Phase 3, Double-Blind, Randomized STARS Trial of Apraglutide Once Weekly in Patients With Short Bowel Syndrome and Intestinal Failure (SBS-IF): Subgroup Analyses by Baseline Demographics and SBS Disease Characteristics

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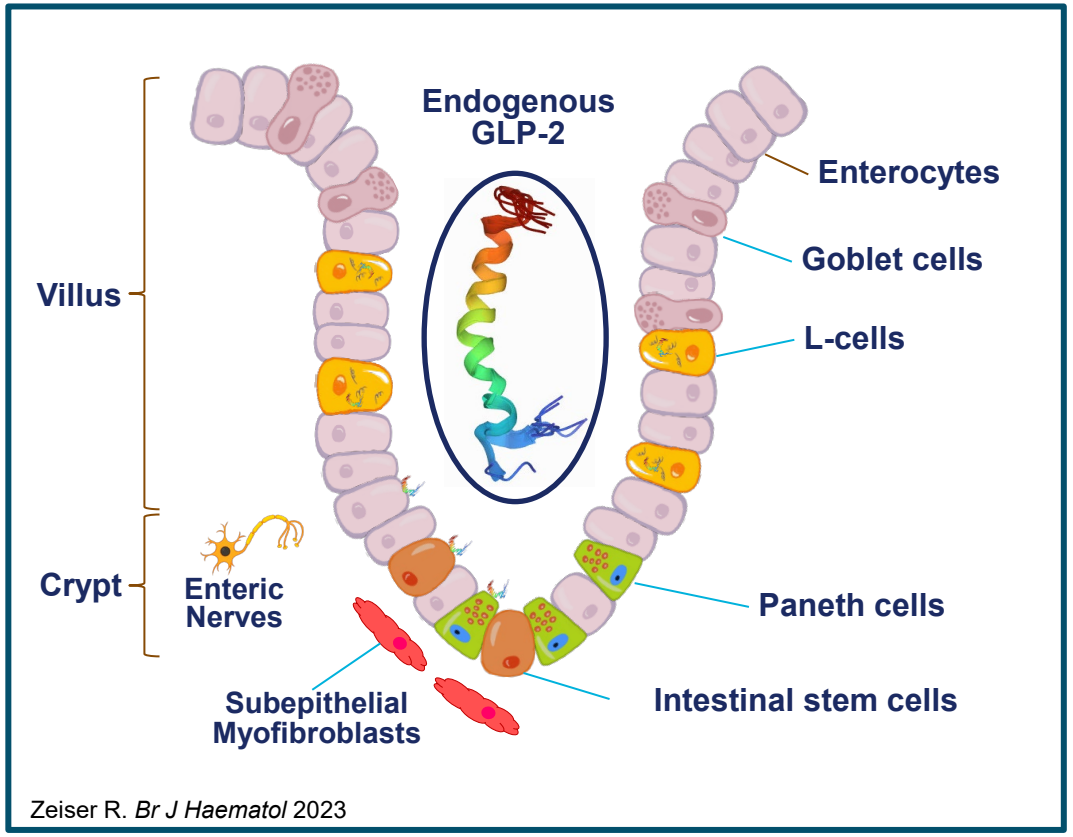
NCT04627025

Introduction

- SBS-IF is a chronic malabsorptive condition requiring parenteral support[1]
- SBS-IF is anatomically heterogeneous based on remnant bowel anatomy (stoma or colon-in-continuity)[1]
- Response to treatment can also vary due to:[1]
  - Extent of physical intestinal loss
  - Capability of the remnant bowel to adapt
  - Specific patient and disease characteristics
- Apraglutide is a synthetic GLP-2 analog with a unique pharmacokinetic profile compared with endogenous GLP-2[2–4]
  - Increased GLP-2 receptor potency and selectivity results in intestinotrophic effects
  - Long half-life allows for once-weekly dosing



Zeiser R. *Br J Haematol* 2023

GI, gastrointestinal; GLP-2, glucagon-like peptide-2; SBS-IF, short bowel syndrome with intestinal failure.

