Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome.

Carter BA[1], Cohran VC[2], Cole CR[3], Corkins MR[4], Dimmitt RA[5], Duggan C[6], Hill S[7], Horslen S[8], Lim JD[9], Mercer DF[10], Merritt RJ[11], Nichol PF[12], Sigurdsson L[13], Teitelbaum DH[14], Thompson J[15], Vanderpool C[16], Vaughan JF[17], Li B[18], Youssef NN[19], Venick RS[20], Kocoshis SA[3].

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Trial was supported by NPS Pharmaceuticals, Inc.,* Bedminster, NJ
***A wholly owned indirect subsidiary of Shire plc**

Oral Presentation Oley Foundation Annual Conference, July 5-8, 2017, New Greenwich CT, USA

DISCLOSURE

- Beth Carter, MD served as a study investigator and received research support from NPS Pharmaceuticals/ Shire
- Beth Carter, MD has been a speaker (Webinar) for Thrive Rx

INTRODUCTION

- **Children with SBS**
  - Diminished absorptive capacity
  - May remain parenteral support (PS) dependent for many months with little intestinal adaptation under current standards of care

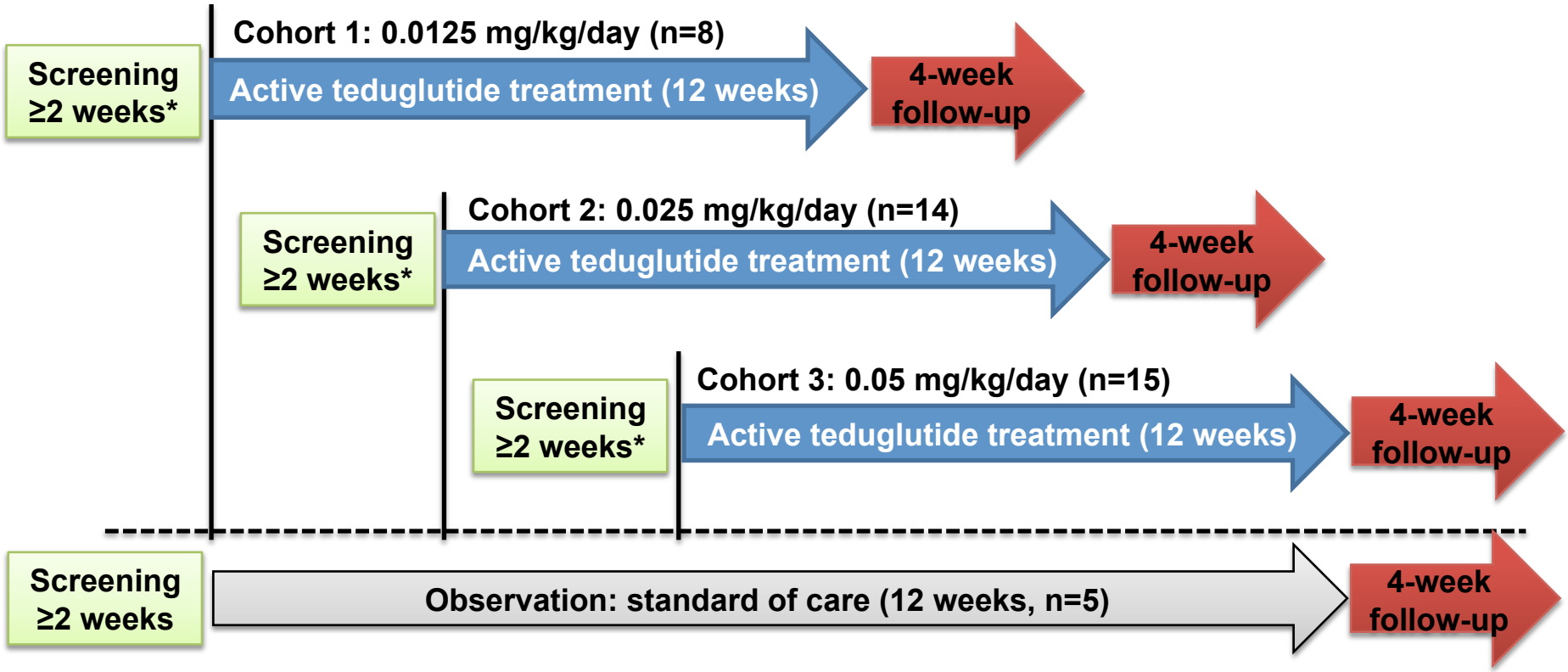
- **Teduglutide (GLP-2 analogue)[1-3]**
  - Approved for adults with SBS dependent on PS
  - Approved for children with SBS aged ≥ 1 year in the EU
  - Stimulates small bowel growth
  - Mediates intestinal adaptation

