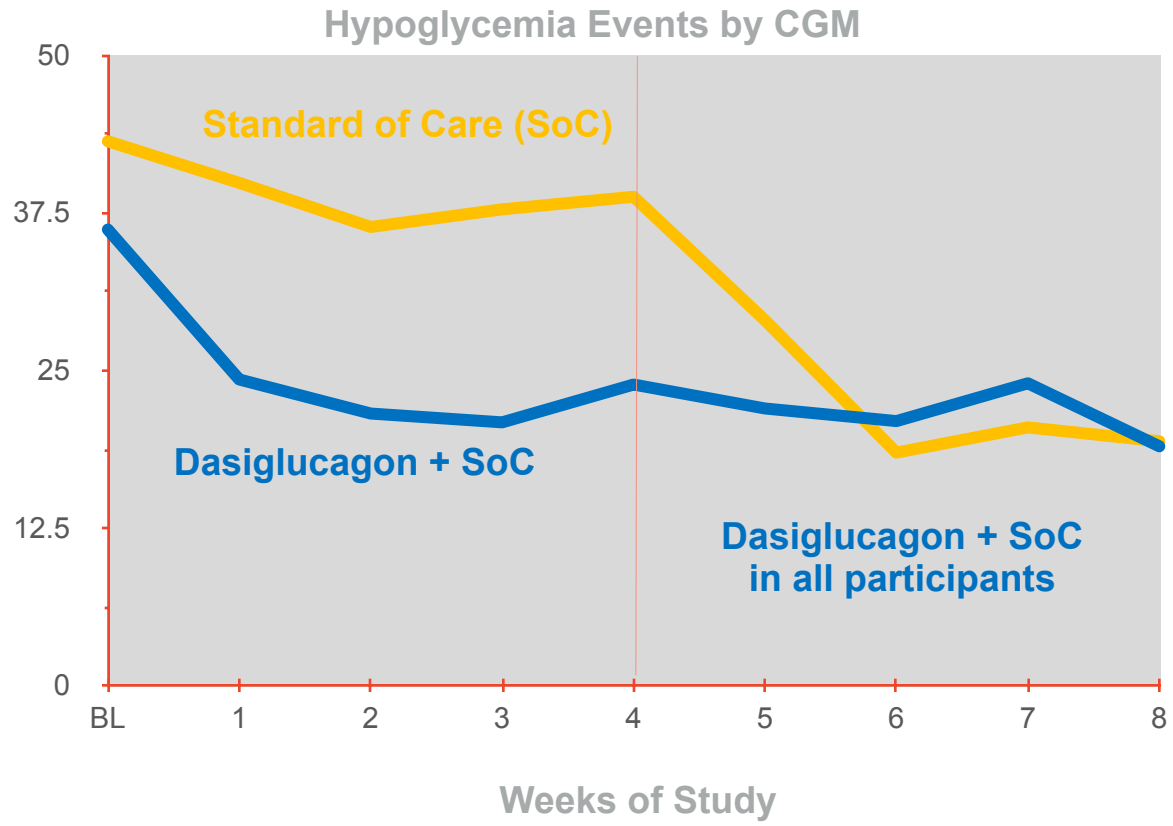
- Two-period, open-label study to assess safety and efficacy of DASI when added to SoC in children with CHI and persistent hypoglycemia
  - 32 children (mean age 4.3 [0.6–10.9] years) randomized to continued SoC vs SoC+DASI
  - All patients were treated with DASI during Period 2
- Primary efficacy measure: hypoglycemia episode rate, defined as average weekly number of hypoglycemic episodes (< 70 mg/dL or 3.9 mmol/L) during Weeks 2-4, as detected by SMPG



Phase 3 trial in children with CHI having multiple hypoglycemic events despite maximum standard of care