1. Jeppesen PB. *JPEN J Parenter Enteral Nutr.* 2014;38(1 Suppl):8S-13S; 2. Drucker DJ. *Gastroenterology.* 2002;122:531-544; 3. Eliasson J, *et al. JPEN J Parenter Enteral Nutr.* 2022;46:1639-1649; 4. Wiśniewski K, *et al. J Med Chem.* 2016; 59:3129-3139.

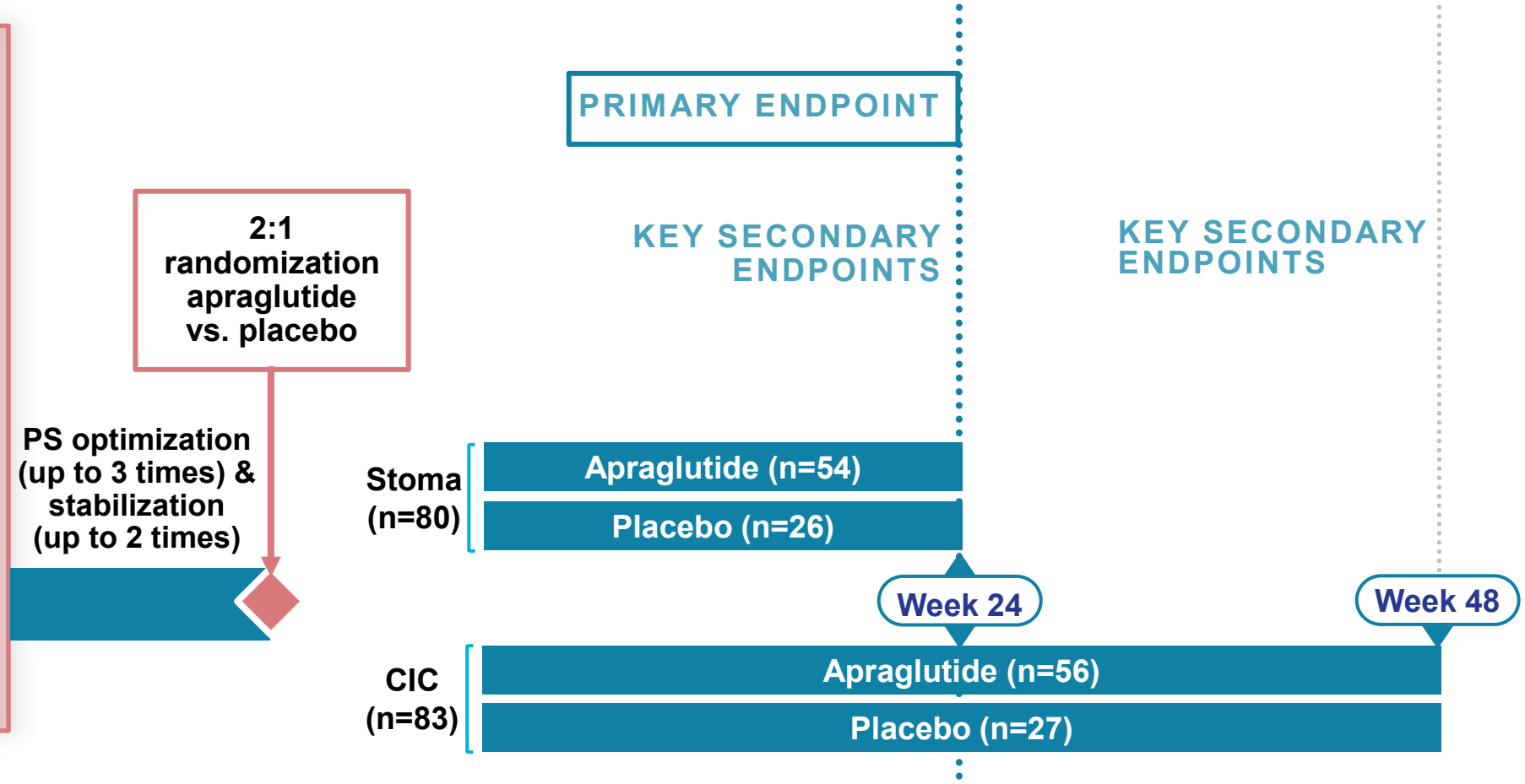
STARS Study Design: Efficacy and Safety of Apraglutide in Adult Patients With SBS-IF