- **Pediatric clinical study**
  - To evaluate whether teduglutide enhances intestinal adaptation in PS-dependent children with SBS with no significant advance in enteral nutrition (EN)

EN=enteral nutrition (formula taken by mouth and/or tube feeding); GLP-2=glucagon-like peptide 2; PS=parenteral support (parenteral nutrition and/or intravenous fluids); SBS=short bowel syndrome

1. Tappenden KA. J Parenter Enteral Nutr. 2014;38(suppl 1):23S-31S; 2. GATTEX® (teduglutide [rDNA origin]). Full Prescribing Information. NPS Pharmaceuticals, Inc., Bedminster, NJ. 2014; 3. REVESTIVE® (teduglutide [rDNA origin]). Summary of Product Characteristics. NPS Pharmaceuticals, Inc., Bedr

STUDY DESIGN



*Safety data were assessed after ≥28 days of teduglutide treatment before the next dosing cohort could proceed

ClinicalTrials.gov: NCT01952080; EudraCT: 2013-004588-30

METHODS

- Aged 1–17 years with SBS for ≥12 months, on PS for ≥30% of caloric and/or fluid/electrolyte needs
  - ≤10% change in PS or advance in EN feeds for ≥3 months
- EN calorie and volume data were based on commercially available liquid feed taken orally/given via tube feeding only
  - Additional solid foods and liquids considered “ad lib” nutrition and not included in calculation of EN
- Statistical analysis
  - Data assessed by descriptive statistics (eg, median, minimum, maximum, number of patients, percentage of patients)

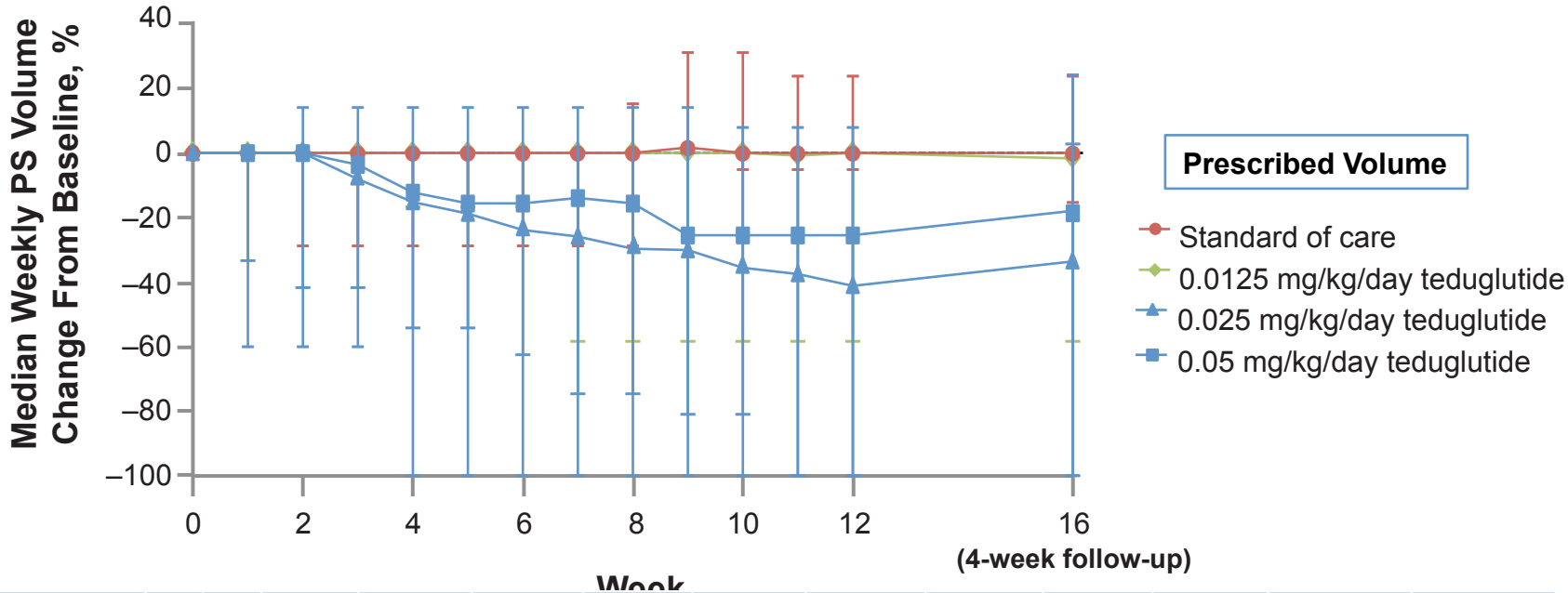
EN=enteral nutrition (formula taken by mouth and/or tube feeding); PS=parenteral support (parenteral nutrition and/or intravenous fluids); SBS=short bowel syndrome