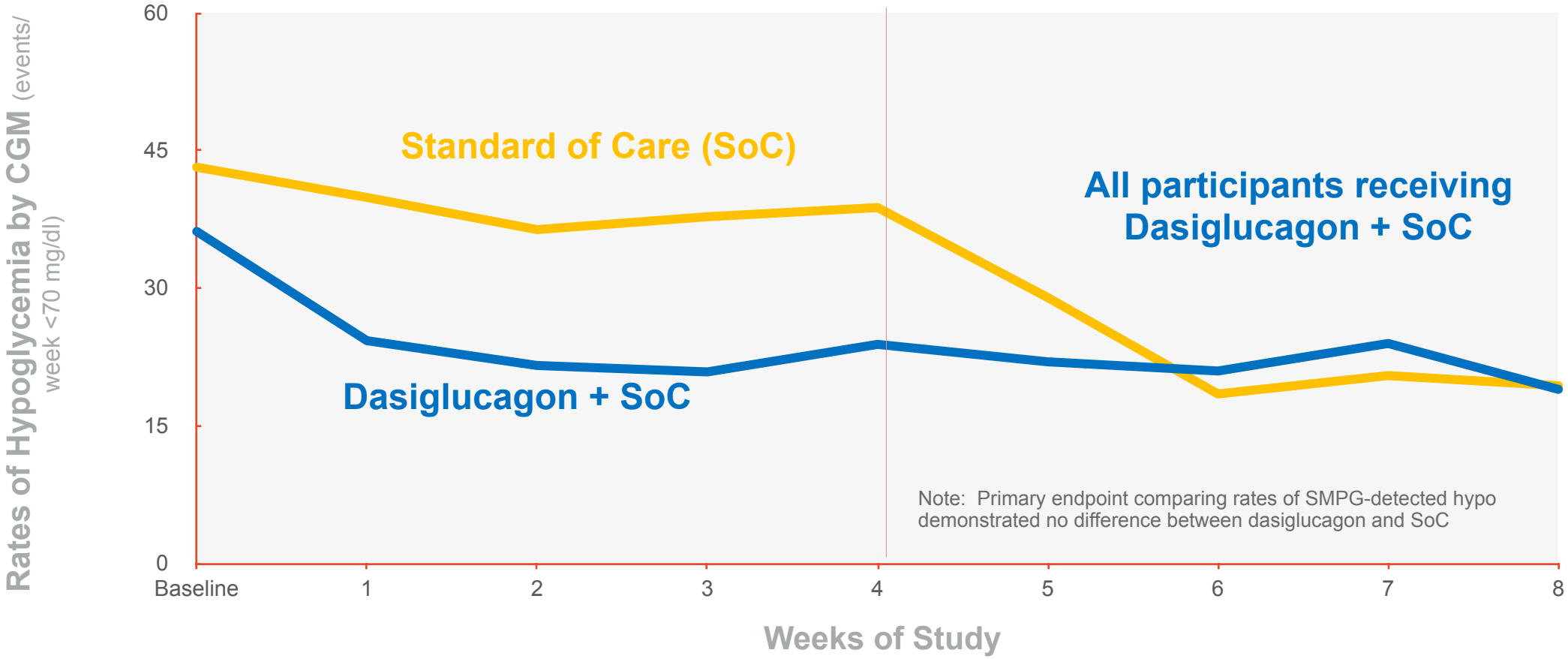
Dasiglucagon (plus SoC) treatment reduced CGM-detected hypoglycemia when compared with SoC treatment alone. There was no significant difference in rates of SMPG-detected hypo





Phase 3 trial in children with CHI having multiple hypoglycemic events despite maximum standard of care

Dasiglucagon (plus SoC) treatment reduced rates of CGM-detected hypoglycemia when compared with SoC treatment alone



Post-hoc analyses, CGM detected hypoglycemia

Endpoint	Expressed as	Posthoc Analysis
CGM-detected hypoglycemia episodes during Treatment Period 1 (<70 mg/dL)	Event rate ratio (95% CI of event rate ratio), *P* value	0.57 (0.39; 0.83), *P* = 0.0029
CGM-detected clinically significant hypoglycemia episodes during Treatment Period 1 (<54 mg/dL)	Event rate ratio (95% CI of event rate ratio), *P* value	0.56 (0.37; 0.86), *P* = 0.0075
CGM Percent time in hypoglycemia <70 mg/dL during Treatment Period 1	Estimate of LS means ratio (95% CI of LS means ratio), *P* value	0.53 (0.36; 0.79), *P* = 0.0017
CGM Percent time in clinically significant hypoglycemia <54 mg/dL during Treatment Period 1	Estimate of LS means ratio (95% CI of LS means ratio), *P* value	0.49 (0.30; 0.82), *P* = 0.0061

