



## Short Bowel Syndrome and Complex Crohn's Perianal Fistulas



February 24, 2022

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## Agenda

## Presenters

**1. Takeda's Initiatives in Gastroenterology (GI) Therapeutic Area**

**Mitsuhiro Shikamura**  
Senior Clinical Science Director, Therapeutic Area Strategy Unit (GI)

**2. Short Bowel Syndrome**

Masakazu Miyamoto  
Manager, Marketed Product Group, Therapeutic Area Strategy Unit

**3. Complex Crohn's Perianal Fistulas**

Tomoko Tanaka  
Associate Medical Director, Therapeutic Area Strategy Unit (GI)  
Takayoshi Yamaguchi  
Manager, Therapeutic Area Strategy Unit (GI)

**4. Q&A Session**

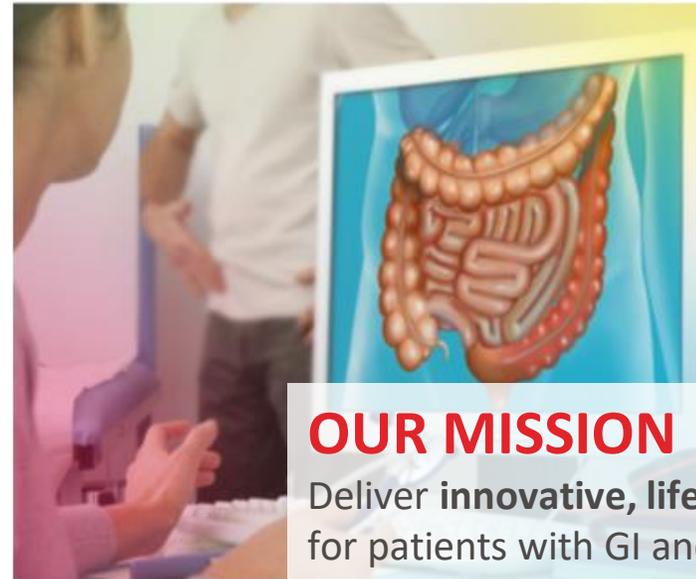
Q&A Panelists

# We aspire to be the leading GI company



## OUR VISION

Restore Life to Living for patients suffering with GI and liver diseases



## OUR MISSION

Deliver innovative, life-changing therapeutics for patients with GI and liver diseases

# Our GI strategy has evolved to focus on leadership in critical unmet needs in GI and liver diseases



## Maintaining the lead in GI

### MARKETED PRODUCTS:

Maximize & Create Value for Patients



## Progressing GI TA strategic pillars

### CURRENT PORTFOLIO:

Progress GI Therapeutic Area Strategic Pillars



LIVER

TAK-999, TAK-039



GI INFLAMMATION

TAK-101, TAK-062, sibofimloc



MOTILITY

TAK-906, TAK-954,  
TAK-951, TAK-510,  
TAK-105

## Agenda

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## 2. Short Bowel Syndrome



### □ What is Short Bowel Syndrome?

- Definition
- Epidemiology
- Symptoms and Burden on Daily Life
- Recommended treatment strategy/methods

### □ GATTEX/REVESTIVE<sup>1</sup> (Generic name Teduglutide)

- First and only approved GLP-2 analog for SBS treatment
- Clinical Trials

# Definition: What is Short Bowel Syndrome (SBS)?



SBS is often accompanied by Intestinal Failure (IF), caused as a result of a surgical resection of large parts of the small intestine, compromising the ability to absorb nutrients needed to survive

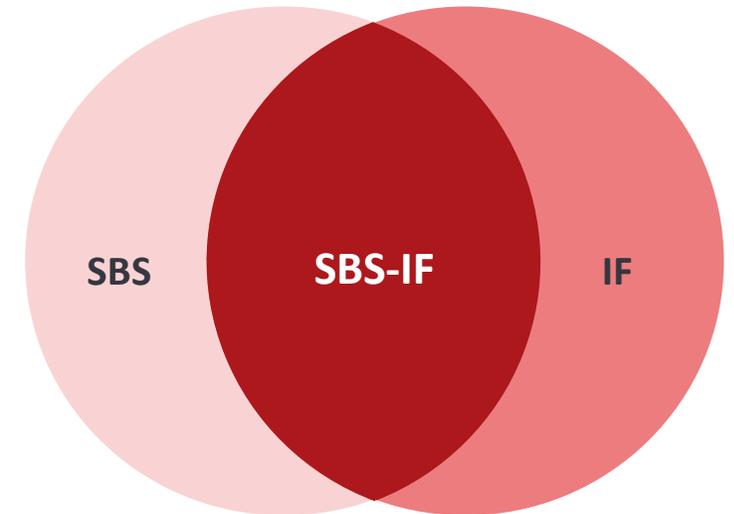
## ● Definition of short bowel syndrome



"A condition in which the need for water, electrolytes, macronutrients, micronutrients, and vitamins is not met by standard oral or enteral nutrition **due to a deficiency in the length of the small intestine that is needed to absorb nutrients and a reduced capacity to absorb them as a result of extensive intestinal resection**\*."<sup>1</sup>



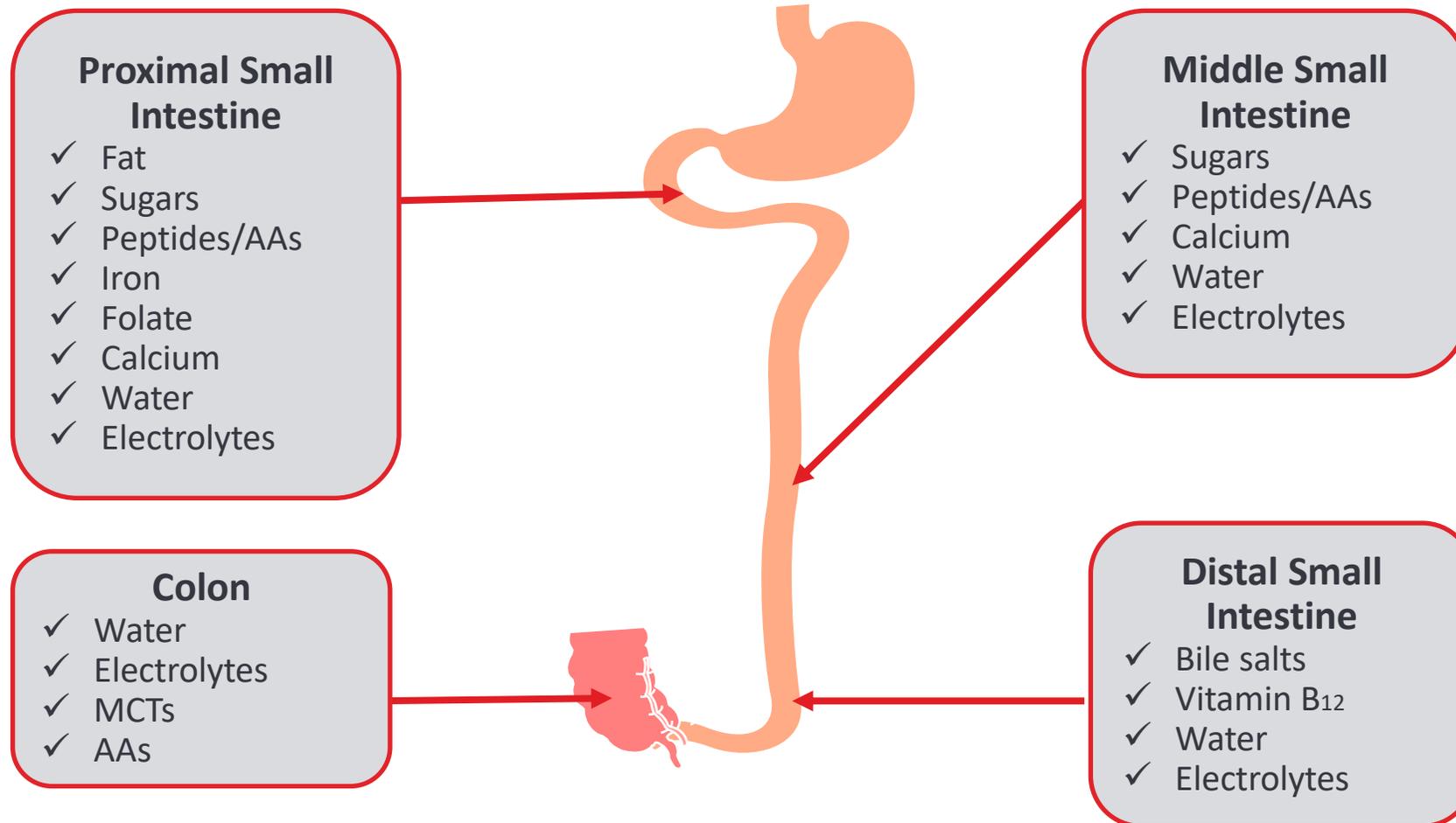
SBS in adults is "The clinical condition associated with **the remaining small bowel in continuity** (even though the total small bowel length including that bypassed may be normal) **of less than 200 cm** is defined as short bowel syndrome."<sup>2</sup>



\*This condition is medically called intestinal failure.

# Definition: Absorptive function of the gastrointestinal tract by parts

Different parts of the intestine absorb different nutrients, and the small intestine absorbs essential nutrients



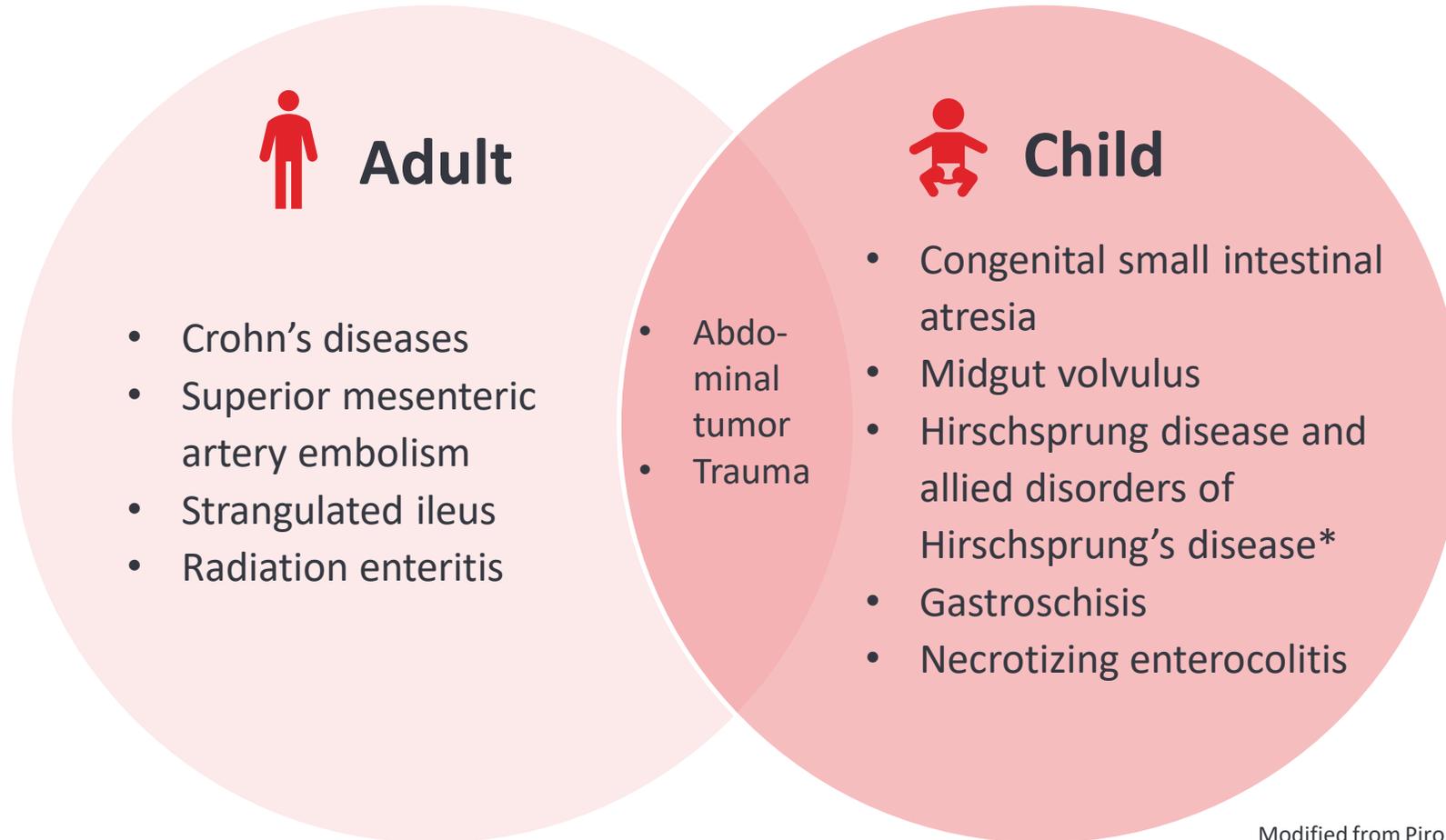
AA: amino acid; MCT: medium-chain triglyceride