BASELINE CHARACTERISTICS
40/42 patients completed the study

	Standard of Care (n=5)	Teduglutide, mg/kg/day 0.0125 (n=8)	0.025 (n=14)	0.05 (n=15)
Age, years				
Median (min, max)	2.0 (2, 3)	3.0 (1, 14)	4.0 (1, 14)	4.0 (1, 14)
Male, n (%)	3 (60)	6 (75)	11 (79)	8 (53)
Median BMI, kg/m^2 (min, max)	16.8 (14.3, 18.4)	15.4 (13.8, 19.4)	16.2 (14.8, 18.2)	15.9 (14.3, 18.4)
Duration of PS dependency, years				
Median (min, max)	2.4 (2, 3)	3.6 (1, 12)	4.2 (1, 9)	4.0 (0.5, 12)
Stoma, n (%)	0	1 (13)	1 (7)	1 (7)
Colon-in-continuity, n (%)*	5 (100)	7 (100)	12 (86)	14 (100)
Median estimated residual small intestine length, cm (min, max)	35 (10, 75)	15 (2, 75)	68 (15, 145)	26 (0, 68)
Median PS volume at baseline, L/week (min, max)	7.7 (4.4, 9.8)	5.4 (4.2, 13.9)	8.1 (4.4, 16.0)	5.6 (4.0, 13.1)
Median EN volume at baseline, L/week (min, max)	5.1 (0.9, 6.0)	8.1 (2.9, 12.6)	7.0 (1.9, 13.4)	3.4 (0.3, 6.3)

