Oley Foundation
June 2023

IMPACT OF GLEPAGLUTIDE ON CLINICAL AND PATIENT REPORTED OUTCOMES IN PATIENTS WITH SHORT BOWEL SYNDROME CHRONIC INTESTINAL FAILURE: RESULTS OF PHASE 3 TRIAL

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On behalf of the EASE Investigators

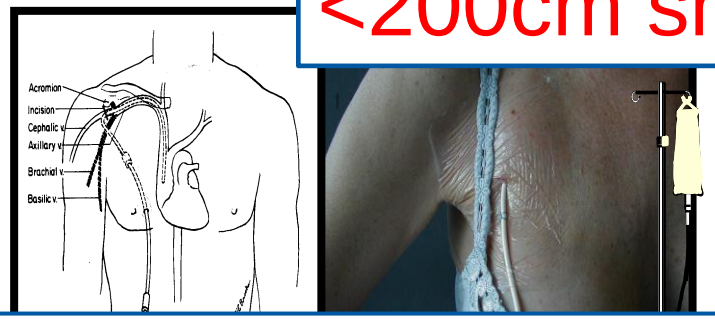
Sukanya Subramanian, Disclosures

Grants, research support, honoraria, or consultation fees from:

- Takeda
- Zealand Pharma A/S

Short Bowel Syndrome (SBS)

<200cm small intestine



Intravenous supplementation is required to maintain health and/or growth

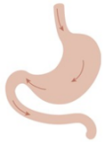
Intestinal failure is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth

The reduction of gut absorptive function that doesn't require intravenous supplementation to maintain health and/or growth, can be considered as **"intestinal insufficiency"**

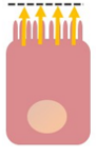
Pironi L *et al. Clin Nutr* 2015;34:171–80.

Gastrointestinal (GI) Effects of Glucagon-Like Peptide-2 (GLP-2)

- Reduces accelerated GI transit

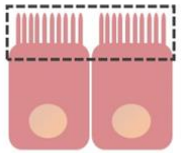


- Reduces gastric and pancreatico-biliary hypersecretion

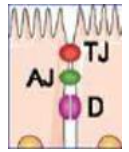


- Increases the impaired intestinal blood flow

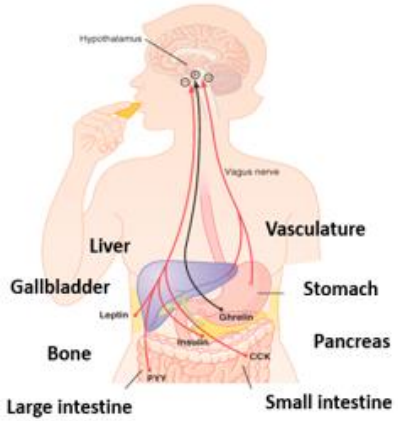
- Increases blunted mucosal surface area



- Improves/restores barrier function



- Improves/restores gut-organ-axis signalling

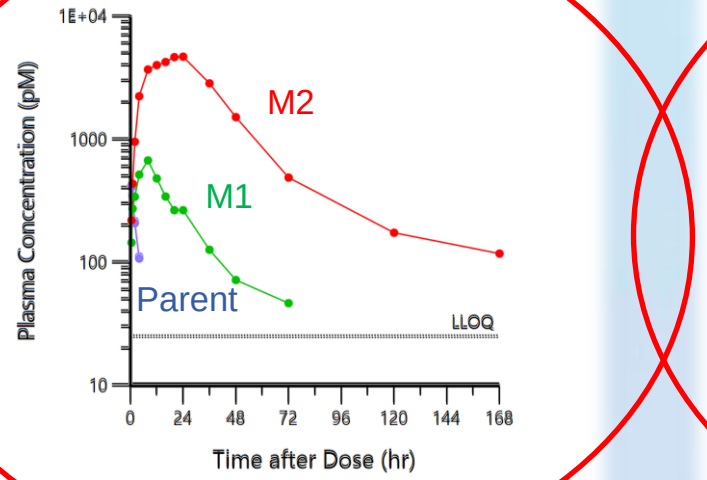


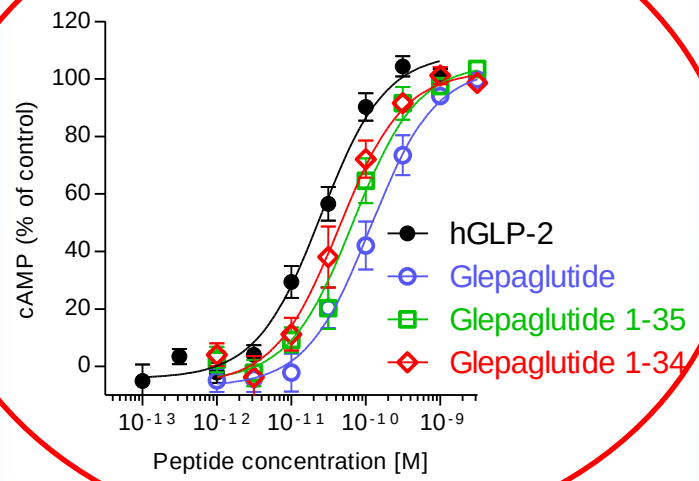
- Improves intestinal absorption

Improves metabolism and sustains organ functions

Meier JJ *et al*. *Gastroenterology* 2006;130:44–54; Brubaker PL. *Comp Physiol* 2018;8:1185–210; Guan X. *Am J Physiol Regul Integr Comp Physiol* 2014;307:R585–96.

Glepaglutide: A Long-Acting GLP-2 Analog in Development for SBS as a Liquid Formulation for Subcutaneous Injection





Effective half-life:

88 hours

39-amino-acid peptide forms a depot at the injection site

The long half-life is the result of nine amino acid modifications to human GLP-2 (hGLP-2) and a SIP tail

The sequence similarity of the backbone is about 64% that of native GLP-2.
LLOQ=lower limit of quantification; M1& M2=glepaglutide metabolites; SIP=structural inducing probe.
Data on file and Agersnap MA *et al*. *Clin Pharmacokinet* 2023;DOI: https://doi.org/10.1007/s40262-023-01215-9.