Buchman AI. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th edition. Philadelphia, PA: Saunders/Elsevier; 2010:2257–2276

# Definition: Main Causes of Short Bowel Syndrome (SBS)



The diseases that cause SBS are different between adults and children.  
SBS may occur shortly after birth because some congenital diseases can lead to SBS<sup>1,2</sup>



Modified from Pironi L, et al. Clin Nutr. 2015; 34: 171-180.

\* Allied disorders of Hirschsprung's disease is a disease group characterized by symptoms and signs similar to those of Hirschsprung's disease, such as bowel obstruction, intestinal dilatation, and chronic constipation, despite the presence of ganglionic cells in the rectum<sup>3</sup>

# Epidemiology: Prevalence estimates of SBS



The exact prevalence of SBS is unknown and may vary per geographic region<sup>1</sup>  
 SBS is a rare disease with a prevalence that appears to be increasing

Survey region/ year		No. of cases	Prevalence estimates of HPN* (per million inhabitants)	
Europe	1998 survey <sup>2</sup>	494	Denmark	12.7
			UK	3.7
			Netherlands	3.7
			France	3.6
			Belgium	3.0
			Poland	1.1
			Spain	0.65
Spain	2008 survey <sup>3</sup>	201	Spain	5.1
Germany	2011/2012 survey <sup>4</sup>	2,808	Germany	34
Denmark	1970-2010 cohort study <sup>5</sup>	450	Denmark	80
UK	2015 survey <sup>6</sup>	420	UK	17.7
Italy	2012 survey <sup>7</sup>	13,046	Italy	46.1
US	2013 Medicare beneficiary data <sup>8</sup>	20,883	US	79

\*Does not include patients with SBS who do not require Parenteral Support (PS); PS referred to as Home Parenteral Nutrition (HPN) in some of the cited studies  
 BANS: British Association of Parenteral and Enteral Nutrition; HPN: Home Parenteral Nutrition; PS: Parenteral Support (parenteral nutrition and/or intravenous fluids);  
 SBS: Short Bowel Syndrome

1. Kelly D et al. *JPEN J Parent Enteral Nutr.* 2014;38:427–437; 2. Van Gossum A et al. *Clin Nutr.* 1999;18:135–140; 3. Juana-Roa J et al. *Nutr Hosp.* 2011;26:364–368; 4. von Websky MW et al. *Chirurg.* 2014;85:433–439.;  
 5. Brandt CF et al. *JPEN J Parent Enteral Nutr.* 2017;41:1178–1187; 6. British Association of Parenteral and Enteral Nutrition (BANS) Report 2016, Artificial Nutrition Support in the UK 2005-2015. Adult Home Parenteral Nutrition & Home Intravenous Fluids. <http://www.bapen.org.uk/>; 7. Pironi L & Regional Coordinators of SINPE. *BMC Nutr.* 2017;3:6; 8. Mundi MS et al. *Nutr Clin Pract.* 2017;32:799–805

Short Bowel Syndrome (SBS) mainly causes symptoms such as diarrhea, dehydration and malnutrition due to decreased absorption from small intestine

## Clinical features of SBS<sup>1,2</sup>

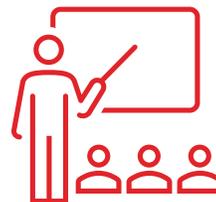
Diarrhea
Dehydration
Fatty stools
Electrolyte disturbances
Malnutrition

## Mechanisms leading to SBS<sup>3</sup>

Reduced absorptive mucosal surface
Increased intestinal losses of fluids and electrolytes
Restricted oral/enteral nutrition
Disease-related hypophagia
Lack of adaptive hyperphagia
Accelerated GI transit time
Small bowel bacterial overgrowth

## Key points:

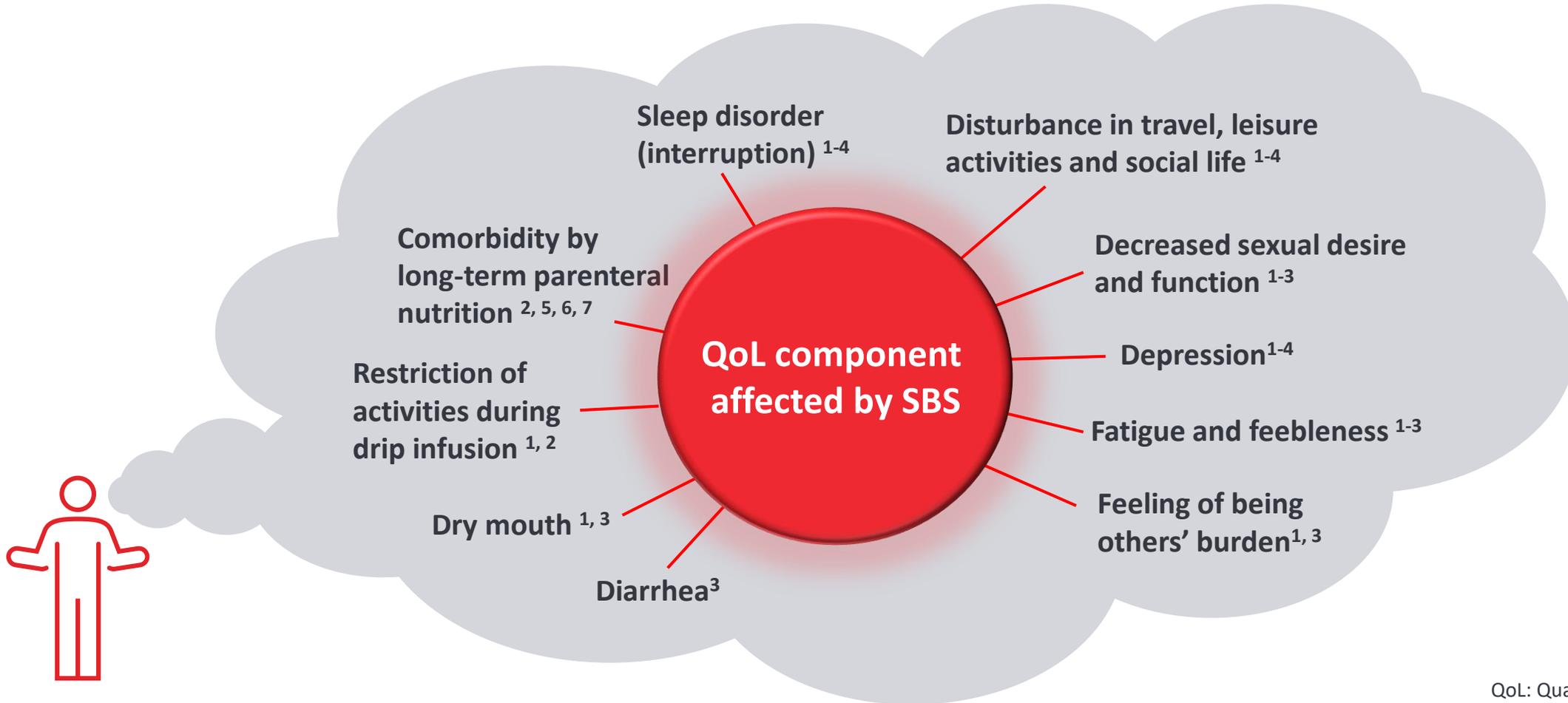
- SBS primarily results from loss of intestinal absorptive capacity<sup>1-3</sup>
- Characterized by inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance with conventional diet<sup>4</sup>
- Severity of clinical features varies from patient to patient<sup>1,2</sup>



# Symptoms and Burden on Daily Life: Burden on patient daily life



Patients with Short Bowel Syndrome (SBS) experience various difficulties in daily life depending on their symptoms and treatment



QoL: Quality of Life

1. Kelly DG, et al. JPEN J Parenter Enteral Nutr. 2014; 38(4): 427-437.

2. Hofstetter S, et al. Curr Med Res Opin. 2013; 29(5): 495-504.

3. Huisman-de Waal G, et al. Clin Nutr. 2007; 26(3): 275-288.

4. Winkler MF, et al. JPEN J Parenter Enteral Nutr. 2014; 38(1 Suppl): 32S-37S.

5. Jeppesen PB. JPEN J Parenter Enteral Nutr. 2014; 38(1 Suppl): 8S-13S.

6. Misiakos EP, et al. J Clin Gastroenterol. 2007; 41(1):5-18.

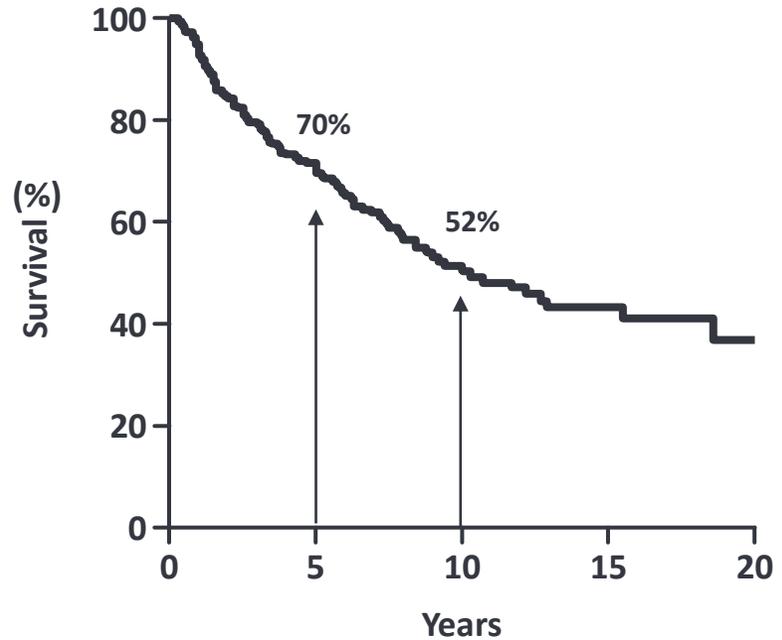
7. Mullady DK, et al. Nat Clin Pract Gastroenterol Hepatol. 2006; 3(9): 492-504.