*Percentages based on patients with remaining colon

DECREASE IN PS VOLUME



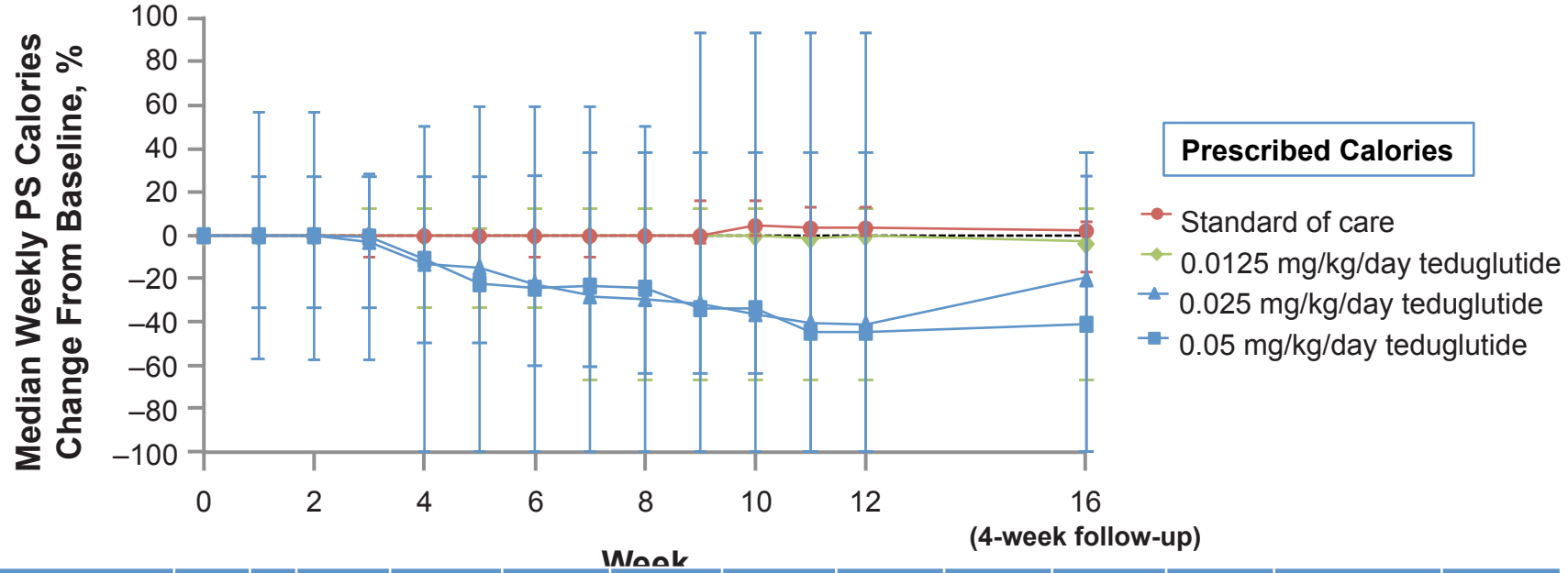
Median Weekly PS Volume, % Change From Baseline	1	2	3	4	5	6	7	8	9	10	11	12	16
Standard of care*	0	0	0	0	0	0	0	0	1.7	0	0	**0**	0
0.0125 mg/kg/day†	0	0	0	0	0	0	0	0	0	0	-0.8	**0**	-1.7
0.025 mg/kg/day‡	0	0	-8.1	-15.2	-18.8	-23.9	-25.9	-29.7	-30.0	-35.5	-37.5	**-41.1**	-33.6
0.05 mg/kg/day§	0	0	-3.6	-12.2	-15.6	-15.6	-13.9	-15.6	-25.4	-25.4	-25.4	**-25.4**	-17.9

*n=5 (except n=4 at Week 5); †n=8 (except n=6 at Week 11 and n=7 at Weeks 1, 4–10, 12, and 16); ‡n=14 (except n=13 at Week 12);§n=15 (except n=14 at Weeks 7, 9–12, and 16)

PS=parenteral support (parenteral nutrition and/or intravenous fluids)

Data points are median values, and error bars are the min and max values

DECREASE IN PS CALORIES



Median Weekly PS Calories, % Change From Baseline	1	2	3	4	5	6	7	8	9	10	11	12	16
Standard of care*	0	0	0	0	0	0	0	0	0	4.8	3.7	**3.7**	2.4
0.0125 mg/kg/day†	0		0	0	0	0	0	0	0	0	-1.3	**0**	-2.6
0.025 mg/kg/day‡	0	0	-3.0	-13.2	-14.9	-22.5	-28.2	-29.5	-31.6	-36.4	-40.5	**-41.2**	-19.3
0.05 mg/kg/day§	0		-0.5	-10.9	-22.3	-24.2	-23.2	-24.2	-33.7	-33.7	-44.7	**-44.7**	-40.9
		0											
		0											