EASE (Efficacy And Safety Evaluation) SBS 1 Trial

Objectives and Design

Clinical Trial ZP1848-17111

EASE SBS 1 Trial Objectives

Primary objective

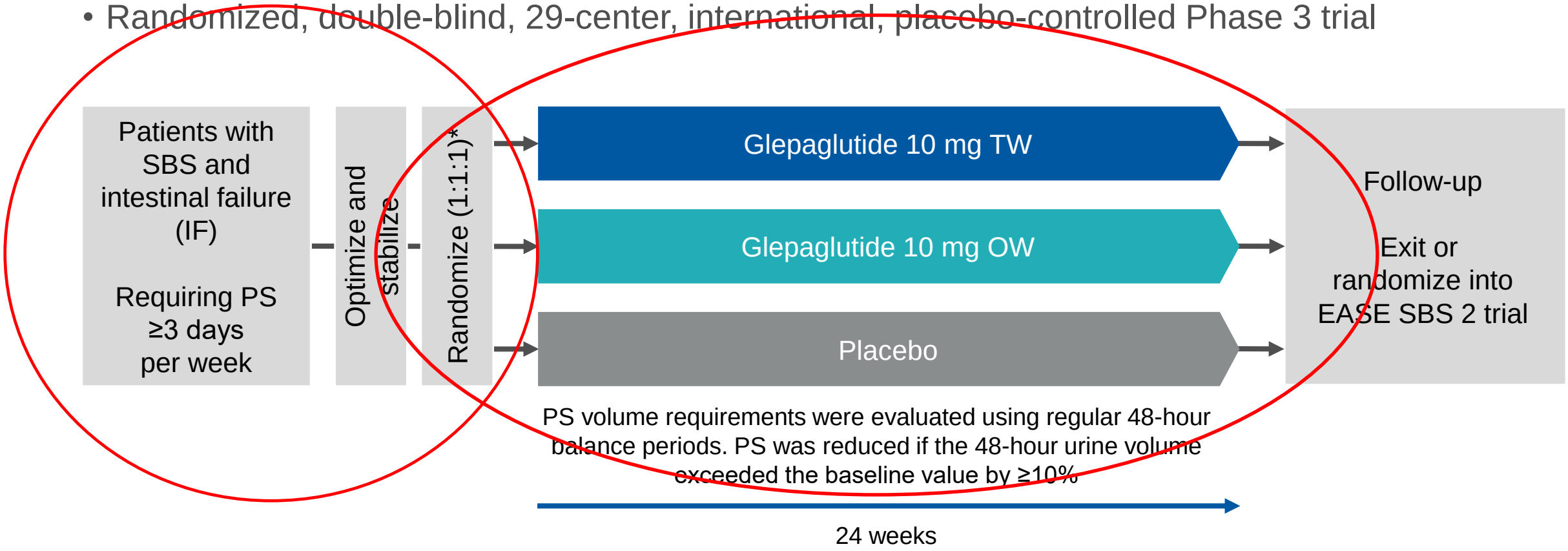
- To confirm the efficacy of glepaglutide in reducing parenteral support (PS) volume in patients with SBS

Secondary objectives

- To evaluate the efficacy of glepaglutide on other efficacy endpoints in patients with SBS
- To evaluate the safety and tolerability of glepaglutide in patients with SBS

EASE SBS 1 Trial Design

- Randomized, double-blind, 29-center, international, placebo-controlled Phase 3 trial



*Stratified by patient's weekly PS volume requirements (<12 L/week vs ≥12 L/week).
OW=once weekly; TW=twice weekly.

Key EASE SBS 1 Trial Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
• Diagnosis of SBS, defined as an estimated <200 cm of remaining small bowel in continuity • Latest intestinal resection ≥6 months before screening • Patient considered stable regarding PS needs • PS required ≥3 days per week • Willing to adhere to an individual predefined drinking menu and urine measurement during the 48-hour measuring intervals • Aged 18–90 years	• History of colon cancer • History of any other cancers unless disease-free state for at least 5 years • Severe cardiac impairment* • Severe kidney impairment† • Severe hepatic impairment‡ • Known or suspected hypersensitivity to glepaglutide or related products • Previous exposure to glepaglutide

*Defined as decompensated heart failure (NYHA Class III–IV), unstable angina pectoris, and/or myocardial infarction during 6 months before screening.
†Estimated creatinine clearance <30 mL/min (using the Cockcroft–Gault formula).
‡Defined as total bilirubin ≥2 times upper limit of normal (ULN), aspartate aminotransferase ≥5 times ULN, or alanine transaminase ≥5 times ULN.

EASE SBS 1 Trial Endpoints

Primary endpoint

- Change in actual weekly PS volume from baseline to weeks 24

Key secondary endpoints

- ≥20% reduction in actual absolute weekly PS volume from baseline to weeks 20 and 24
- ≥1 day per week reduction in actual absolute weekly PS days from baseline to week 24
- Change in actual absolute weekly PS volume from baseline to week 12
- 100% reduction (weaned off, enteral autonomy) in actual absolute weekly PS volume from baseline to week 24
- **Safety**

EASE SBS 1 Trial Endpoints

Secondary efficacy endpoints

- Reduction of at least 20% in PS volume from baseline to both Weeks 12 and 24
- Change in fluid composite effect (FCE) from baseline to Week 24
- Reduction in calculated energy content of parenteral macronutrients from baseline to Week 24
- Reduction in number of days on PS per week from baseline to Week 24
- Reduction of at least 40% in PS volume from baseline to both Weeks 20 and 24
- **PGIC improvement at Weeks 4, 12, 20, and 24**
- Change in weight from baseline to Week 24

Other efficacy endpoints

- Reduction in days on PS ≥ 2 days/week from baseline to Week 24
- Reduction in days on PS ≥ 3 days/week from baseline to Week 24
- Reduction in duration of PS infusions per week from baseline
- Concentration trough levels of glepaglutide and metabolites
- Change in plasma citrulline level from baseline to Week 24
- Change in weekly need for parenteral micronutrients (sodium, potassium, magnesium and calcium) from baseline to Week 24
- **Change in patient-reported outcomes (SBS-I and EQ-5D-5L) from baseline to Week 24**