# Symptoms and Burden on Daily Life: SBS Patient's Voice



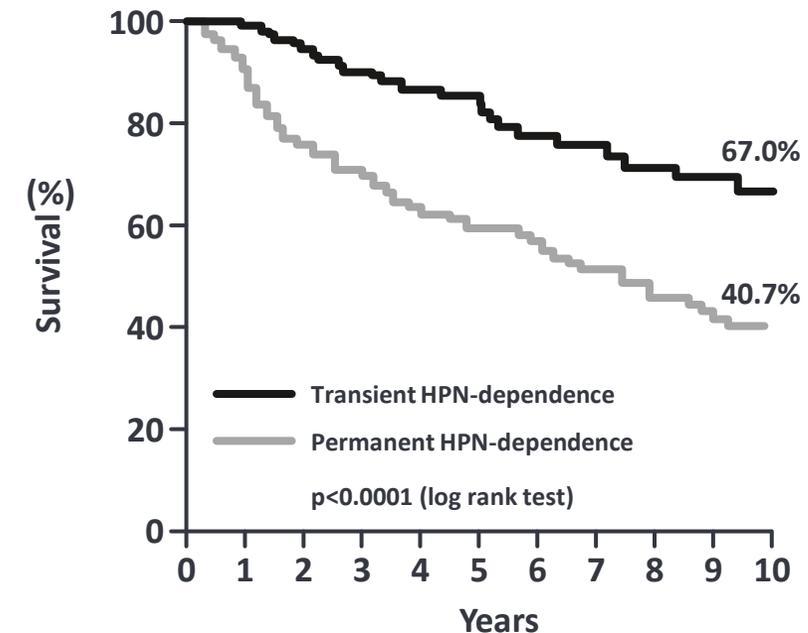
VIDEO

SBS is also known as disease to affect patient life prognosis in addition to daily life burden



N at risk	268	118	52	22	6
SE		0.03	0.04	0.04	0.05

Figure.1 Actuarial survival probability of adult SBS patients on home parenteral nutrition (n=268)



N at risk											
Transient	144	122	96	85	72	63	55	47	41	32	30
Permanent	124	115	92	83	68	55	44	39	34	27	22

Figure.2 Actuarial survival probability of adult SBS patients (n=268), according to HPN dependence or independence

**Patient population:** From January 1980 to April 2006, all consecutive adult patients with a SBS (remnant small intestine length of  $\leq 150$  cm) that have required HPN excluding the patients with evolving primary malignancies present within the first year of the follow-up, the patients who had received treatments other than HPN for intestinal failure, e.g., recombinant human growth hormone or teduglutide and the patients that have discontinued HPN within 3 months

**Methods:** Retrospective cohort study to analyses the patient survival. Median follow-up period is 4.4 (0.3 - 24) years

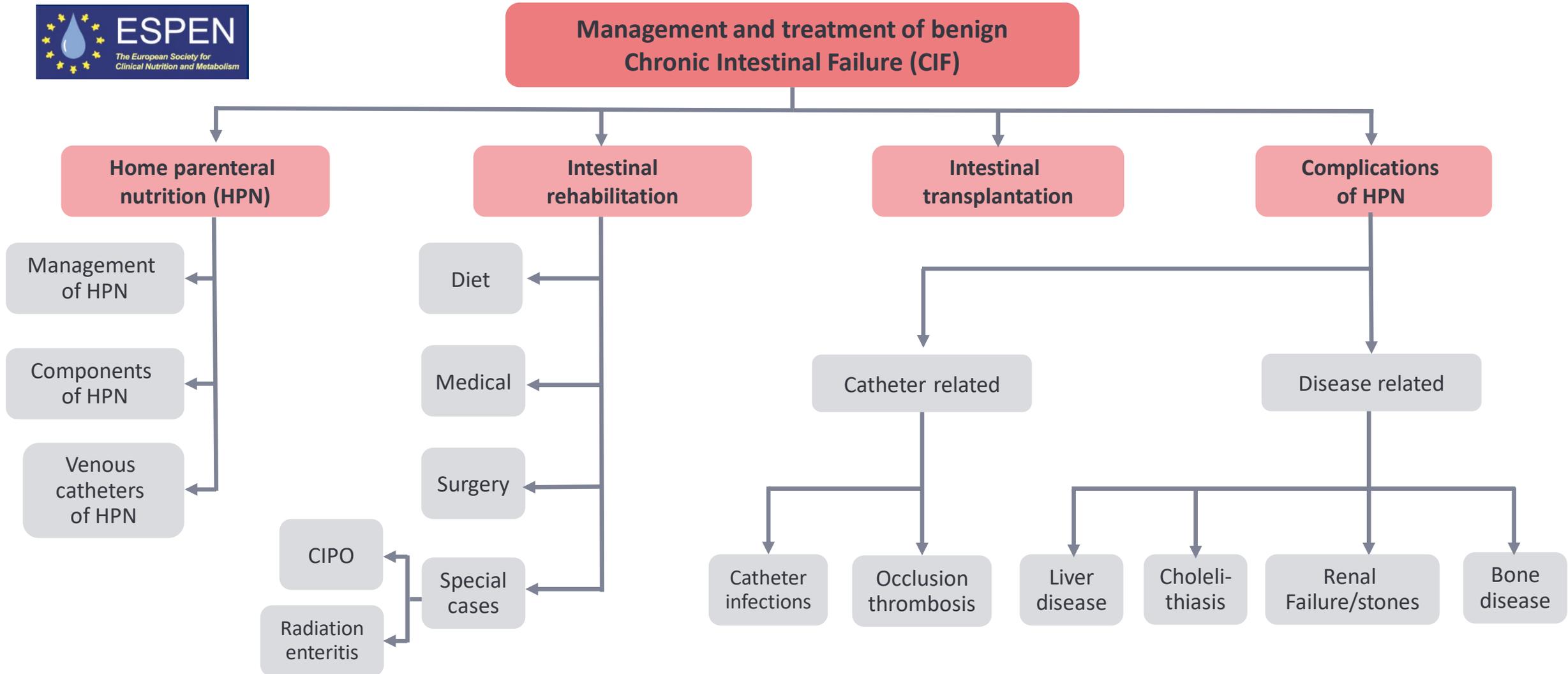
**Study limitation:** Long follow-up period (25 years and more), specified SBS patients (see patient population)

SBS: short bowel syndrome  
 HPN: home parenteral nutrition  
 Amiot A, et al. Clin Nutr. 2013; 32(3): 368-374.

# Recommended treatment strategy/methods: SBS management/treatment strategy flow chart by ESPEN



The management/treatment strategy by ESPEN is structured in 4 main chapters and diverse subchapters



# Recommended treatment strategy/methods: Therapeutic approaches and Goals for SBS patients



Key treatment target is to enhance intestinal adaptation and it is necessary to care for proper growth/development of pediatric patients

## Nutritional and hydration support<sup>1</sup>

- Fluid and electrolyte management
- Macronutrients and dietary therapy
- Micronutrients and trace element supplementation

## Medical treatment: Management of GI symptoms<sup>2,3</sup> and Growth factor therapies<sup>2\*</sup>

- Antisecretory agents
- Antimotility/antidiarrheal drugs
- Antibiotics
- GLP-2 analog (teduglutide)
- Growth hormone<sup>6</sup> (somatropin)

## Surgical options<sup>3</sup>

- Nontransplant surgery
- Intestinal transplantation



### Treatment goal: Adults

To wean patients off parenteral nutrition, by promoting intestinal adaptation<sup>4</sup>



### Treatment goal: Children

To achieve intestinal adaptation while maintaining proper growth and development<sup>5</sup>

\*Not all growth factor therapies are available in every jurisdiction

GI: gastrointestinal; GLP-2: glucagon-like peptide-2; SBS: short bowel syndrome

1. Buchman AL et al. *Gastroenterology*. 2003;124:1111–1134; 2. Jeppesen PB. *Expert Opin Orphan Drugs*. 2013;1:527–538; 3. Thompson JS et al. *Curr Probl Surg*. 2012;49:52–115;

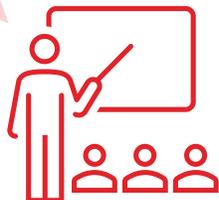
4. Neelis EG et al. *Best Pract Res Clin Gastroenterol*. 2016;30:249-261; 5. Channabasappa N et al, *Nutr Clin Pract*. 2020;35:848–854; 6. Only indicated in the US for short-term use (up to 4 weeks)

# Recommended treatment strategy/methods: How to enhance intestinal adaptation by growth factors?



Nutrient and fluid absorption in the remnant small bowel can be enhanced by nutrient and non-nutrient factors. GLP-2 is one of the non-nutrient factors

- Intestinal adaptation is the natural compensatory process that occurs after small bowel resection. This improves nutrient and fluid absorption in the remnant small bowel<sup>1</sup>
- Enteral nutrition is required for maximal intestinal adaptation<sup>2</sup>



Non-nutrient factors <sup>3, 4</sup>	Effect
Growth hormone	Increase bowel length and function moderately
Insulin-like growth factors (IGF-1)	Increase crypt cell and smooth muscle proliferation
Epidermal growth factors (EGF, TGF $\alpha$ )	Increase enterocyte proliferation and reduce apoptosis
Glucagon-like peptides (GLP-2)	Increase crypt cell proliferation, villus height and crypt depth, reduced gastric motility and secretion, improved intestinal barrier function, increased blood flow
Others (KGF, neurotensin)	<b>KGF:</b> increase epithelial cell proliferation; reduce apoptosis <b>neurotensin:</b> increase villus height

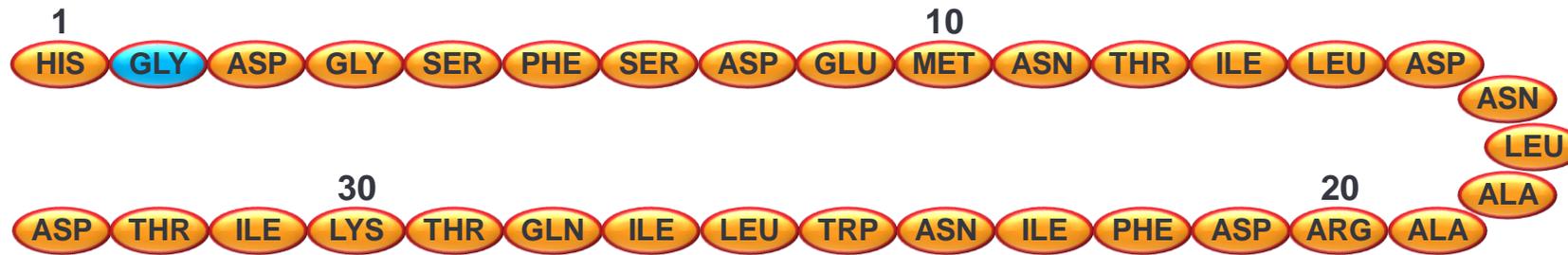
EGF: epidermal growth factor; GLP-2: glucagon-like peptide-2; IGF: insulin-like growth factor; KGF: keratinocyte growth factor; TGF $\alpha$ : transforming growth factor alpha

1. Neelis EG et al. *Best Pract Res Clin Gastroenterol.* 2016;30:249-261;
2. Pironi L et al. *Clin Nutr.* 2016;35:247–307;
3. Weale AR et al. *Postgrad Med J.* 2005;81:178–184;
4. Rubin DC and Levin MS. *Best Pract Res Clin Gastroenterol.* 2016;30:237–248

# GATTEX/REVESTIVE is the first and only approved GLP-2 analog for the treatment of SBS



- GATTEX/REVESTIVE is a recombinant human GLP-2 analog designed to have a longer half-life than native GLP-2
- Approved in 47 countries with established efficacy and safety profile through 9+ years of clinical evidence



- GATTEX/REVESTIVE is a GLP-2 agonist with an identical amino-acid sequence to endogenous GLP-2, except for the replacement of an alanine with glycine at position 2 ([Gly2]GLP-2)<sup>1,2</sup>
- This single amino-acid substitution resists degradation by DPP-IV<sup>2-4</sup>, increasing potency and lengthening mean half-life from 7 min for endogenous GLP-2 to ~2 h in healthy subjects and 1.3 h in patients with SBS<sup>1,2,4,5</sup>



DPP-IV: dipeptidyl peptidase 4; GLP-2: glucagon-like peptide-2; [Gly2]GLP-2: degradation-resistant analog of GLP-2 (teduglutide);

SBS: short bowel syndrome

1. Gattex [package insert]. Lexington, MA: Shire-NPS Pharmaceuticals, Inc., 7/16. 2. Revestive [summary of product characteristics]. Dublin, Ireland: Shire Pharmaceuticals Ireland Ltd, 7/17.