Data points are median values. and error bars are the min and max values

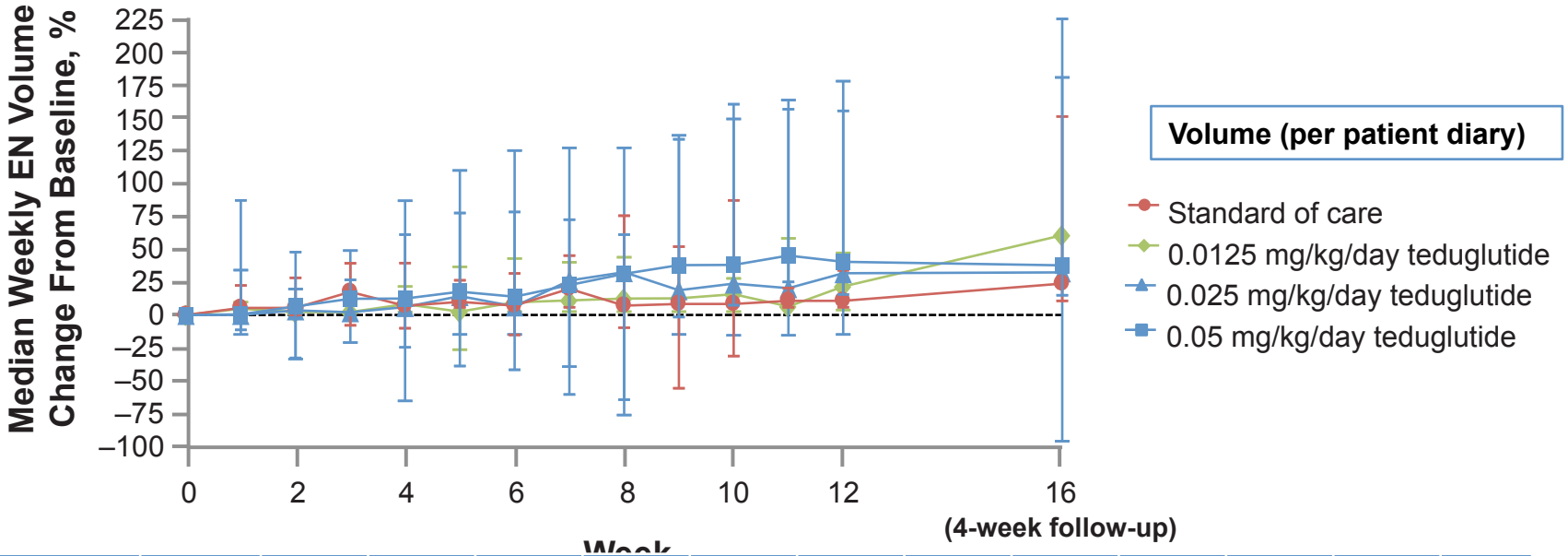
GAIN IN TIME OFF PS
WEEK 12

	Standard of Care (n=5)	Teduglutide, mg/kg/day 0.0125 (n=8)	0.025 (n=14)	0.05 (n=15)
Change in hours per day of PS infusion, median (min, max) change from baseline	0 (–2.0, 0.6)	0 (0, 2.0)†	**–4.0** (–9.0, 2.0)‡	**–3.0** (–12.0, 0.8)‡
Patients who gained ≥3 days per week off PS, n (%)	0 (0)	0 (0)	**1** (7)	**4** (27)
Patients who achieved PS independence, n (%)*	0 (0)	0 (0)	**1** (7)	**3** (20)

*2 patients resumed PS 4 weeks after teduglutide treatment ended
†n=7; ‡n=12

PS=parenteral support (parenteral nutrition and/or intravenous fluids)