Source: Section 14.5, Table 14.5.1, Table 14.5.2, Table 14.5.3, Table 14.5.12.2
Abbreviations: CI = confidence interval; CGM = continuous glucose monitoring; LS = least squares

Safety Summary

- Overall, dasiglucagon was assessed as safe and well-tolerated
- During controlled Part 1, most common AEs reported in dasiglucagon arm were
  - Infections and infestations
  - Skin and subcutaneous disorders
  - Gastrointestinal disorders
- No clinically meaningful trends in remaining safety parameters (such as laboratory parameters and vital signs)

Phase 3 trial in children and adolescents with CHI treated with standard of care therapies, conclusion

Dasiglucagon (plus SoC) treatment reduced rates of CGM-detected hypoglycemia when compared with SoC treatment alone

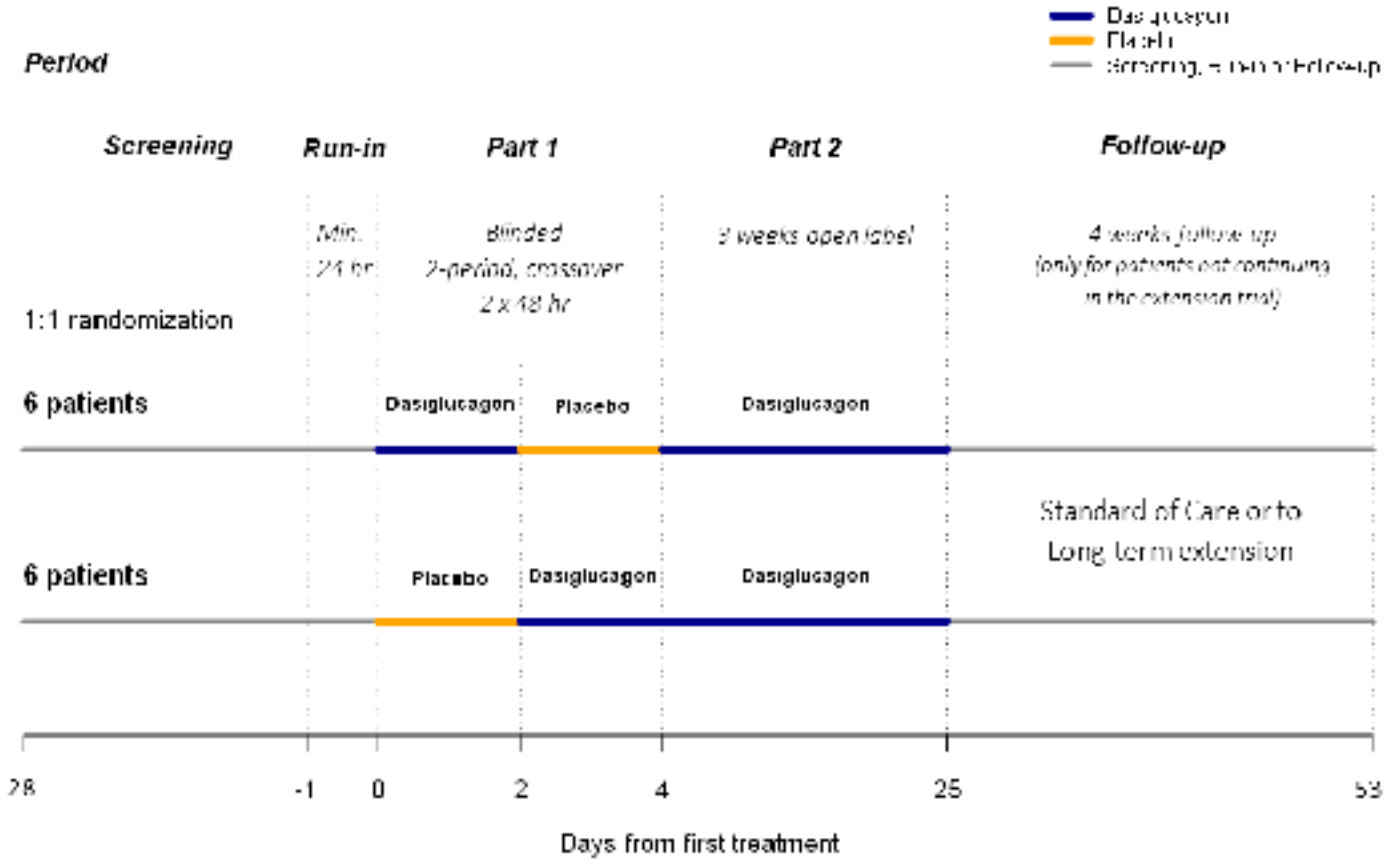
- Rates of hypoglycemia as measured by SMPG declined over time and to a similar degree with both DASI + SoC when compared with SoC alone (Primary Endpoint)