A pivotal, Phase 3, double-blind, placebo-controlled trial

Global study
- 68 centers in 18 countries

Two arms (stratified by stoma and CIC)
- Apraglutide vs. placebo subcutaneous once weekly <50 kg (2.5 mg); ≥50 kg (5 mg)

PS reduction algorithm
- Adapted to remnant bowel anatomy



CIC, colon-in-continuity; PS, parenteral support; SBS-IF, short bowel syndrome with intestinal failure.
ClinicalTrials.gov: NCT04627025.

Inclusion & Exclusion Criteria

Key Inclusion Criteria

- Receiving PS after surgical resection of the small intestine with <200 cm from duodeno-jejunal flexure, with either:
  - **Stoma**: latest intestinal resection ≥6 months prior to screening
  - **CIC**: latest intestinal resection ≥12 months prior to screening
- PS requirement ≥3 days/week
- Patient considered stable with regards to PS volume requirement, drinking volume, and urinary output at the last stability visit and randomization visit

Key Exclusion Criteria

- Major abdominal surgery within last 6 months
- Acute cholecystitis, biliary obstruction, or IBD
- Radiation enteritis, scleroderma or residual evidence of intestinal dysmotility
- History of liver disease
- eGFR <20 mL/min/1.73 m^2
- Short-acting GLP-2 analogues within 3 months of randomization
- Longer-acting experimental GLP-2 analogues within 6 months of randomization

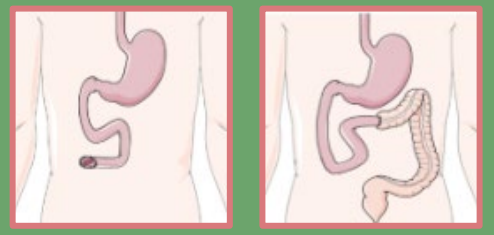
See ClinicalTrials.gov: NCT04627025 for full list of inclusion and exclusion criteria

CIC, colon-in-continuity; eGFR, estimated glomerular filtration rate; GLP-2, glucagon-like peptide-2; IBD, inflammatory bowel disease; PS, parenteral support; ;SBS-IF, short bowel syndrome with intestinal failure.
ClinicalTrials.gov: NCT04627025.

Primary & Key Secondary Endpoints

Primary Endpoint

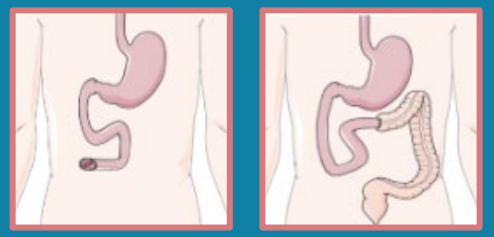
Overall population



- Relative change from baseline in weekly PS volume at Week 24

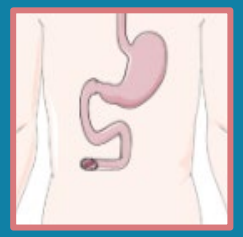
Key Secondary Endpoints

Overall population



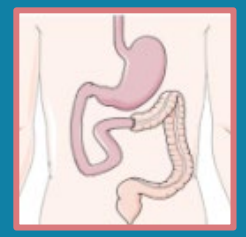
- Additional ≥1 day/week off PS at Week 24

Stoma



- Relative change from baseline in weekly PS volume at Week 24

CIC



- Additional ≥1 day/week off PS from baseline at Week 48
- Enteral autonomy at Week 48

CIC, colon-in-continuity; PS, parenteral support.