ADVANCES IN EN VOLUME

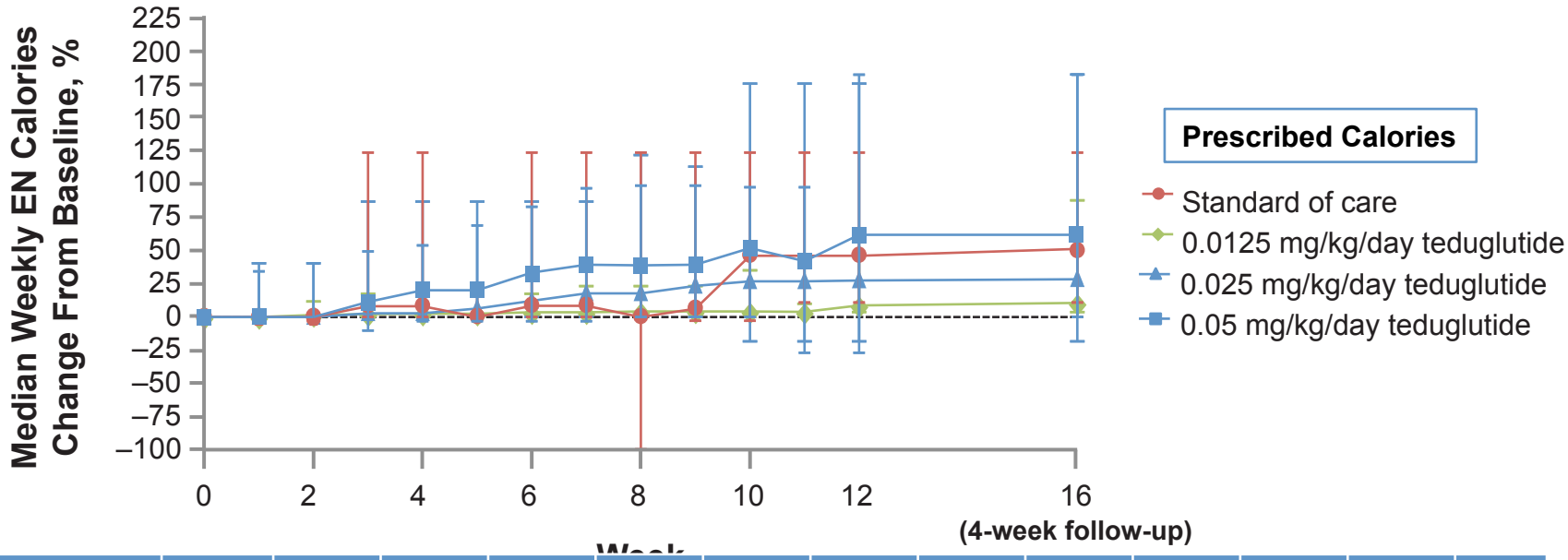


Median Weekly EN Volume, % Change From Baseline	1	2	3	4	5	6	7	8	9	10	11	12	16
Standard of care*	5.4	5.4	17.4	7.0	10.0	7.1	19.9	7.1	8.3	8.3	10.7	**10.7**	**23.8**
0.0125 mg/kg/day†	4.8	2.3	2.3	8.2	2.5	9.6	11.0	12.5	12.6	15.7	6.5	**21.6**	**60.3**
0.025 mg/kg/day‡	0	3.5	2.1	6.0	14.4	6.5	26.1	32.4	18.8	23.7	20.3	**31.5**	**32.2**
0.05 mg/kg/day§	0.6	6.4	12.3	12.5	17.5	13.9	22.6	31.2	37.6	37.9	44.9	**40.2**	**37.5**

*n=4 (except n=3 at Weeks 5, 11, and 12); †n=4 (except n=1 at Week 16 and n=3 at Weeks 1–3, 5, and 11); ‡n=13 (except n=11 at Week 16 and n=12 at Weeks 4, 7, 8, and 12); §n=10 (except n=8 at Weeks 1 and 12 and n=9 at Weeks 2–4, 9–11, and 16)

EN=enteral nutrition (formula taken by mouth and/or tube feeding)
Data points are median values, and error bars are the min and max values

ADVANCES IN EN CALORIES



Median Weekly EN Calories, % Change From Baseline	1	2	3	4	5	6	7	8	9	10	11	12	16
Standard of care*	0	0	8.2	8.2	0	8.5	8.5	0	6.3	46.3	46.3	**46.3**	**51.5**
0.0125 mg/kg/day†	0	1.6	2.3	2.6	2.6	3.6	3.6	4.3	4.3	4.3	4.0	**8.8**	**10.8**
0.025 mg/kg/day‡	0	0	2.9	2.9	6.5	12.2	17.9	17.9	23.6	27.0	27.0	**27.7**	**28.6**
0.05 mg/kg/day§	0	0	11.5	20.2	20.2	33.6	39.6	39.2	39.6	52.1	42.2	**62.2**	**62.2**