- There was a **clinically meaningful reduction in measures of hypoglycemia, as assessed by blinded continuous glucose monitoring** with DASI + SoC when compared with SoC alone (Exploratory Endpoint)

- DASI treatment was generally considered safe and well tolerated in the study
  - Higher rates of treatment emergent adverse events (TEAEs) were seen with DASI + SoC (87.5%) than with SoC alone (50%)
  - The majority of TEAEs were reported to be mild in severity
  - One patient discontinued in Period 2 due to persistent hyperglycemia despite reduced DASI dose

Trial 17103

Trial 103
Randomized, double-blind, placebo-controlled, crossover



Primary endpoint

Part 1 (Day 1 to 4)

- Mean IV GIR in the last 12 hours of each treatment period during Part 1 (dasiglucagon or placebo administration)

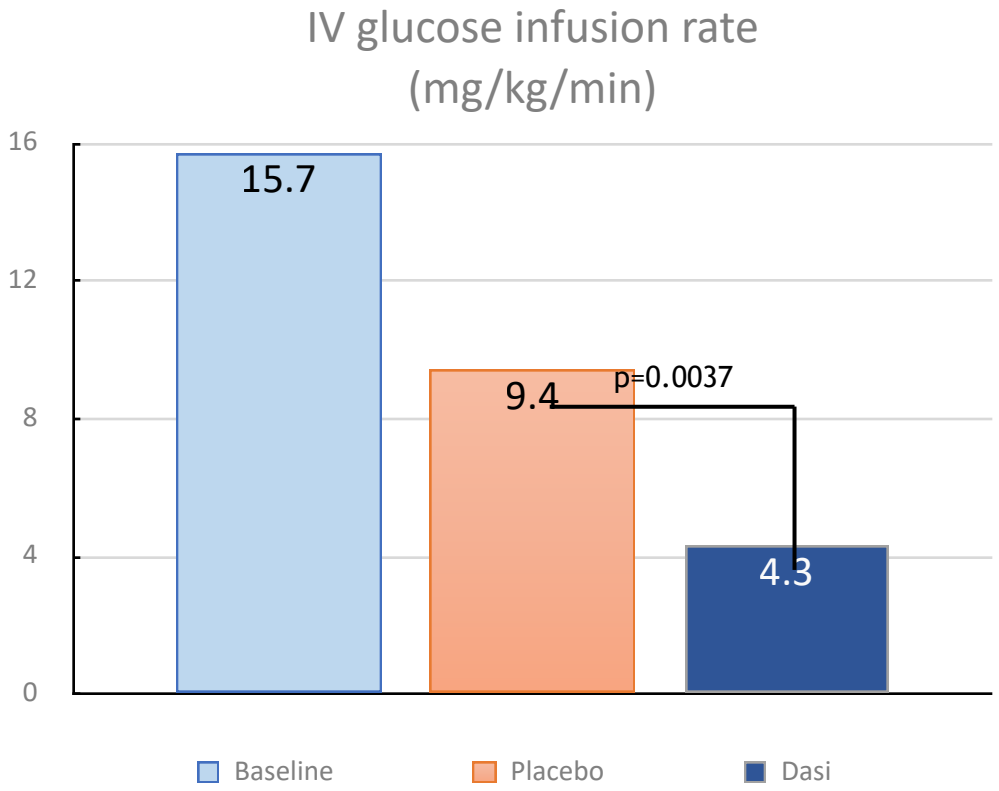
Key secondary efficacy endpoints

Part 1 (Day 1 to 4, for each 48-hour treatment period)