Subgroup Analyses
Primary Endpoint by Baseline Demographics and SBS Disease Characteristics

Subgroups defined per protocol

By baseline demographics

- Gender (M/F)
- Age (< or ≥ median; < 65 or ≥ 65 years old)
- Region (EU, USA, or rest of the world)
- Race (Asian, Caucasian, or other)
- Ethnicity (Hispanic/Latino or not)

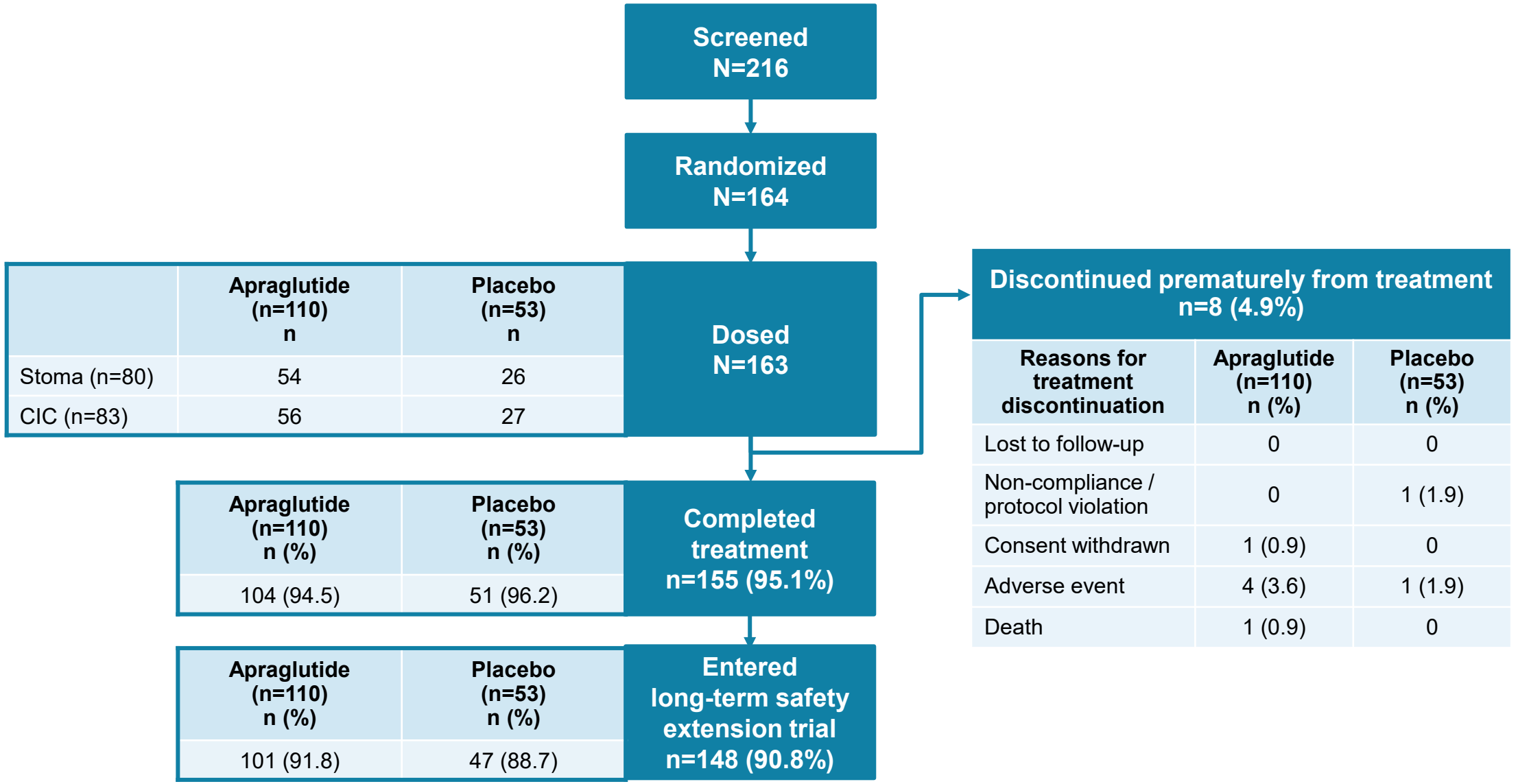
By baseline SBS disease characteristics

- Body weight (< 50 or ≥ 50 kg)
- PS volume (< 12 or ≥ 12 L)
- Length of remnant small intestine (< 80 cm or ≥ 80 cm)
- Time from SBS diagnosis (< 65.7 or ≥ 65.7 months)

Similar to the primary endpoint analysis,