SBS-I

SBS-Impact Scale

SBS-Impact Scale (SBS-I)
as used in the EASE-SBS trial program

- Assess the symptoms and the impact of SBS on your everyday life
- Questions(/items) using scale from 0-10 where 0=Not at all and 10=Worst possible

1. How affected have you been by gastrointestinal symptoms related to SBS such as diarrhea, nausea or bloating in the last week?
2. How affected have you been by pain in your muscles or bones due to your illness (SBS) in the last week?
3. How affected have you been by pain in your abdomen due to your illness (SBS) in the last week?
4. How exhausted or tired have you been due to your illness (SBS) in the last week?
5. How much has your illness (SBS) affected your sleep in the last week?
6. To what degree has your illness (SBS) interfered with the things you wanted to do in the last week?
7. How much has your illness (SBS) affected your mood in the last week?
8. How affected have you been by stress or anxiety related to SBS in the last week?

Patient Disposition, Demographics, and Baseline Characteristics

Disclaimer: some demographic data have been redacted to maintain the blinding and integrity of EASE SBS 2 trial.

Patient Disposition
96% Completed Trial

Patients	Total, N
Screened	154
Randomized	**106**
Full analysis set	106
Safety analysis set	106
Treatment completers	101
Treatment discontinuation Primary reason Adverse events Patient decision	5 3 2
Trial completers Attended week 24 visit	102 **102/106 (96%)**

Patients who discontinued treatment but completed all visits are considered to have completed the trial.

Patient Demographics Well-Balanced

	Glepaglutide 10 mg TW (N=35)	Glepaglutide 10 mg OW (N=35)	Placebo (N=36)	Total (N=106)
Age, years				
Mean (SD)	56.9 (13.4)	54.0 (12.0)	54.0 (11.8)	55.0 (12.4)
Age group, years				
18–<65	23 (65.7)	28 (80.0)	30 (83.3)	**81 (76.4)**
≥65	12 (34.3)	7 (20.0)	6 (16.7)	25 (23.6)
≥75	2 (5.7)	0	2 (5.6)	4 (3.8)
Sex, n (%)				
Female	19 (54.3)	18 (51.4)	20 (55.6)	**57 (53.8)**
Male	16 (45.7)	17 (48.6)	16 (44.4)	49 (46.2)

SD=standard deviation.

Patient Baseline Characteristics (I)

	Glepaglutide 10 mg TW (N=35)	Glepaglutide 10 mg OW (N=35)	Placebo (N=36)	Total (N=106)
SBS anatomical classification, n (%)				
Group 1 (jejunostomy)	14 (40.0)	18 (51.4)	20 (55.6)	52 (49.1)
Group 2 (jejuno-colonic anastomosis)	19 (54.3)	15 (42.9)	14 (38.9)	48 (45.3)
Group 3 (jejuno-ileo-colonic anastomosis)	2 (5.7)	2 (5.7)	2 (5.6)	6 (5.7)
Stoma, n (%)				
No	18 (51.4)	15 (42.9)	15 (41.7)	48 (45.3)
Yes	17 (48.6)	20 (57.1)	21 (58.3)	58 (54.7)
Underlying cause of SBS, n (%)				
Crohn's disease	14 (40.0)	12 (34.3)	16 (44.4)	42 (39.6)
Mesenteric vascular disease	10 (28.6)	7 (20.0)	4 (11.1)	21 (19.8)
Surgical complications	3 (8.6)	13 (37.1)	9 (25.0)	25 (23.6)
Intestinal volvulus	4 (11.4)	1 (2.9)	1 (2.8)	6 (5.7)
Abdominal trauma	3 (8.6)	1 (2.9)	2 (5.6)	6 (5.7)
Other	1 (2.9)	1 (2.9)	4 (11.1)	6 (5.7)

Patient Baseline Characteristics (II)

	Glepaglutide 10 mg TW (N=35)	Glepaglutide 10 mg OW (N=35)	Placebo (N=36)	Total (N=106)
Weekly PS volume requirements, L/week				
Mean (SD)	13.79 (8.12)	14.51 (7.53)	14.82 (7.95)	14.37 (7.81)
Median	12.20	12.50	14.70	12.55
PS stratification factor, n (%)				
<12 L/week	15 (42.9)	16 (45.7)	15 (41.7)	46 (43.4)
≥12 L/week	20 (57.1)	19 (54.3)	21 (58.3)	60 (56.6)
Weekly PS, days				
Mean (SD)	5.6 (1.8)	6.4 (1.2)	5.8 (1.6)	5.9 (1.5)
Median	7.0	7.0	7.0	7.0
Weight, kg				
Mean (SD)	67.13 (13.05)	64.00 (13.98)	65.74 (12.08)	65.62 (12.99)
Median	64.70	59.70	65.55	63.35
BMI, kg/m^2, n (%)				
<18.5	0	1 (2.9)	1 (2.8)	2 (1.9)
18.5–<25	25 (71.4)	29 (82.9)	25 (69.4)	79 (74.5)
25–<30	7 (20.0)	4 (11.4)	8 (22.2)	19 (17.9)
≥30	3 (8.6)	1 (2.9)	2 (5.6)	6 (5.7)

BMI=body mass index.