3. Drucker DJ, et al. *Nat Biotechnol*. 1997;15:673–677. 4. Tavares W, et al. *Am J Physiol Endocrinol Metab*. 2000;278:E134–E139. 5. Hartmann B, et al. *J Clin Endocrinol Metab*. 2000;85:2884–2888

# Clinical Trials:

## GATTEX/REVESTIVE Phase 3 study with adult SBS patients (STEPS study)



 Adult data



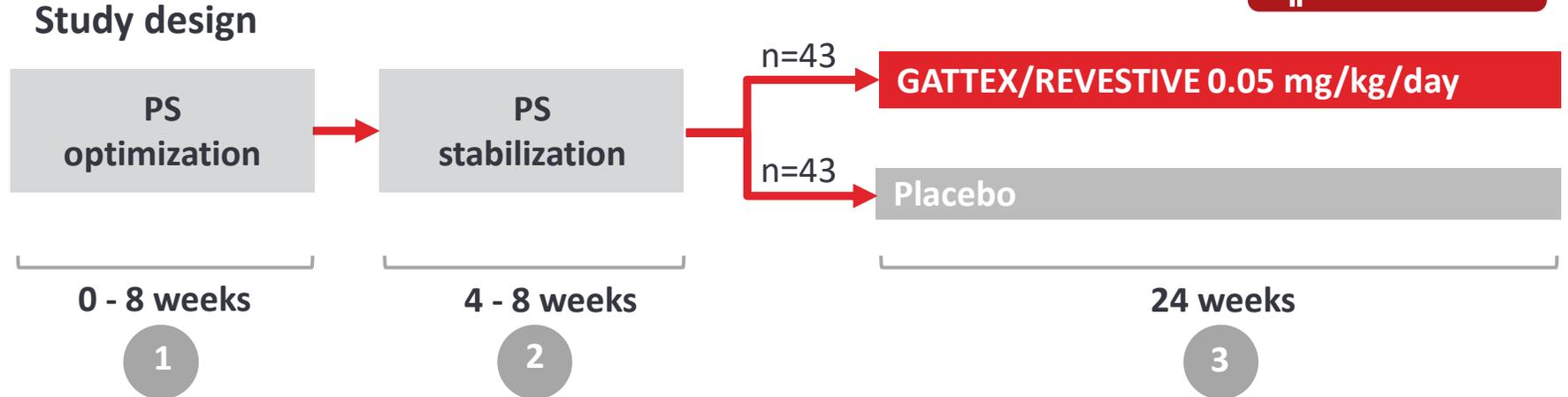
### Patients:

Male/Female patients (≥ 18 years of age) who have a history of SBS that result in a dependency on PS for at least 12 months



### Primary efficacy endpoint:

The number of responders (patients with ≥20% reduction in PS volume from baseline at weeks 20 and 24)



1

PS optimization- to establish stable target urine output of 1-2 L/day

2

PS stabilization- to ensure prescribed and actual PS usage matched, and oral fluid intake and urine output were within 25% of optimized levels

3

On-Treatment Phase- randomized, 24-week treatment period; algorithm in place for adjusting parenteral support/volume

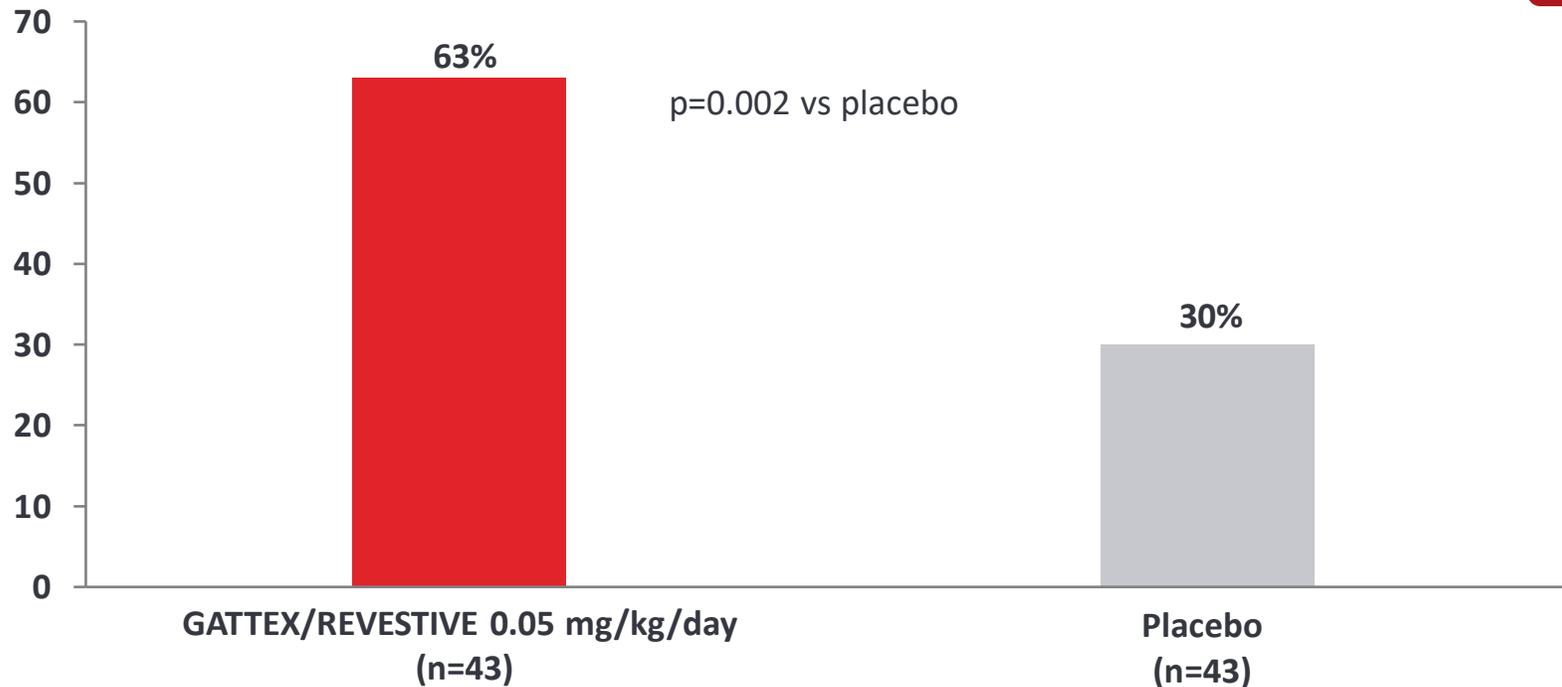
# Clinical Trials: STEPS Results – Primary Endpoint Responder Rate



Significantly more responders in the GATTEX/REVESTIVE group (27/43 [63%]) than the placebo group (13/43 [30%]; P =0.002)

Responders (%)  
(ITT population)

 Adult data



- Responders defined as subjects with 20–100% reduction from baseline in weekly Parenteral Support (PS) and/or intravenous fluids volume at Weeks 20 and 24
- Primary endpoint was achieved and significant difference in responder rate observed between GATTEX/REVESTIVE and placebo

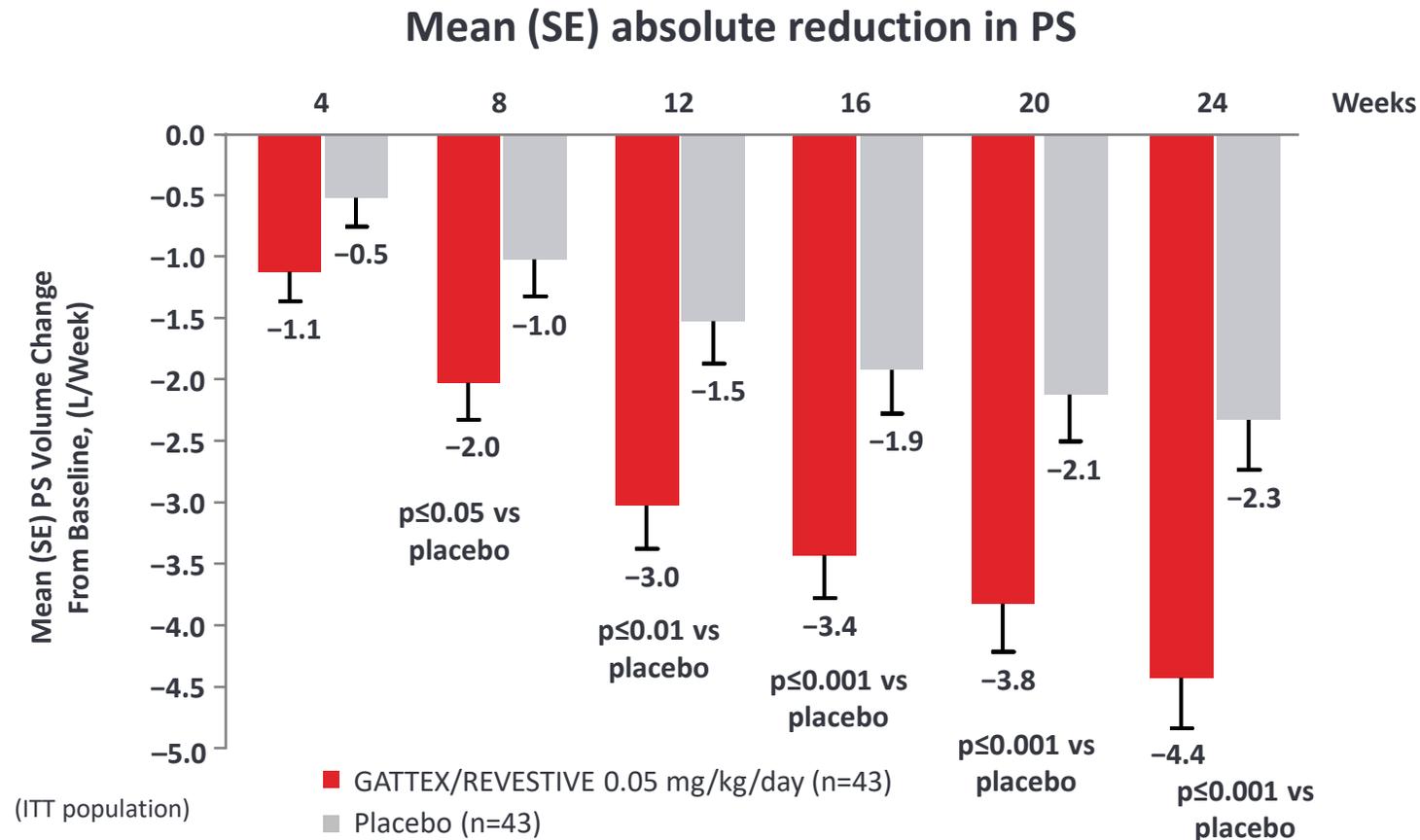
# Clinical Trials:

## STEPS Results – Secondary Endpoint Absolute Reduction PS Volume



Mean PS volume reduction from baseline in the GATTEX/REVESTIVE group was observed at all visits and it was statistically significant from week 8 to week 24 compared with placebo group

Adult data



# Clinical Trials: STEPS Results – Adverse Events



The rate of TEAEs, TESAEs, TEAEs leading to study discontinuation were comparable between groups

 Adult data

	<b>GATTEX/REVESTIVE n=42</b>	<b>Placebo n=43</b>	<b>Total n=85</b>
	<b># of patients (%)</b>	<b># of patients (%)</b>	<b># of patients</b>
Any TEAEs	35 (83%)	34 (79%)	69
TEAEs leading to premature discontinuation*	2 (5%)**	3 (7%)	5
Any TESAЕ	15 (36%)**	12 (28%)	27
Deaths	0	0	0

\*None considered serious

\*\*Deemed related to study drug (acute cholecystitis and small intestinal stenosis) and both resolved

(Safety analysis set)

AE: adverse event; TEAE: treatment emergent adverse event; TESAЕ: treatment emergent serious adverse events

# Clinical Trials: STEPS Results – Adverse Events



The most frequently reported TEAE in the GATTEX/REVESTIVE-treated groups were gastrointestinal in nature

TEAEs Reported in >5% of Subjects in Safety Population, n (%)	GATTEX/REVESTIVE n=42	Placebo n=43
All TEAEs	35 (83%)	34 (79%)
Abdominal pain	13 (31%)	10 (23%)
Nausea	12 (29%)	8 (19%)
GI stoma change*	10 (24%)	3 (7%)
Abdominal distension	9 (21%)	1 (2%)
Central line systemic infections**	7 (17%)	7 (16%)
Peripheral edema	7 (17%)	2 (5%)
Urinary tract infection	6 (14%)	4 (9%)
Flatulence	5 (12%)	3 (7%)
Vomiting	5 (12%)	4 (9%)
Fatigue	4 (10%)	3 (7%)
Pyrexia	4 (10%)	4 (9%)
Diarrhea	3 (7%)	5 (12%)
Weight increase	3 (7%)	3 (7%)
Dyspnea	3 (7%)	0
Nasopharyngitis	3 (7%)	0

 Adult data

\* Complications defined as reports of swelling, growth, hypertrophy, enlargement, or increased size of stoma or stoma nipple

\*\* Includes catheter-related infection, central line infection, catheter sepsis, infective thrombosis, and bacteremia

(Safety analysis set)

# Clinical Trials:

## GATTEX/REVESTIVE Phase 3 study with pediatric SBS patients (TED-C14-006 study)



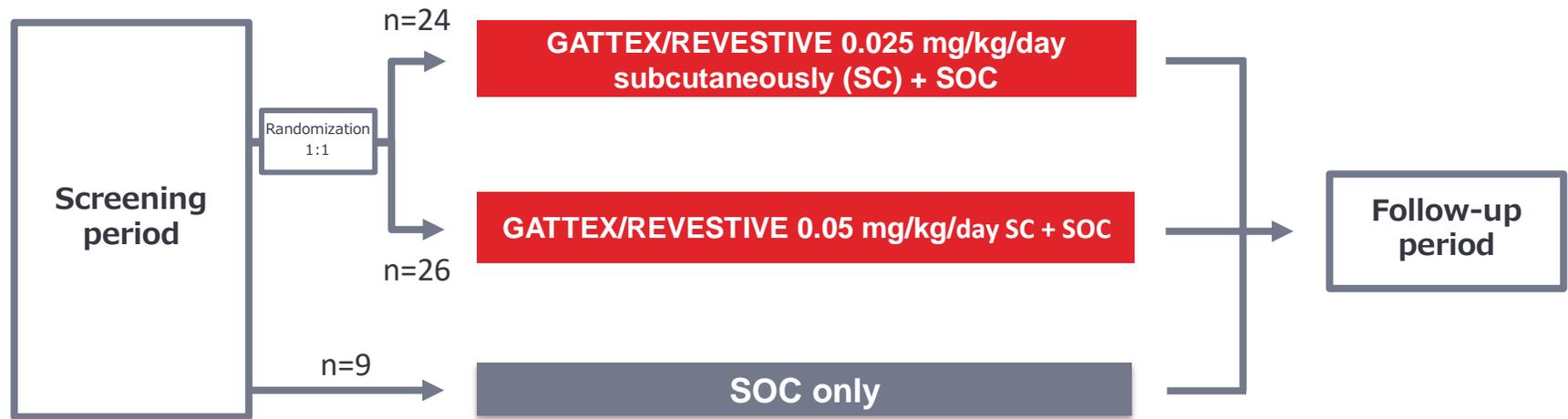
 Pediatric data

### Study design

2 weeks minimum

24 weeks

4 weeks



Site visits at weeks 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 28; telephone visits at all other weeks.



### Patients:

Male/Female children and adolescent patients (< 18 years of age) with SBS who are dependent on parenteral support



### Primary efficacy endpoint:

The number and percentage of subjects who achieved at least a 20% weight-normalized reduction in PS volume at week 24/EOT

SBS: short bowel syndrome; SC: subcutaneous; SOC: standard of care (i.e. standard medical therapy); PS: parenteral support (parenteral nutrition and/or intravenous fluids)

# Clinical Trials: TED-C14-006 Results – Primary endpoint

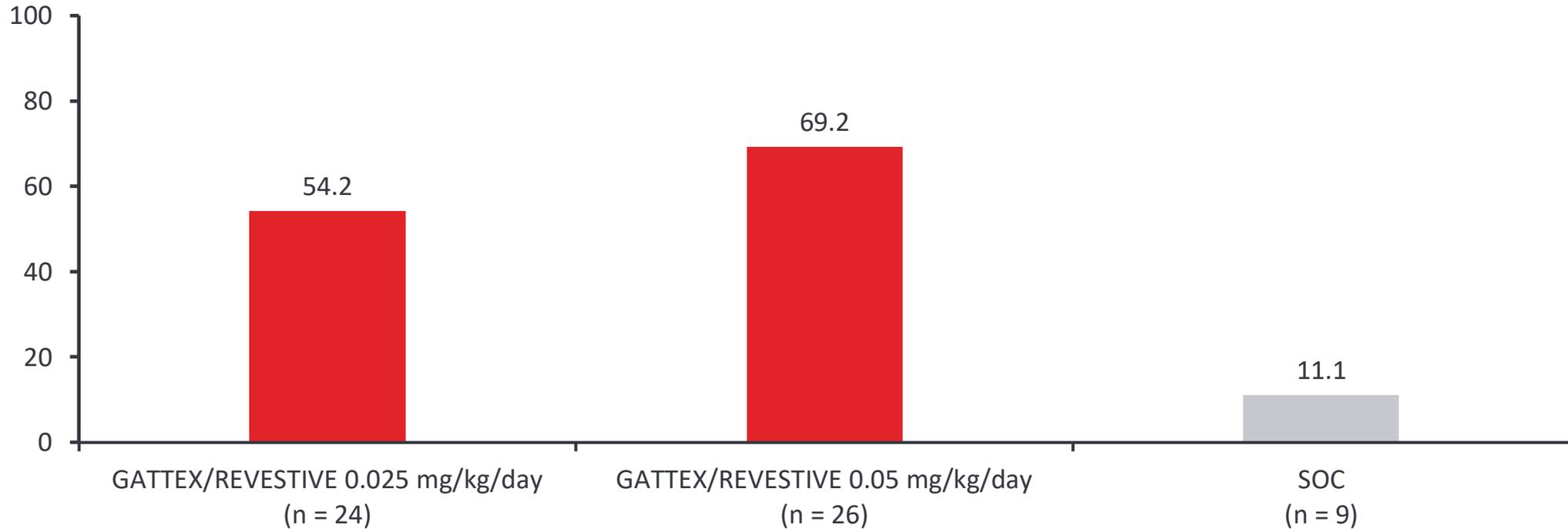


Administration of 0.025 and 0.05 mg/kg/day of GATTEX/REVESTIVE for up to 24 weeks reduced PS support in pediatric subjects with SBS

 Pediatric data

Proportion of patients (%)

Primary endpoint:  $\geq 20\%$  weight-normalized reduction in PS volume at week 24/EOT (ITT population)



Based on patient diary data

SBS: short bowel syndrome; EOT: end of treatment; ITT: intent to treat; PS: parenteral support (parenteral nutrition and/or intravenous fluids); SOC: standard of care

Kocoshis SA, et al. JPEN J Parenter Enteral Nutr. 2020; 44 (4) : 621-631.

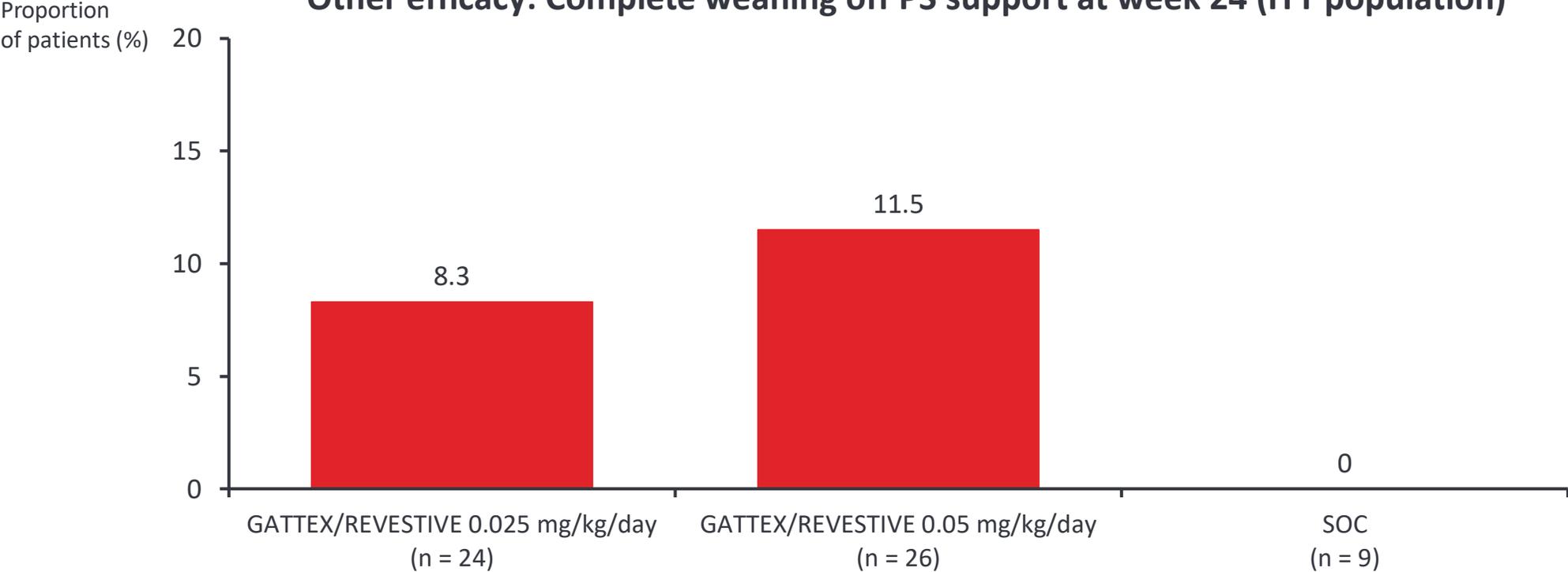
# Clinical Trials: TED-C14-006 Results – Other efficacy