subgroup analyses used a mixed effect model for repeated measures

F, female; M, male; PS, parenteral support; SBS, small bowel syndrome.

Patient Disposition



	Apraglutide (n=110) n	Placebo (n=53) n
Stoma (n=80)	54	26
CIC (n=83)	56	27

Apraglutide (n=110) n (%)	Placebo (n=53) n (%)
104 (94.5)	51 (96.2)

Apraglutide (n=110) n (%)	Placebo (n=53) n (%)
101 (91.8)	47 (88.7)

Reasons for treatment discontinuation	Apraglutide (n=110) n (%)	Placebo (n=53) n (%)
Lost to follow-up	0	0
Non-compliance / protocol violation	0	1 (1.9)
Consent withdrawn	1 (0.9)	0
Adverse event	4 (3.6)	1 (1.9)
Death	1 (0.9)	0

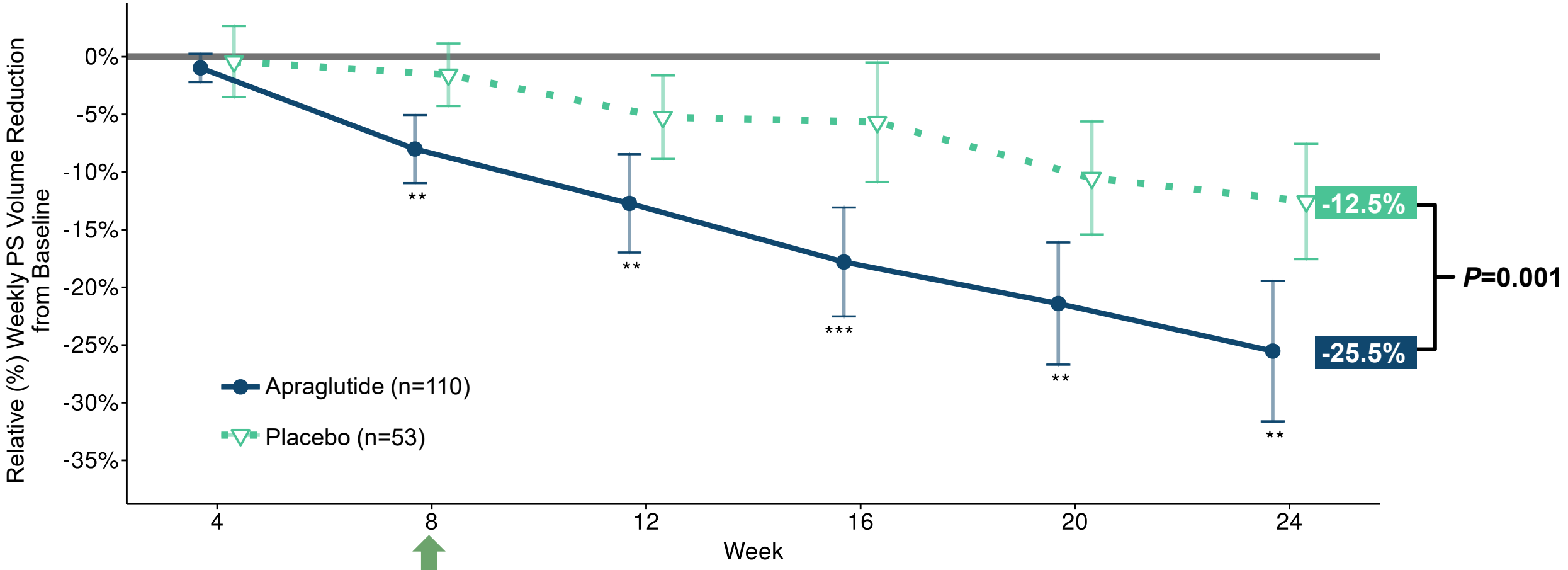
CIC, colon-in-continuity.