*n=4 (except n=3 at Week 5); †n=4 (except n=3 at Weeks 5 and 11); ‡n=13;§n=10 (except n=9 at Weeks 7, 9–12, and 16)

EN=enteral nutrition (formula taken by mouth and/or tube feeding)
Data points are median values, and error bars are the min and max values

NUTRITIONAL STATUS BASELINE AND WEEK 12

- Clinical and nutritional status parameters were maintained despite PS reductions with teduglutide 0.025 or 0.05 mg/kg/day
  - Albumin, blood urea nitrogen, creatinine, and electrolytes (calcium, magnesium, phosphate) were stable at Week 12 compared with baseline

Median Weight (min, max)	Standard of Care (n=5)	Teduglutide, mg/kg/day 0.0125 (n=8)	0.025 (n=14)	0.05 (n=15)
Baseline	12.3 (11.2, 14.8)	13.3 (10.1, 48.7)	17.4 (10.3, 44.3)	16.1 (10.5, 38.5)
Week 12	13.1 (11.7, 15.7)	16.0 (11.2, 50.4)*	17.2 (10.2, 53.4)†	16.1 (10.8, 35.8)‡

*n=7; †n=12; ‡n=13

PS=parenteral support (parenteral nutrition and/or intravenous fluids)

SAFETY: TEAEs* (TREATMENT-EMERGENT ADVERSE EVENTS)

- All patients experienced ≥1 TEAE; most were mild or moderate

TEAEs by Preferred Term, n (%) Patients†	Standard of Care (n=5)	All Teduglutide (n=37)
Vomiting	0	12 (32)
Upper respiratory tract infection	2 (40)	10 (27)
Catheter-related complication	1 (20)	9 (24)
Pyrexia	2 (40)	9 (24)
Cough	1 (20)	7 (19)
Abdominal pain	1 (20)	6 (16)
Headache	0	5 (14)
Nausea	0	5 (14)
Fatigue	0	5 (14)
Blood bicarbonate decreased	2 (40)	5 (14)
Diarrhea	1 (20)	4 (11)
Fecal volume decreased	0	4 (11)
Central line infection	0	4 (11)
Gastrointestinal stoma complication‡	0	1 (25)

*TEAEs occurring in ≥10% of teduglutide-treated patients; †percentages based on the number of patients in each treatment group; ‡percentages based on the number of patients with a stoma in each treatment group

TEAE=treatment-emergent adverse event

SAFETY (cont'd)

- Serious TEAEs were experienced by patients in teduglutide and standard of care groups (46% and 60%, respectively); none were considered related to study treatment
- There were no reports of intestinal obstruction, fluid overload, biliary complications (ie, cholecystitis, pancreatitis), or colonic polyp formation
- No patients developed neutralizing antibodies to teduglutide

Serious TEAEs by Preferred Term,* n (%) Patients†	Standard of Care (n=5)	Teduglutide, mg/kg/day 0.0125 (n=8)	0.025 (n=14)	0.05 (n=15)	Total (n=37)
Central line infection	0	0	3 (21)	1 (7)	4 (11)
Pyrexia	2 (40)	0	1 (7)	3 (20)	4 (11)
Catheter-related complication	1 (20)	0	2 (14)	1 (7)	3 (8)
Parainfluenza virus infection	0	0	1 (7)	1 (7)	2 (5)

*Serious TEAEs occurring in ≥2 teduglutide-treated patients
†Percentages based on the number of patients in each treatment group

TEAE=treatment-emergent adverse event

CONCLUSIONS

- Treatment with teduglutide in children whose intestinal rehabilitation had plateaued was associated with
  - < PS volume and calories + > EN volume
- Teduglutide 0.05 mg/kg/day
  - Reduced PS volume by 25% and calories by 45%
  - Advanced EN volume by 40% and calories by 62%
  - PS independence was achieved by 20% (3/15) patients
  - 27% (4/15) gained ≥3 days per week off PS
  - At 4 weeks after discontinuing teduglutide, EN improvements were maintained and 2 patients remained PS independent
- Teduglutide had a generally good safety profile and well tolerated in this pediatric population
- Clinical and nutritional status was maintained in teduglutide-treated patients despite reductions in PS, suggesting improved intestinal absorption