2 children in 0.025 mg/kg group and 3 children in the 0.05 mg/kg group achieved complete weaning off of PS support. No children in the SOC arm achieved enteral autonomy during the study

Pediatric data

**Other efficacy: Complete weaning off PS support at week 24 (ITT population)**



ITT: intent to treat; PS: parenteral support (parenteral nutrition and/or intravenous fluids); SOC: standard of care

# Clinical Trials: TED-C14-006 Results

## – Most common AEs occurring in patients treated with GATTEX/REVESTIVE



There was no clear difference in AE frequency between the two GATTEX/REVESTIVE dose groups

Preferred term, n (%)	GATTEX/REVESTIVE 0.025 mg/kg/day (n = 24)	GATTEX/REVESTIVE 0.05 mg/kg/day (n = 26)	Total GATTEX/REVESTIVE (n = 50)	SOC (n = 9)
Pyrexia	8 (33.3)	11 (42.3)	19 (38.0)	4 (44.4)
Vomiting	10 (41.7)	8 (30.8)	18 (36.0)	5 (55.6)
Upper RTI	7 (29.2)	8 (30.8)	15 (30.0)	4 (44.4)
Cough	2 (8.3)	10 (38.5)	12 (24.0)	3 (33.3)
Diarrhea	8 (33.3)	3 (11.5)	11 (22.0)	1 (11.1)
Nasopharyngitis	4 (16.7)	6 (23.1)	10 (20.0)	2 (22.2)
Abdominal pain	4 (16.7)	6 (23.1)	10 (20.0)	0 (0.0)
Dehydration	8 (33.3)	1 (3.8)	9 (18.0)	0 (0.0)
ALT increased	7 (29.2)	2 (7.7)	9 (18.0)	0 (0.0)
Headache	3 (12.5)	5 (19.2)	8 (16.0)	1 (11.1)
Device-related infection	1 (4.2)	5 (19.2)	6 (12.0)	0 (0.0)
Rhinitis	1 (4.2)	5 (19.2)	6 (12.0)	0 (0.0)
Viral infection	3 (12.5)	3 (11.5)	6 (12.0)	1 (11.1)
Device breakage	3 (12.5)	3 (11.5)	6 (12.0)	0 (0.0)
Influenza	2 (8.3)	3 (11.5)	5 (10.0)	0 (0.0)
AST increased	5 (20.8)	0	5 (10.0)	0 (0.0)

Pediatric data

ALT: alanine aminotransferase; AST: aspartate aminotransferase; RTI: respiratory tract infection; SOC: standard of care; AE: adverse event

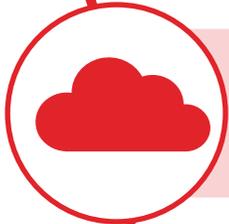
(Safety analysis set)

Kocoshis SA, et al. JPEN J Parenter Enteral Nutr. 2020; 44 (4): 621-631.

# Take-home Messages



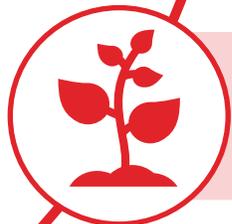
SBS is often accompanied by Intestinal Failure (IF), caused as a result of a surgical resection of large parts of the small intestine, compromising the ability to absorb nutrients needed to survive



Patients with SBS experience various difficulties in daily life, face reduced QoL, and have a shorter life-expectancy



Treatment target is to restore the intestinal absorptive capacity, enhance intestinal adaptation and proper growth/development of pediatric patients



GATTEX/REVESTIVE is a recombinant human GLP-2 analog which enhances intestinal absorption. The efficacy and safety have been confirmed by adult and pediatric (including infant) clinical trials

## Agenda

## Presenters

### 1. Takeda's Initiatives in Gastroenterology (GI) Therapeutic Area

Mitsuhiro Shikamura  
Senior Clinical Science Director, Therapeutic Area Strategy Unit (GI)

### 2. Short Bowel Syndrome

Masakazu Miyamoto  
Manager, Marketed Product Group, Therapeutic Area Strategy Unit

### 3. Complex Crohn's Perianal Fistulas

**Tomoko Tanaka**  
Associate Medical Director, Therapeutic Area Strategy Unit (GI)  
**Takayoshi Yamaguchi**  
Manager, Therapeutic Area Strategy Unit (GI)

### 4. Q&A Session

Q&A Panelists

# 3. Complex Crohn's Perianal Fistulas



## □ What are Crohn's Perianal Fistulas?

- Disease Background
- Current Standard of Care
- Symptoms and Burden on Daily Life

## □ ALOFISEL (Generic name Darvadstrocel: Takeda's 1<sup>st</sup> Cell Therapy)

- Characteristic
- Clinical Trials
- Manufacturing and logistics

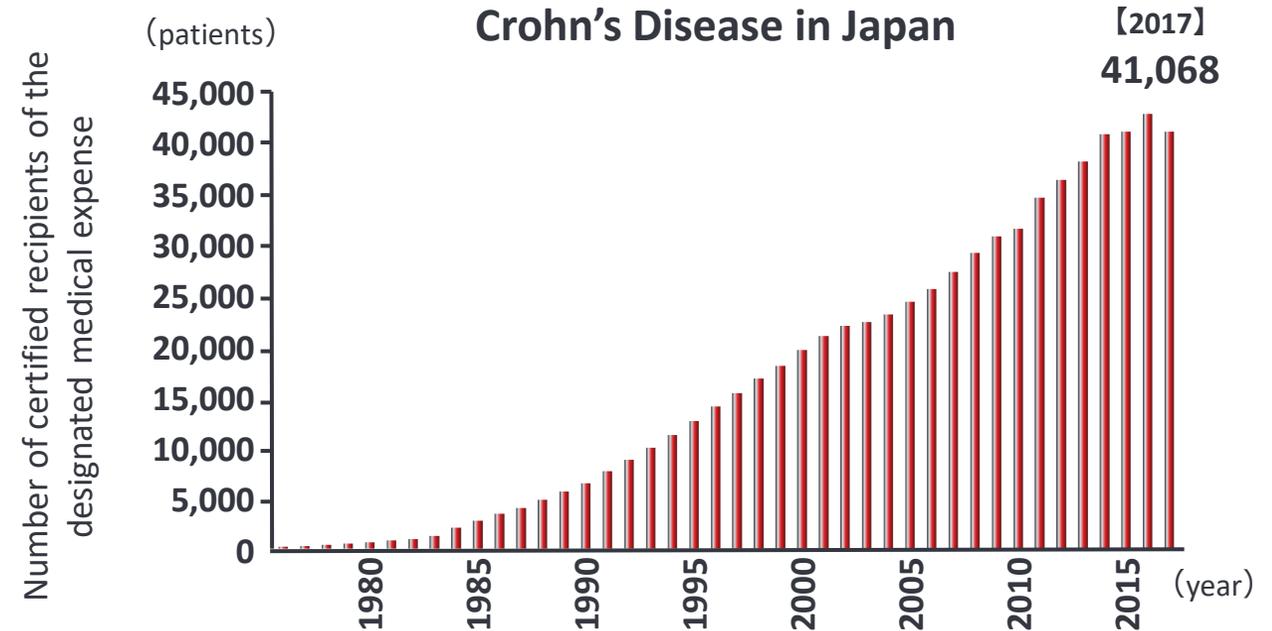
# Disease Background: What is Crohn's Disease?



The number of patients with Crohn's disease is growing in both Japan and abroad

## Crohn's Disease

- Chronic inflammatory disease<sup>1</sup>
  - idiopathic transmural inflammation
  - anywhere along the gastrointestinal tract
- The increasing incidence and the difficulties of treating some lesions represent real challenges for public health and medical management<sup>2</sup>
  - US : 800,000 patients
  - EU : 590,000 patients
  - Japan : 40,000 patients



Number of patients who have received certifications for specified medical expenses  
- Japan Intractable Diseases Information Center (<http://www.nanbyou.or.jp/entry/1356>).  
Health Administrative Reports by the Japanese Ministry of Health, Labour and Welfare (<https://www.mhlw.go.jp/toukei/list/36-19.html>).

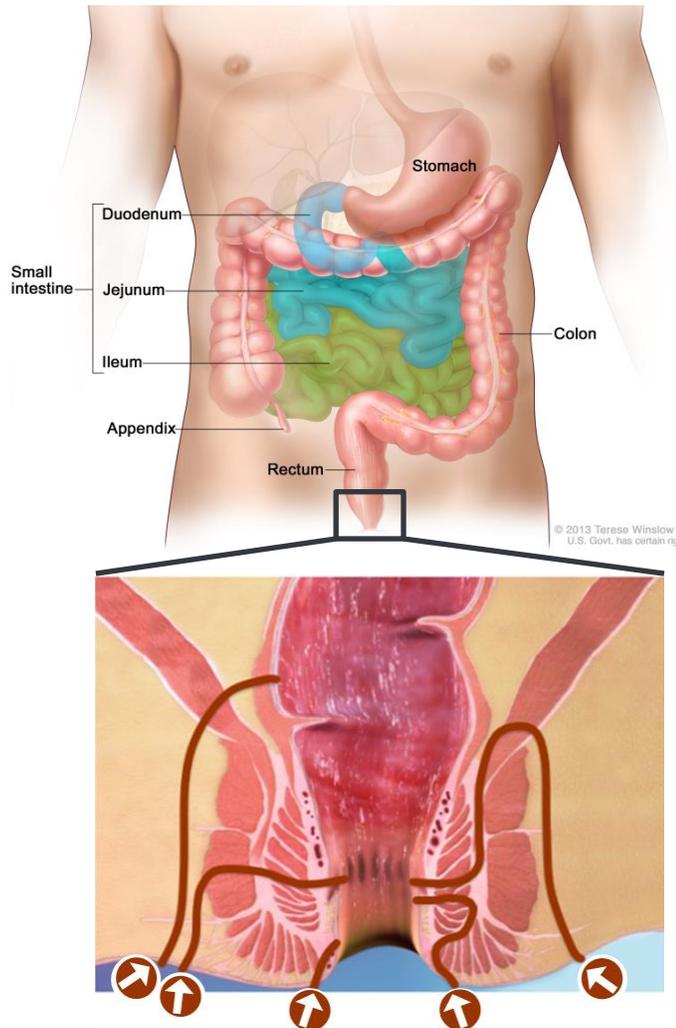
1. Buscail (2021)

2. Landscape & Forecast, QRG, Feb 2020

# Disease Background: What are Crohn's Perianal Fistulas (CPF)?



Abnormal connection between bowel epithelium and perineal skin due to chronic inflammation



## Patients with Crohn's Disease (n=650)\*

Perianal lesions	Number of patients	Frequency (%)
<b>Perianal fistula/abscess</b>	<b>416</b>	<b>64.0</b>
Anal fissure/ulcer	184	28.3
Skin tag	180	27.7
Anorectal stricture	92	14.2
Hypertrophied anal papilla	77	11.8
Hemorrhoid	18	2.8
Carcinoma in rectum/anal canal	5	0.8
Mixed lesions	316	60.3

\* FUKUOKA UNIVERSITY CHIKUSHI HOSPITAL

80% of patients with Crohn's disease have perianal lesions.  
Of all, Perianal Fistulas are the most frequent (Japan data)

[https://www.ncbi.nlm.nih.gov/books/NBK66026/figure/CDR0000350260\\_\\_184/](https://www.ncbi.nlm.nih.gov/books/NBK66026/figure/CDR0000350260__184/)

Higashi D, Futami K: Practice lectured by hands-on experts! IBD Treatment (edited by Watanabe M), 20-29, Igaku Shuppan, 2014.