1. Total amount of carbohydrates administered (via IV infusion, nasogastric tube, gastrostomy, or oral route) per day.

Dasiglucagon in Infants and Newborns with CHI

Primary Endpoint

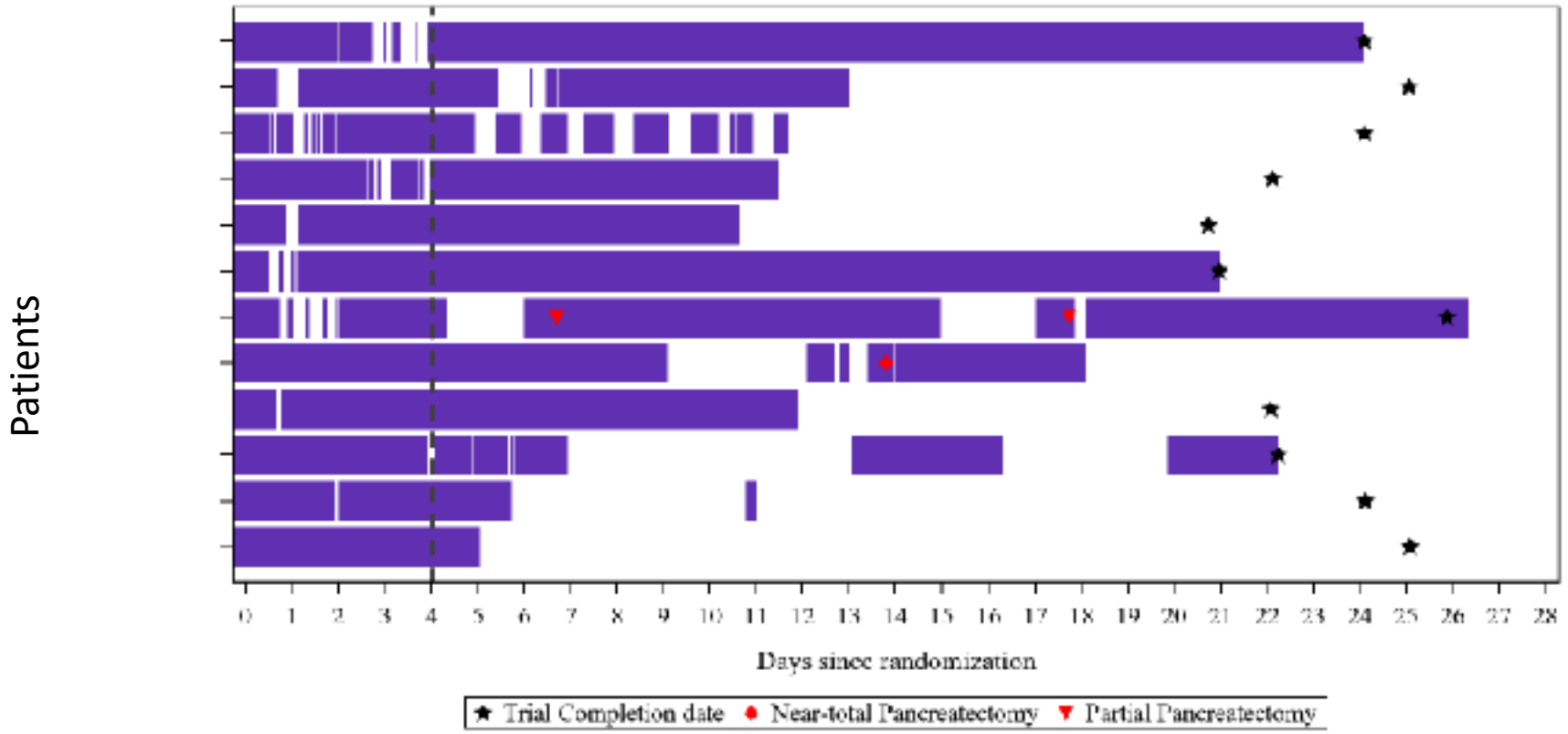


Significant reduction in mean IV glucose infusion in final 12 hours of treatment

- 55% reduction in GIR - dasiglucagon vs placebo
- 10/12 individual subjects with reduction in GIR
- 9/12 with GIR < 10mg/kg/min on dasiglucagon
- 6/12 with GIR < 10mg/kg/min on placebo