Baseline Demographics and SBS Disease Characteristics

Parameter	Apraglutide (n=110)	Placebo (n=53)
Baseline demographics		
Gender (n, %)		
Male	44 (40.0)	27 (50.9)
Age (years; mean [SD])	51.1 (14.2)	52.3 (16.0)
Region (n, %)		
US	21 (19.1)	7 (13.2)
EU + UK	75 (68.2)	37 (69.8)
ROW	14 (12.7)	9 (17.0)
Race (n, %)		
White	94 (85.5)	43 (81.1)
Asian	12 (10.9)	8 (15.1)
Other	3 (2.7)	2 (3.8)
Ethnicity (n, %)		
Hispanic or Latino	6 (5.5)	2 (3.8)
Not Hispanic or Latino	102 (92.7)	50 (94.3)
SBS disease characteristics		
Body weight (kg; mean [SD])		
<50 kg (2.5 mg)	15 (13.6)	3 (5.7)
≥50 kg (5 mg)	95 (86.4)	50 (94.3)
Baseline weekly PS volume (L; mean [SD])	13.1 (7.8)	12.9 (7.0)
Length of remnant small intestine (cm; mean [SD])	86.2 (54.2)	91.3 (53.5)
Time from SBS diagnosis (months; mean [SD])	104.0 (100.4)	93.1 (95.5)

BMI, body mass index; max, maximum; min, minimum; PS, parenteral support; ROW, rest of the world; SBS, short bowel syndrome; SBS-IF, short bowel syndrome with intestinal failure; SD, standard deviation.

Primary Endpoint Met (Overall Population): Significantly Greater Relative Reduction in Weekly PS Volume at Week 24



Apraglutide treatment effect observed at Week 8 and onward

*P<0.05; ** P<0.01; ***P<0.001
PS, parenteral support.

Consistent Apraglutide Effects Across Baseline Demographics

Subgroup analyses of the primary endpoint relative change in PS at week 24 by baseline demographics (full analysis set)

Subgroup	n		LS-means (%)		Adjusted mean difference (APRA - PBO)*	Difference (95% CI)	p†
	APRA	PBO	APRA	PBO			
Gender							
Female	66	26	-24.8	-8.8		-16.0 (-26.1,-5.9)	0.002
Male	44	27	-26.7	-16.2		-10.5 (-22.9,1.9)	0.097
Age (median)							
< Median	54	26	-27.0	-14.9		-12.1 (-23.2,-0.9)	0.033
≥ Median	56	27	-24.1	-10.3		-13.8 (-25.0,-2.6)	0.015
Age (65 years old)							
< 65	87	37	-27.0	-15.0		-12.0 (-21.5,-2.5)	0.013
≥ 65	23	16	-20.1	-6.9		-13.1 (-27.0,0.7)	0.063
Region							
EU (Incl. UK)	75	37	-24.2	-12.2		-12.0 (-21.2,-2.8)	0.010
Rest Of the World	14	9	-23.4	-10.8		-12.6 (-32.9,7.8)	0.226
USA	21	7	-31.6	-16.5		-15.1 (-38.2,8.1)	0.203
Race							
Asian	12	8	-23.5	-16.1		-7.5 (-27.8,12.9)	0.472
Caucasian	94	43	-25.2	-11.7		-13.6 (-22.1,-5.0)	0.002
Other	4	2	-38.3	-17.9		-20.4 (-66.7,25.8)	0.387
Ethnicity							
Hispanic or Latino	6	2	-38.5	-37.8		-0.7 (-15.7,14.2)	0.922
Not Hispanic or Latino	102	50	-24.7	-11.8		-12.8 (-21.1,-4.6)	0.002