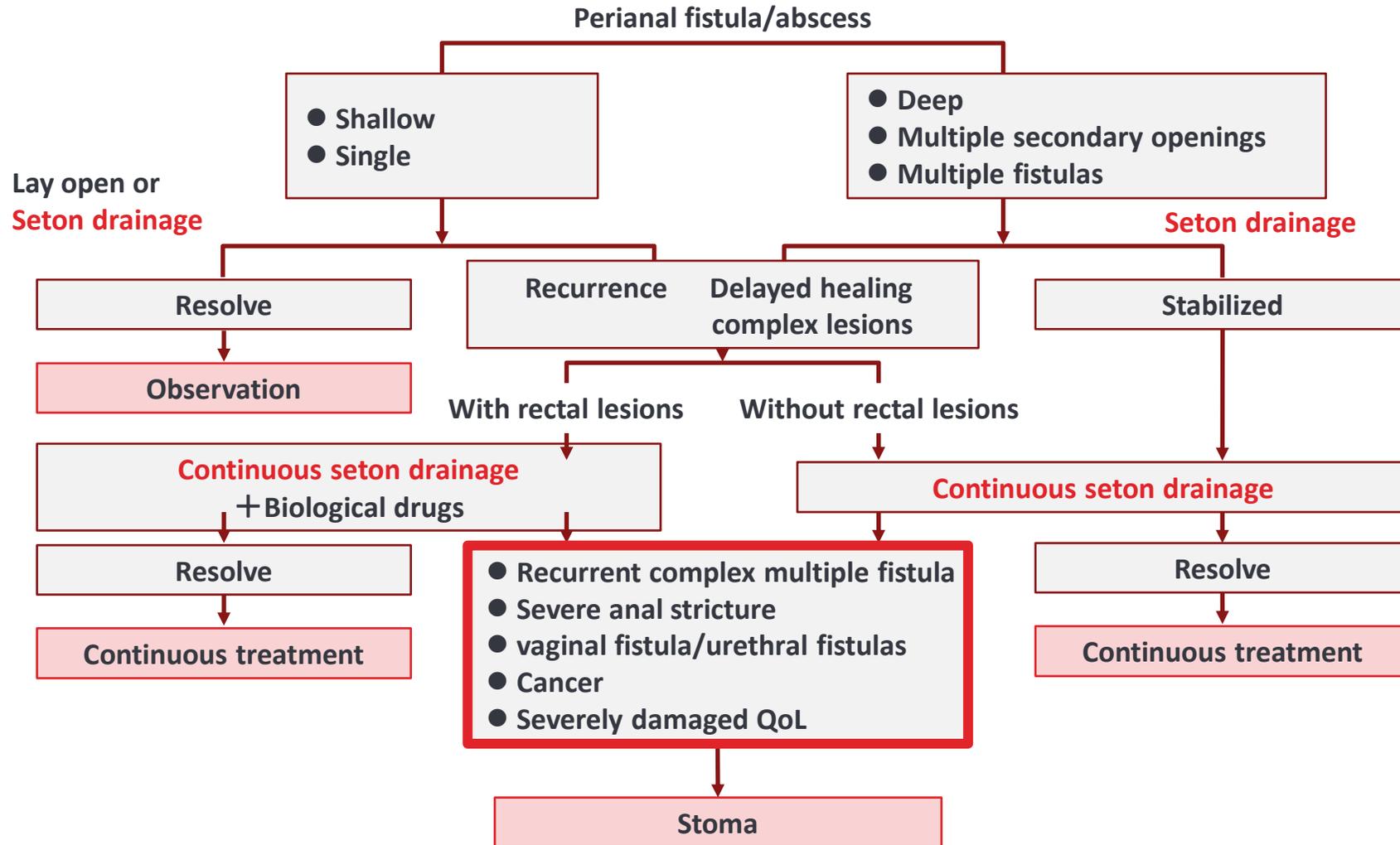
Parks AG, et al.: Br J Surg 1976; 63 (1): 1-12.

Sandborn WJ, et al.: Gastroenterology. 2003; 125 (5): 1508-1530.

# Current standard of care: Despite medical and surgical advancements, Crohn's Perianal Fistulas remain challenging to treat



In both Japan and overseas, seton drainage with or without a biological drug is the standard of care for Crohn's perianal fistula



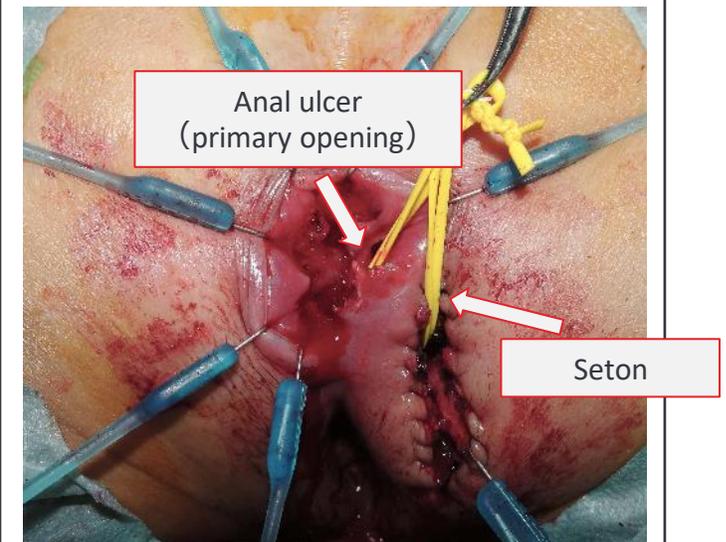
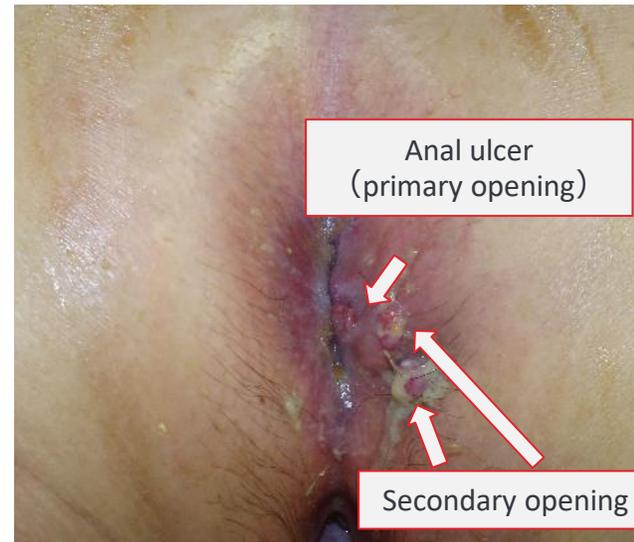
# Symptoms and Burden on Daily Life: What it looks like, if you have CPF and have setons?



Seton drainage causes not only physical but also mental pain in patients and severely damage their QOL

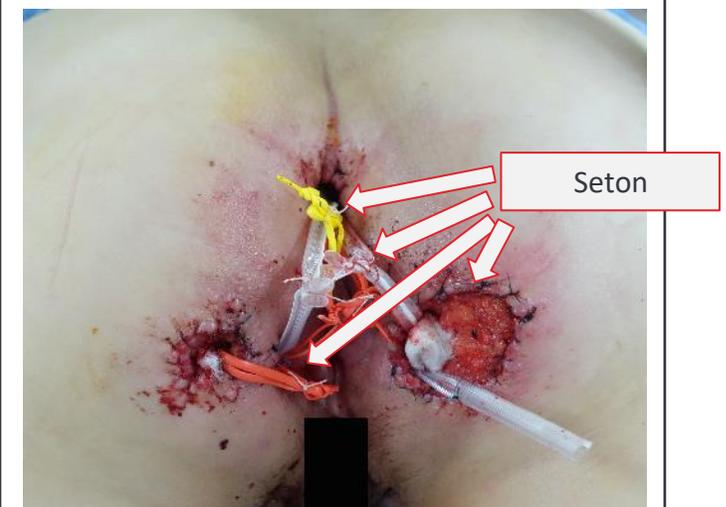
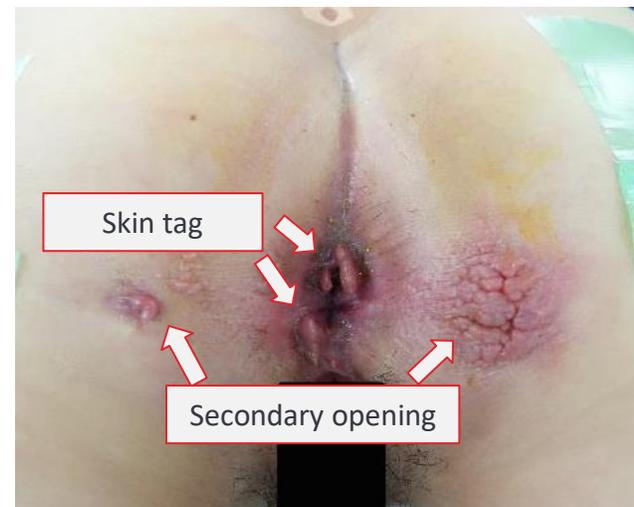
## Case 1

- Male in his 50s
- Ileocolonic Crohn's Disease
- Treatment for Crohn's Disease: 5-ASA, prednisolone



## Case 2

- Female in her teens
- Ileocolonic Crohn's Disease
- Treatment for Crohn's Disease: 5-ASA, adalimumab, metronidazole



# Symptoms and Burden on Daily Life: CPF Patient's Voice

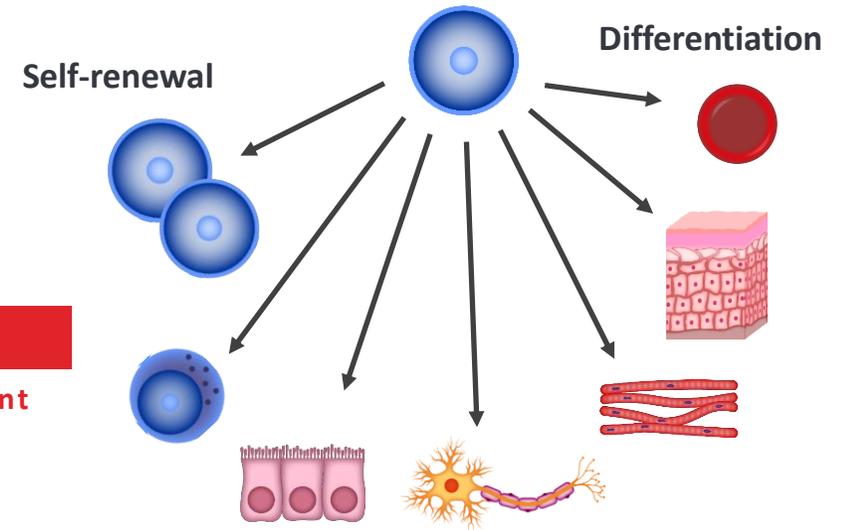


VIDEO

# Characteristics: What are stem cells?

Stem cell research is garnering attention because of its various characteristics

- Undifferentiated cell populations
- Self-renewal capacity  
(the ability to replicate cells that have the same ability as themselves)
- Pluripotency (the ability to differentiate into cells of different lineages)