IV Glucose Infusion Rate (GIR)

(Patient and Day-Post Hoc Analysis-Safety Set)



- 10 patients weaned off IV glucose for at least 12 hours
- 7 patients without pancreatectomy were off IV glucose at trial completion

Hypoglycemic Events by CGM and SMPG (< 3.9 mmol/L, <70mg/dl)

	% time by CGM < 3.9 mmol/L (70 mg/dl) Median	CGM episodes < 3.9 mmol/L (70 mg/dl) Median	SMPG episodes < 3.9 mmol/L (70 mg/dl) Median
Week 1	**7.0**	**22**	**8.5**
Week 2	**7.3**	**26**	**6.0**
Week 3	**5.7**	**19**	**3.8**

- **Maintained CGM time in range between 88-91%**
- **No change in hyperglycemia**

  CGM > 10 mmol/L (180 mg/dl)

Phase 3 trial in hospitalized neonates/infants with CHI: Significant reduction in IV glucose infusion rate

Intravenous glucose (IV) requirements reduced by 55% compared to placebo

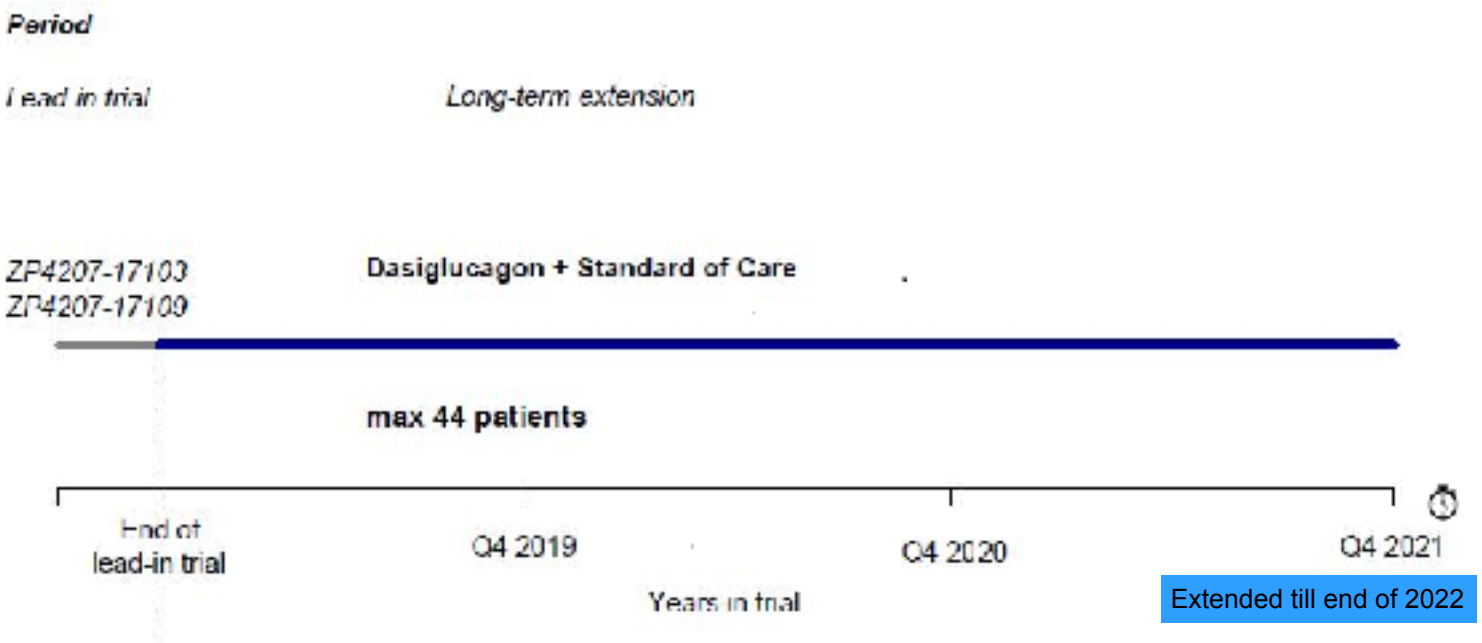
- Primary endpoint – reduction in IV glucose requirements over final 12 hours of treatment
  - 55% reduction in GIR with dasiglucagon treatment vs placebo (blinded cross-over study)