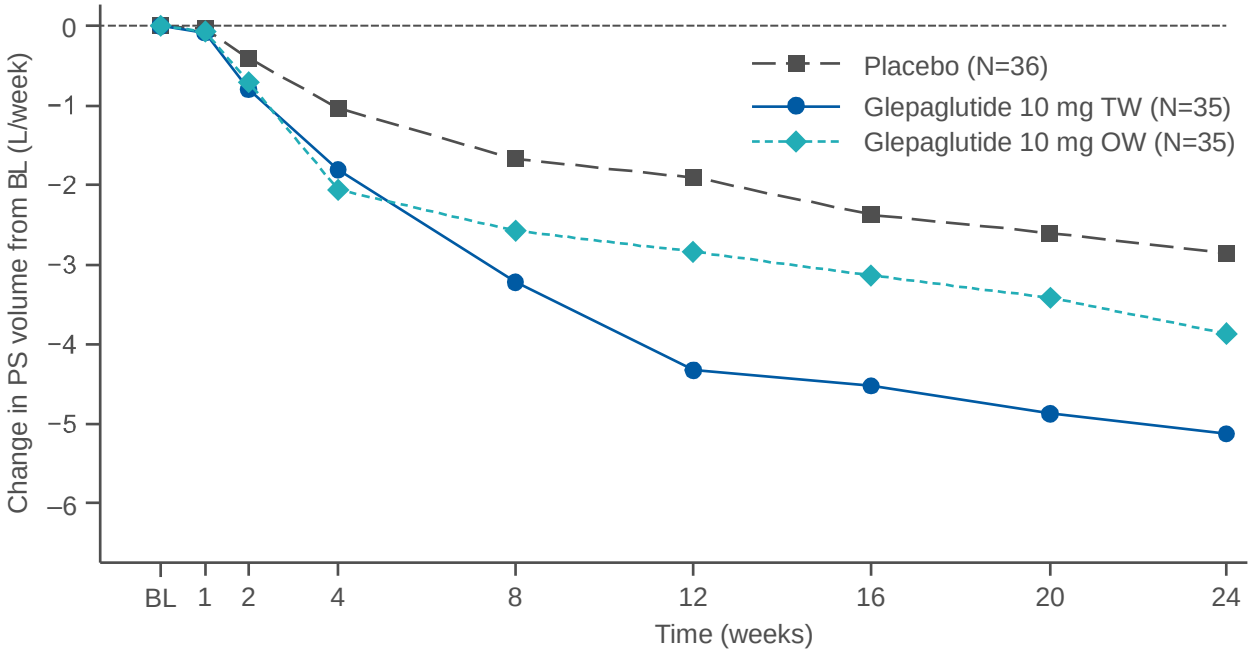
Patient Hepatic and Renal Function at Baseline

	Glepaglutide 10 mg TW (N=35)	Glepaglutide 10 mg OW (N=35)	Placebo (N=36)	Total (N=106)
Liver function at baseline, n (%)				
Normal	23 (65.7)	21 (60.0)	27 (75.0)	71 (67.0)
Mild impairment	11 (31.4)	12 (34.3)	9 (25.0)	**32 (30.2)**
Moderate impairment	1 (2.9)	2 (5.7)	0	3 (2.8)
Severe impairment	0	0	0	0
Renal function at baseline, n (%)				
Normal	9 (25.7)	16 (45.7)	19 (52.8)	44 (41.5)
Mild impairment	19 (54.3)	13 (37.1)	9 (25.0)	**41 (38.7)**
Moderate impairment	7 (20.0)	6 (17.1)	8 (22.2)	**21 (19.8)**
Severe impairment	0	0	0	0

Results

Primary efficacy endpoint: change in PS volume (L/week) from baseline to week 24

Glepaglutide 10 mg TW Significantly Reduced PS Volume in Patients With SBS-IF

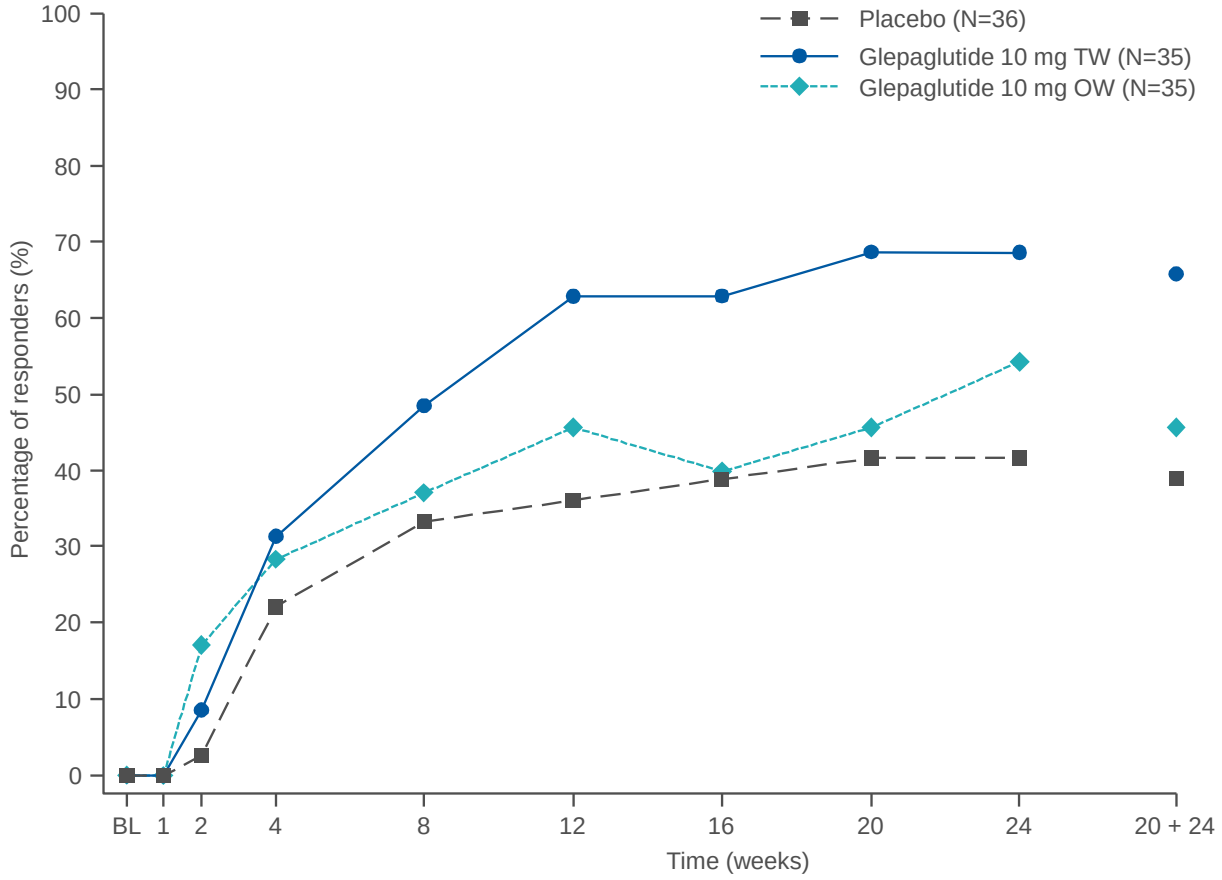


	Placebo (N=36)
Least-squares mean [95% CI]	−2.85 [−3.93, −1.77]
Difference vs placebo [95% CI]	–
p value	–

*In anatomical subgroup analysis for patients without and with colon-in-continuity, the mean PS volume reduction at week 24 was −5.63 L/week and −4.77 L/week, respectively.
BL=baseline; SBS-IF=SBS with IF.