Estimations are from the MMRM with fixed-effect terms.

*The bar extends from lower to upper confidence interval, the point is the difference, 0 is indicated by the gray vertical line. The more the bar extends to the left of the 0 line, the more the difference is favorable to apraglutide. †Unadjusted p-value.
APRA, apraglutide, CI, confidence interval; CIC, colon-in-continuity; LS, least square; PBO, placebo; MMRM, mixed effect model repeated measures; PS, parenteral support; SBS, short bowel syndrome.

Consistent Apraglutide Effects Across Baseline SBS Disease Characteristics

Subgroup analyses of the primary endpoint relative change in PS at week 24 by baseline SBS disease characteristics (full analysis set)

Subgroup	n		LS-means (%)		Adjusted mean difference (APRA - PBO)*	Difference (95% CI)	p†
	APRA	PBO	APRA	PBO			
Body weight (50 kg)							
< 50	15	3	-12.4	3.6		-16.0 (-39.8,7.8)	0.188
≥ 50	95	50	-27.6	-13.5		-14.1 (-22.6,-5.6)	0.001
Baseline weekly PS volume (median)							
< 12L	56	23	-22.7	-9.1		-13.6 (-27.4,0.2)	0.054
≥ 12L	54	30	-28.5	-15.1		-13.4 (-21.9,-4.9)	0.002
Length of remnant small intestine (median)							
< 80cm	53	25	-26.6	-18.4		-8.2 (-18.6,2.3)	0.127
≥ 80cm	57	28	-24.5	-7.3		-17.3 (-28.7,-5.8)	0.003
Time from SBS diagnosis (median)							
< 65.7 months	52	29	-30.0	-12.0		-18.0 (-28.7,-7.3)	0.001
≥ 65.7 months	58	24	-21.5	-13.1		-8.3 (-19.9,3.2)	0.158

Estimations are from the MMRM with fixed-effect terms.

Similar magnitude of treatment effect in subgroups of body weight (<50 kg or ≥50 kg)

Similar magnitude of treatment effect in subgroups of weekly PS volume (<12 L or ≥12 L)

*The bar extends from lower to upper confidence interval, the point is the difference, 0 is indicated by the gray vertical line. The more the bar extends to the left of the 0 line, the more the difference is favorable to apraglutide. †Unadjusted p-value.

Apra, apraglutide, CI, confidence interval; CIC, colon-in-continuity; LS, least square; MMRM, mixed effect model repeated measures; PBO, placebo; PS, parenteral support; SBS, short bowel syndrome.

Summary

- Apraglutide is the first once-weekly GLP-2 analog to show efficacy in a Phase 3 trial in patients with SBS-IF
  - As previously reported, the primary endpoint was met at Week 24, with a significantly larger reduction in weekly PS volume from baseline with apraglutide vs placebo

Subgroup analyses confirmed that the primary endpoint was consistently met across baseline demographics and SBS disease characteristics subgroups

- The consistent treatment effect of apraglutide was observed in all subgroups analyzed
- In particular, similar magnitude of effect was seen regardless of body weight or weekly PS volume at baseline

- Apraglutide was well tolerated, with no new safety signals identified

GLP-2, glucagon-like peptide 2; PS, parenteral support; SBS-IF, short bowel syndrome with intestinal failure.
Generative AI was not used in the development of this presentation.