- Dasiglucagon treatment was assessed to be well-tolerated with no new safety findings reported
  - 11 out of 12 patients continued into the long-term safety extension trial (Study 17106).

- Full data set accepted for presentation at the European Society for Pediatric Endocrinology (September 2022)

Trial 17106

Trial 106
Open-label, long-term safety and efficacy extension



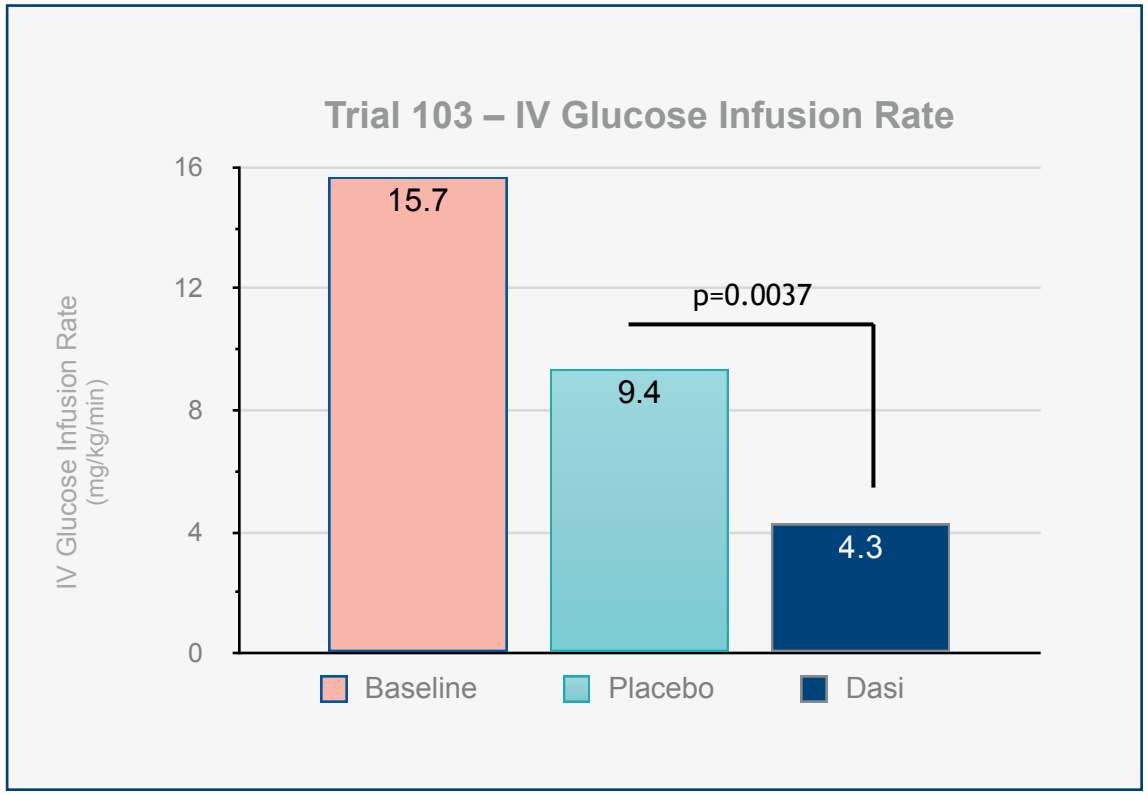
Primary endpoint

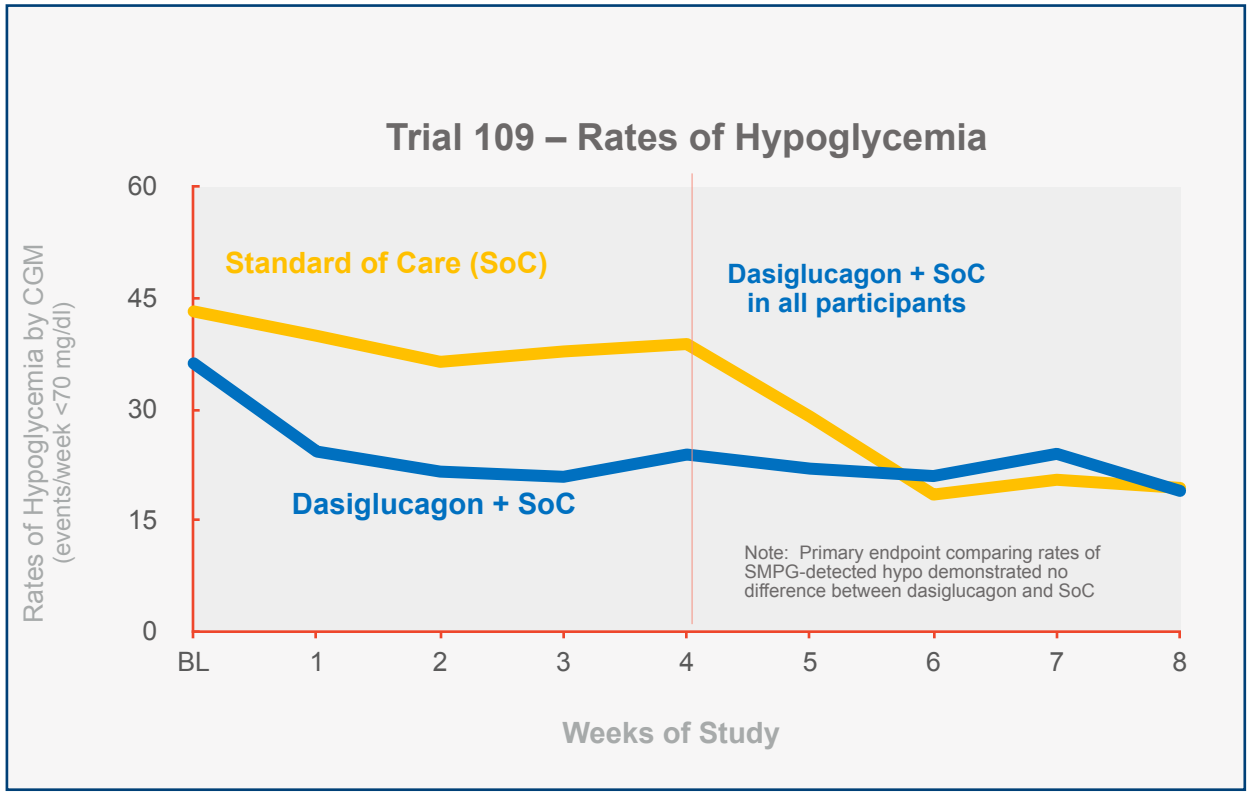
- Adverse events

Key secondary efficacy endpoints

- Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia
- Time to removal of NG tube or gastrostomy
- Time to pancreatic surgery (sub-total or total pancreatectomy)
- Continuous glucose monitoring (CGM) percent time ≤ 70 mg/dL (3.9 mmol/L)
- Rate of CGM detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more
- Rate of CGM detected hypoglycemia episodes <54 mg/dL (3.9 mmol/L) for 15 minutes or more

Phase 3 program of dasiglucagon in CHI:
Results of Pivotal Clinical Trials





- Dasiglucagon therapy achieved a 55% reduction in glucose infusion rate
- Reduced total carbohydrates by ~22%
- 7 of 12 participants weaned off IV glucose by end of study

- Dasiglucagon therapy achieved a 55% reduction in glucose infusion rate
- Reduced total carbohydrates by ~22%
- 7 of 12 participants weaned off IV glucose by end of study

Thank you!