Secondary endpoint: ≥20% reduction in PS volume (L/week) from baseline to weeks 20 and 24

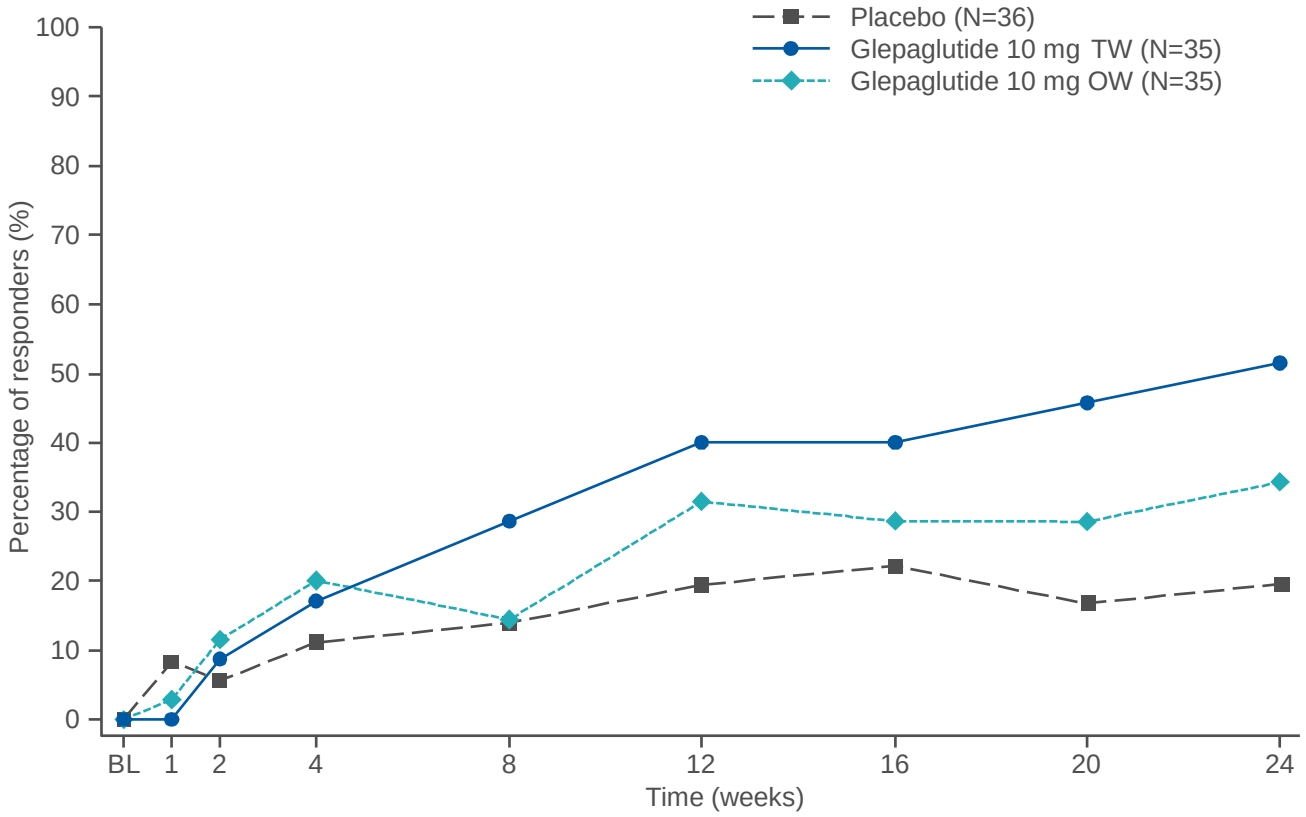
Glepaglutide-Induced Clinical Response



	Placebo (N=36)
n/N (%)	14/36 (38.9)
Difference vs placebo [95% CI]	–
p value	–

Secondary endpoint: ≥1 day per week reduction in weekly PS days from baseline to week 24