EN=enteral nutrition (formula taken by mouth and/or tube feeding); PS=parenteral support (parenteral nutrition and/or intravenous fluids)

ACKNOWLEDGMENT

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- Study co-investigators

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J. Thompson	New York, NY	USA
C. Vanderpool	Indianapolis, IN	USA
J. F. Vaughan	Little Rock, AK	USA
R. S. Venick	Los Angeles, CA	USA

Back-up Slides
for
Beth Carter

Intestinal Adaptation in Children With Short Bowel Syndrome During Treatment With Teduglutide

Oral Presentation Oley Foundation Annual Conference, July 5-8, 2017, New Greenwich CT, USA

STUDY DESIGN
Main Inclusion & Exclusion Criteria

Key Inclusion	Key Exclusion
Male and female patients aged 1–17 years	Body weight <5th percentile for age or <10 kg
Written informed consent by parent or guardian	Hospital admissions: ≥3 SBS- or PS-related within 3 months of screening or any unscheduled within 1 month of screening
History of SBS due to a major intestinal resection for ≥12 months before screening that requires PS (≥30% of caloric and/or fluid/electrolyte needs)	Major gastrointestinal surgical intervention, serial transverse enteroplasty, or any bowel lengthening procedure within the past 3 months
Stable PS for ≥3 months without substantial PS reductions (≤10% change in PS or advance in EN feeds)	Unstable absorption due to cystic fibrosis, untreated Hirschsprung disease, or known DNA abnormalities
Use of acceptable methods of birth control during and for 30 days after the study in girls of childbearing potential	Evidence of untreated intestinal obstruction, active stenosis, upper gastrointestinal obstruction, pseudo-obstruction, or severe dysmotility syndrome
	History of cancer or lymphoproliferative disease (not including resected cutaneous basal or squamous cell carcinoma or in situ nonaggressive and surgically resected cancer)
	Active Crohn's disease treated with biological therapy within 6 months of screening or inflammatory bowel disease treated with chronic systemic immunosuppressant therapy that had been started or changed within 3 months of screening
	Previous use of native GLP-2, GLP-1 analog, human growth hormone, oral or intravenous glutamine, octreotide, or DPP-IV inhibitors within 3 months of screening
	Previous use of teduglutide

DPP-IV=dipeptidyl peptidase-4; EN=enteral nutrition (formula taken by mouth and/or tube feeding); GLP=glucagon-like peptide; PS=parenteral support (parenteral nutrition and/or intravenous fluids); SBS=short bowel syndrome

INCREASE IN PLASMA CITRULLINE LEVELS

Median (min, max)	Teduglutide, mg/kg/day		
	0.0125 (n=8)	0.025 (n=14)	0.05 (n=15)
Baseline, µmol/L	14.7 (3.8, 25.3)	16.1 (6.4, 29.8)	16.8 (4.5, 30.6)‖
Week 12, µmol/L	18.6 (6.2, 48.2)‡	22.0 (7.8, 47.0)§	16.7 (4.2, 72.9)‖
Change from baseline, µmol/L*	**1.0 (-0.8, 22.9)‡**	**5.4 (1.1, 17.2)§**	**7.5 (-13.9, 56.5)§**
Change from baseline, %*	**11.6 (-4.1, 90.5)‡**	**34.2 (10.1, 90.7)§**	**78.2 (-50.7, 344.5)§**
Week 16, µmol/L†	15.1 (6.5, 50.6)‡	17.5 (6.8, 35.8)	9.5 (2.9, 48.2)‖
Change from baseline, µmol/L*	1.0 (-4.2, 25.3)‡	1.9 (-2.4, 6.8)	0.4 (-19.1, 28.2)§
Change from baseline, %*	8 (-30, 100)‡	12 (-21, 50)	5 (-67, 172)§

*Median value from individualized calculated values from baseline to Week 12
†4 weeks after end of study drug treatment
‡n=7;§n=13; ‖n=14