Glepaglutide Increased Days Without PS

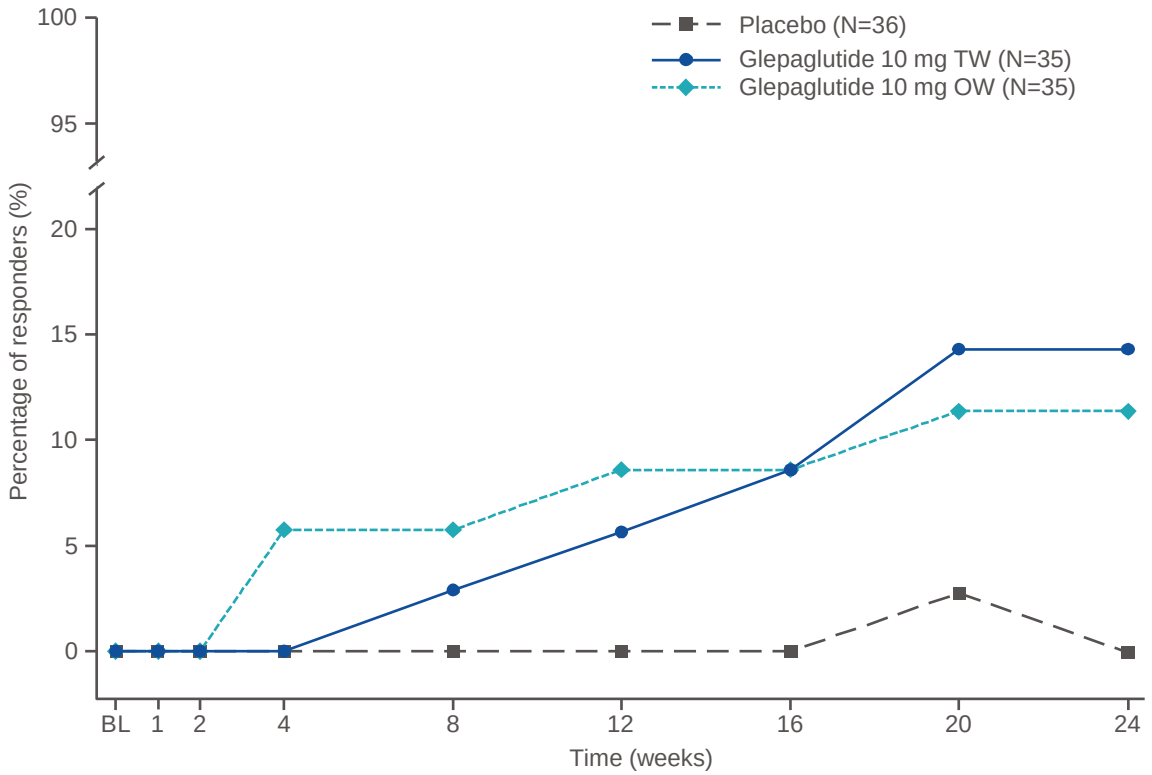


	Placebo (N=36)
n/N (%)	7/36 (19.4)
Difference vs placebo [95% CI]	–
p value	–

Secondary endpoint: 100% reduction in weekly PS volume from baseline to week 24

Glepaglutide-Induced Enteral Autonomy (Total Weaning Off PS)

Reduction in weekly PS volume of 100% at week 24



	Placebo (N=36)
n/N (%)	0/36 (0)
Difference vs placebo [95% CI]	–
Nominal p value	–

Safety Results

Disclaimer: some demographic data have been redacted to maintain the blinding and integrity of EASE 2 and EASE 3 trials.

Adverse Events

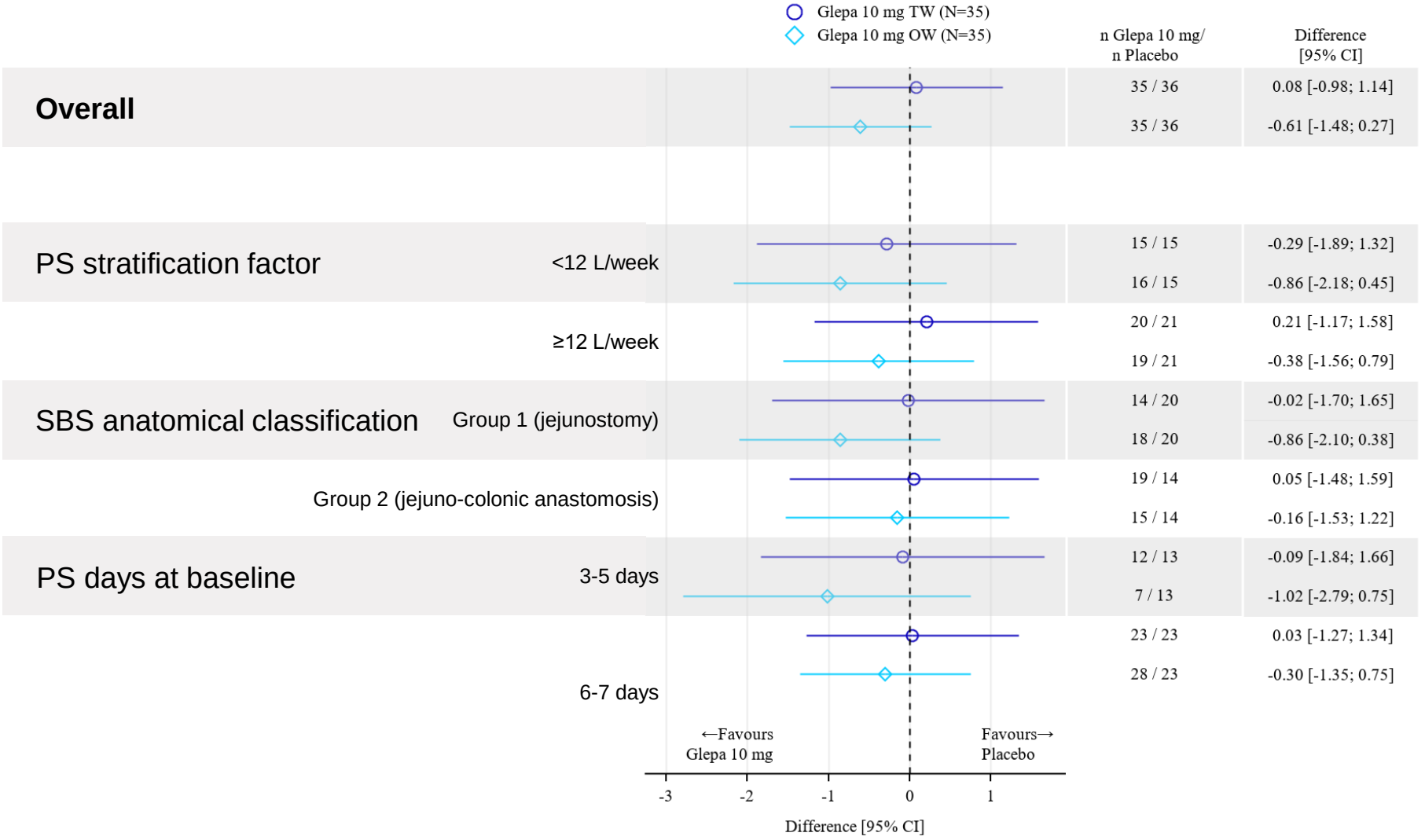
	Glepaglutide 10 mg TW (N=35)	Glepaglutide 10 mg OW (N=35)	Placebo (N=36)
All AEs	33 (94.3) 407	33 (94.3) 364	26 (72.2) 95
Injection site reactions	22 (62.9) 233	20 (57.1) 233	2 (5.6) 2
Serious AEs	9 (25.7) 15	9 (25.7) 11	7 (19.4) 8
Severity of AE			
Severe	10 (28.6) 20	4 (11.4) 4	2 (5.6) 2
Moderate	15 (42.9) 36	17 (48.6) 32	14 (38.9) 32
Mild	28 (80.0) 351	31 (88.6) 328	23 (63.9) 61
Relationship to trial treatment			
Related	27 (77.1) 290	26 (74.3) 277	13 (36.1) 28
Unlikely related	18 (51.4) 45	16 (45.7) 30	9 (25.0) 24
Not related	26 (74.3) 72	23 (65.7) 57	20 (55.6) 43
Outcome			
Recovered/resolved	32 (91.4) 364	30 (85.7) 328	24 (66.7) 65
Fatal	–	–	–
AEs leading to trial withdrawal*	2 (5.7) 2	–	–

Data are presented as n (%) and total number of adverse events
* Hypersensitivity reaction, subileus

SBS-I Results

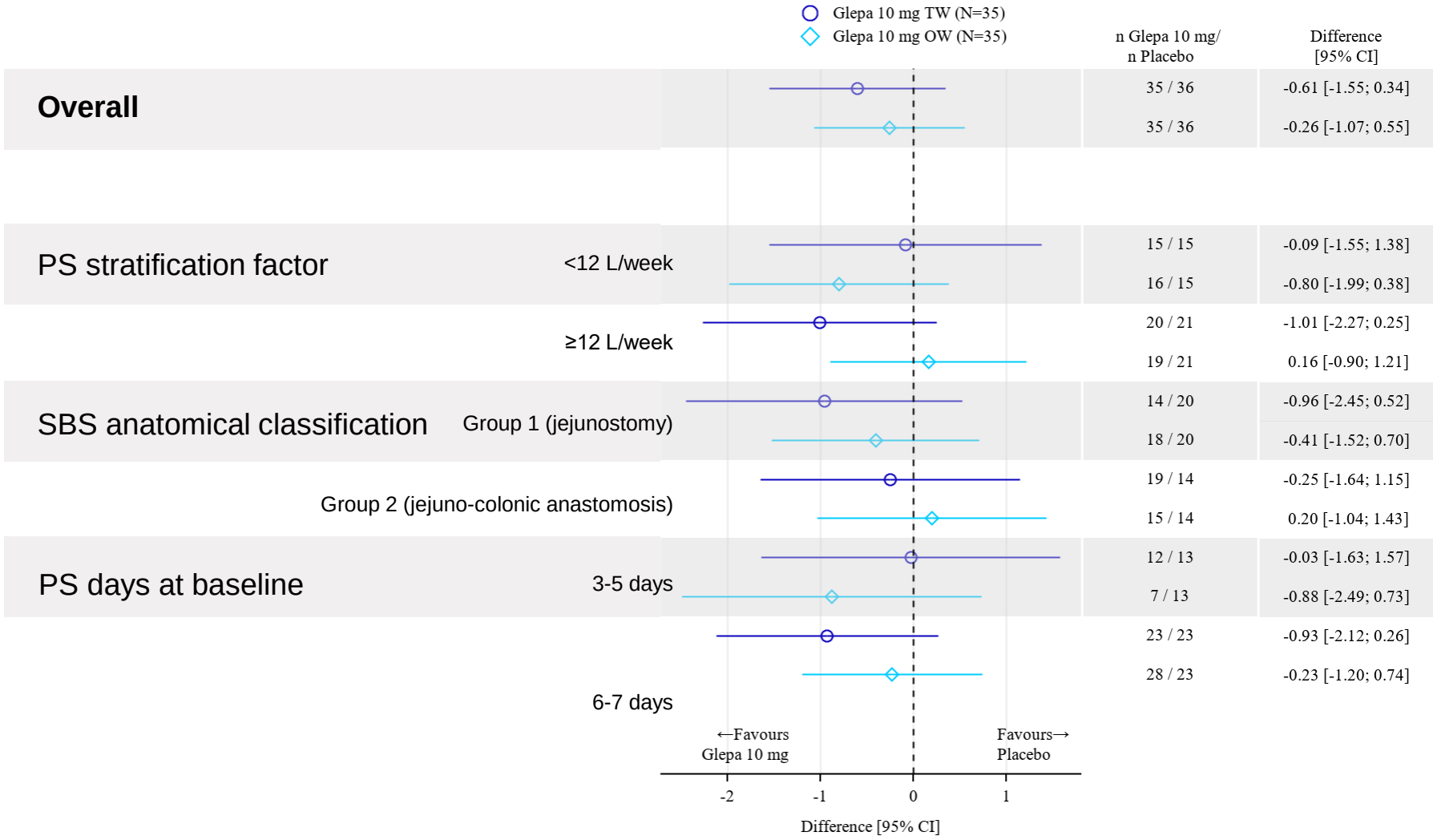
Disclaimer: some demographic data have been redacted to maintain the blinding and integrity of EASE 2 and EASE 3 trials.

Q: Gastrointestinal Symptoms
Change from baseline to week 24 by subgroup



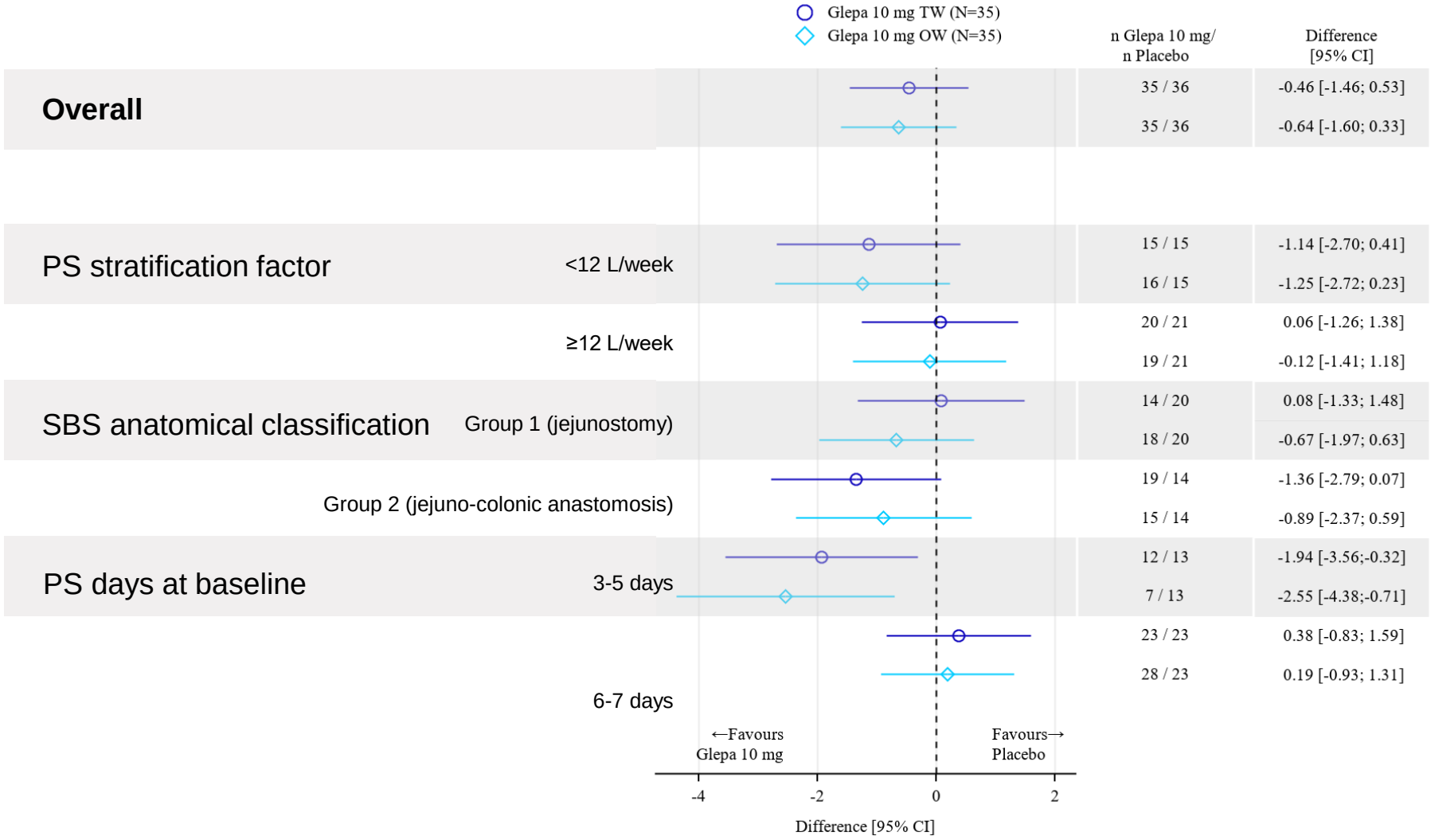
Q: Abdomen Pain

Change from baseline to week 24 by subgroup



Q: Affected Your Sleep

Change from baseline to week 24 by subgroup



Preliminary Excerpts from Patient Exit Interviews


"It allows me to, you know, get on with my life, not being constantly in the bed. And just, you know, just being able to move on with my life."
"I've got my life back. [tears up] I'm sorry...And if they [sponsor] need a spokesperson, I'm their girl. [laughs]."
"Just again, it comes down to freedom to being able to do things ...and now I keep going. I can do this. I can make it through a whole store trip and not have issues. Not get tired."
"I was, you know, sedentary... hardly make a meal without being weak and have to sit down during ...and now I can get up and bake cookies, you know."
"I don't have to empty it as often. I'm not waking up constantly in the middle of the night or worried I'm going to have an accident."
In what way was it meaningful to you?
"I sleep much better on my nights off, so I feel better having an extra night of much less interrupted sleep. It's definitely an improvement to my mental health as well."
"Yes, very much so. I mean, that minimal change took me from wanting to die, or at least considering it, to wanting to live and not just live, but have some hope."
"As I've said before, my physical ability and my lack of fatigue now compared to before has improved to the point where, yes, I get out and do almost anything I could do prior to this whole ordeal... before when I had a supposedly life."
"I feel freer, like I can go out and do things. I don't have to worry about... Do I need fluids. I can't go do that or... It's kind of embarrassing to go out and have, you know, IV lines hanging out of you where everyone can see them. It's freedom."
"By regaining my normal life physically, that has lessened the mental and emotional aspects of dealing with this particular disease."
"I feel like... I feel like my old self again I just have to kind of rebuild my strength and endurance. Yeah. I feel like my full intestinal self."

Summary and Conclusions

Treatment with glepaglutide 10 mg TW

- Significantly reduced PS requirements in patients with SBS and IF
  - Overall reduction of 5.2 L/week (~45% reduction from baseline)
  - 66% of patients achieved clinical response (≥20% reduction in PS from baseline)
  - 51% of patients had a reduced number of days off PS by 1 day or more
- Five of 35 patients (14%) achieved enteral autonomy (vs 0% of patients treated with placebo)
  - 11% of those treated with glepaglutide 10 mg OW also achieved enteral autonomy
- Improved abdominal pain and sleep patterns (SBS-I tool)
- Was well-tolerated and had an acceptable safety profile over the 24 weeks of treatment

**Glepaglutide is a novel long-acting GLP-2 analogue
that can reduce the burden of PS in patients with SBS-IF
and represents an attractive potential treatment option for the management of SBS**

Acknowledgments to Trial Patients, Investigators (below), and the Trial Sponsor Zealand Pharma

Johane Allard

Irina Blumenstein

Elisabeth Blüthner

Cecile Chambrie

Leah Gramlich

Simon Gabe

Kishore Iyer

Francisca Joly

Palle B Jeppesen

Lars V Jensen

Marek Kunecki

Simon Lal

Georg Lamprecht

David F Mercer

Konrad Matysiak

Manpreet S Mundi

Ulrich-Frank Pape

Ji Seok Park

Charlotte Pither

Farooq Rahman

Adam Rahman

Sukanya Subramanian

Carol Semrad

Trevor Smith

Kinga Szczepanek

Tim Vanuytsel

Geert Wanten

Martin von Websky

Dawn A Wiese

Thank You for Your Attention

Q&A