Types of Stem cell			
	Embryonic stem cells (ES cells, ESC)	Adult stem cells (Somatic stem cells)	Artificial pluripotent stem cell (iPS-cells, iPSC)
		 HSC      MSC	
<b>Source</b>	Embryo	Various tissues (Bone marrow, Cord blood, Fat, etc.)	Various tissues (Skin, etc.)
<b>Differentiation Potency</b>	All kinds of cells	Able to differentiate into limited variety of cells	All kinds of cells
<b>Ethical Issues</b>	High (Loss of fertilized eggs)	Low	Low

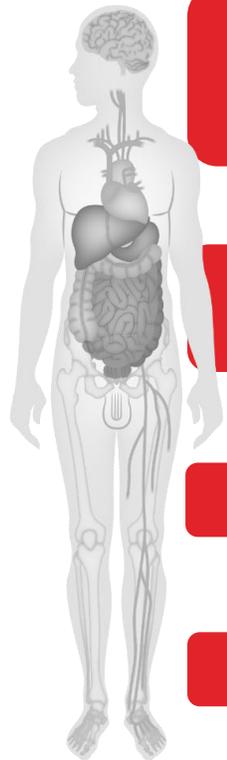
ESC: embryonic stem cell (embryonic stem cells);  
 HSC: hematopoietic stem cell (hematopoietic stem cells);  
 MSC: mesenchymal stem cell (mesenchymal stem cells);  
 iPSC: induced pluripotent stem cell (artificial pluripotent stem cells)

US National Academies. Understanding Stem Cells. (Available at: [https://www.nap.edu/resource/11278/Understanding\\_Stem\\_Cells.pdf](https://www.nap.edu/resource/11278/Understanding_Stem_Cells.pdf))  
 Browsed in April 2021

Satoshi Fujita. : Gijutushi. 2010; 11: 16-19. (Extract, modified)

# Characteristics: What are mesenchymal stem cells (MSCs)?

MSCs are harvested from various tissues and have a wide range of differentiation potential

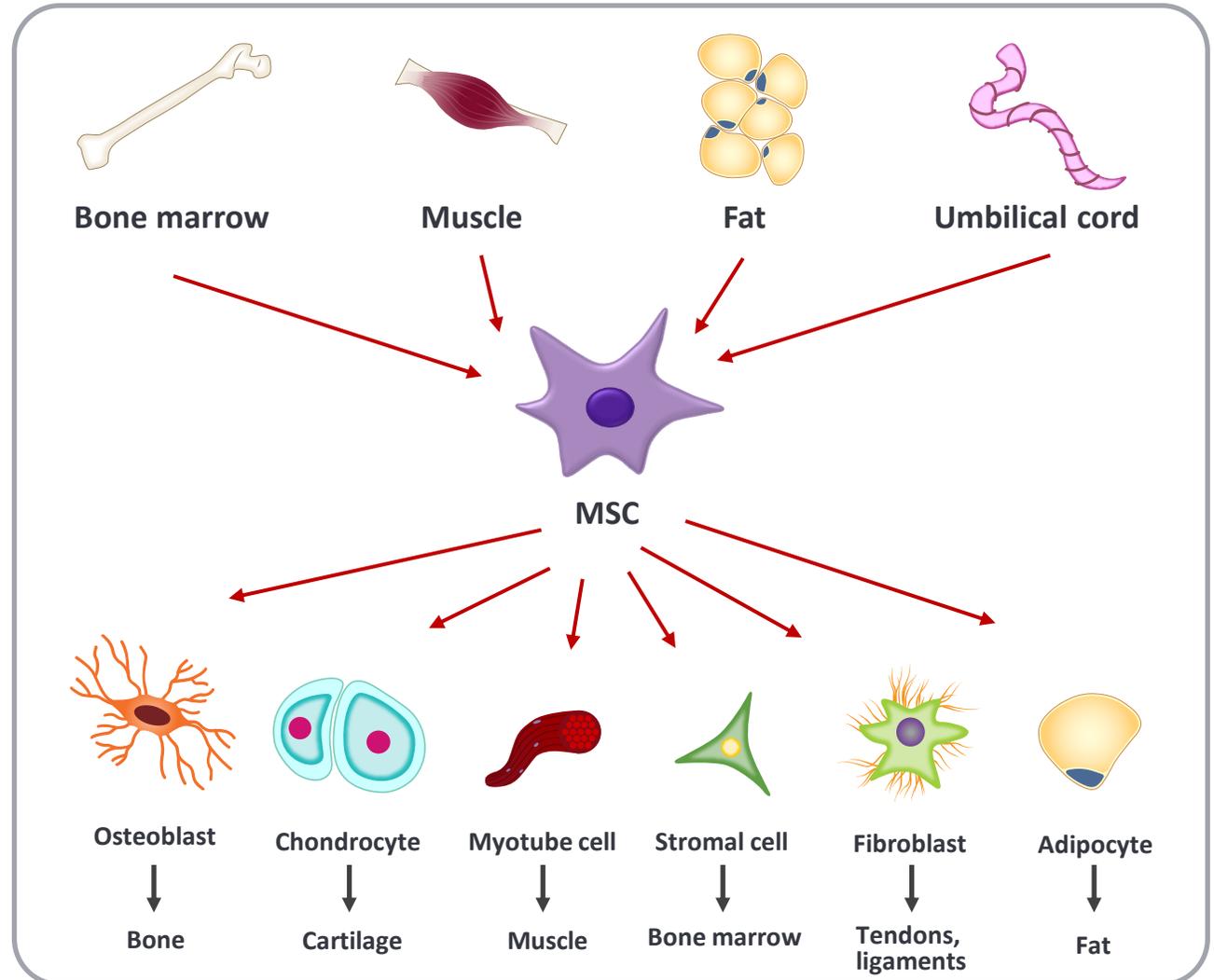


Fibroblast-like cells isolated from bone marrow, muscle, fat, skin, and umbilical cord, etc.

Ability of differentiation into many stromal cell lineages

Able to grow in *in vitro*

Autologous and allogeneic



# Characteristics:

## Therapeutic areas in which clinical trials of MSCs are being conducted

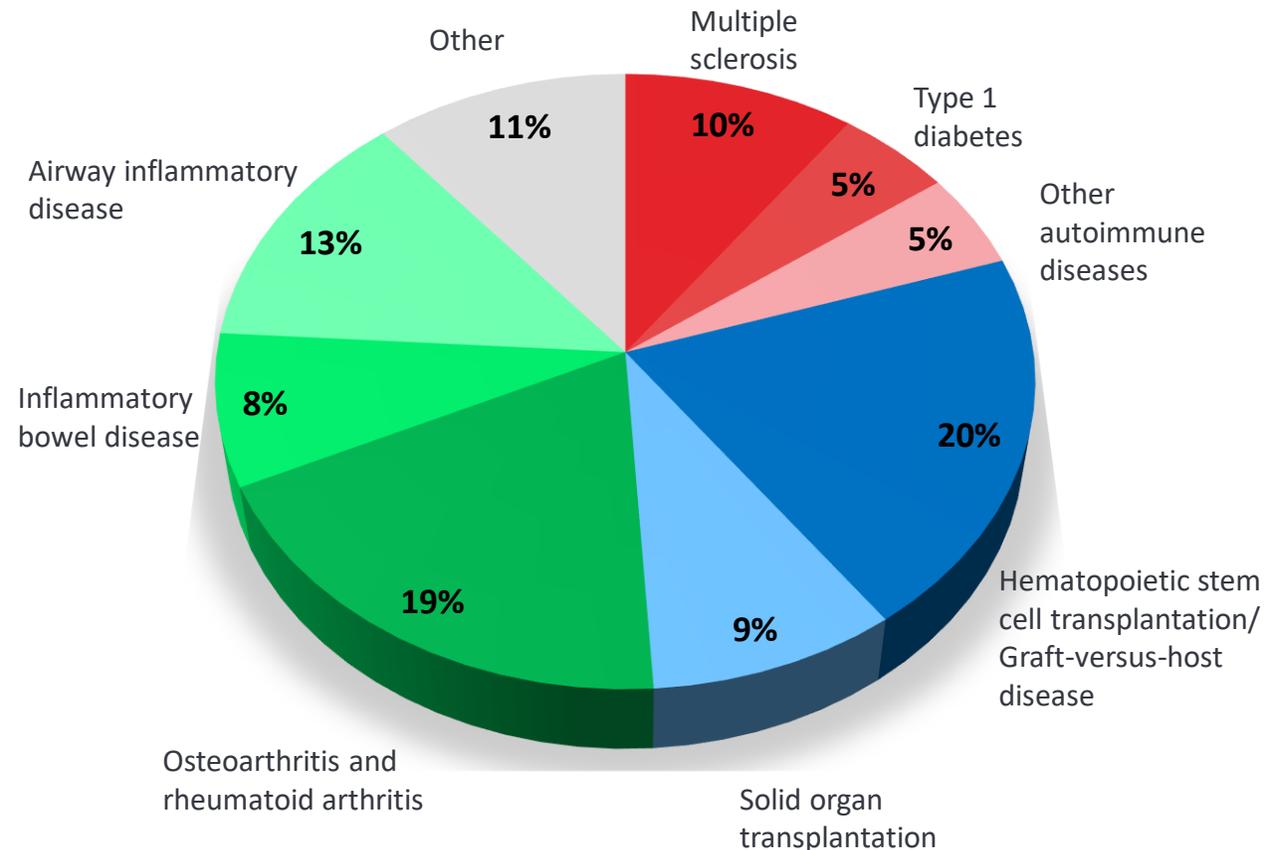


MSCs have high potential for clinical application

- MSCs are expected to have applications in **damaged tissues, transplantation, and autoimmune diseases** due to potent immunomodulatory effects<sup>1</sup>
- **Clinical trials and real-world data demonstrated the immunosuppressive effect of MSCs** on graft-versus-host disease after bone-marrow transplantation with no side effects observed<sup>1</sup>
- **Clinical trials of MSCs have been conducted for various immune-mediated inflammatory diseases<sup>1</sup>**
  - Demyelinating neuropathy (multiple sclerosis)
  - Systemic lupus erythematosus
  - **Crohn's disease**

Clinical trials of MSCs in immune-mediated inflammatory diseases<sup>2</sup> (2016)

[ex-Japan Data]



# Characteristics: Advantages of adipose-derived stem cells (ASCs)



Mesenchymal stem cells (MSCs: mesenchymal stem cell) can be harvested from various tissues. Among them, MSCs harvested and cultured from adipose (fat) tissue are called adipose-derived stem cells (ASCs)

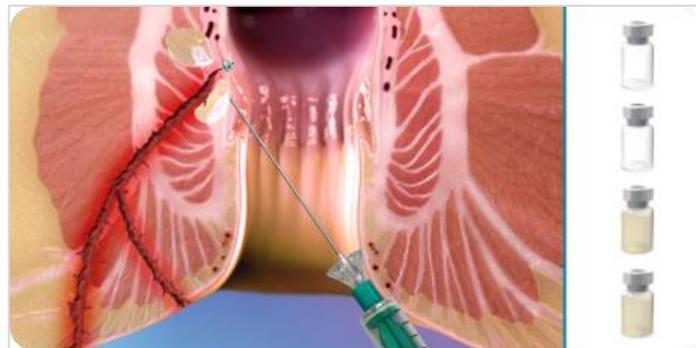
## Advantages of ASCs include;

- Cell collection is convenient (obtained by liposuction, etc.)
- There are more mesenchymal stem cells in the tissue  
(more than 500 times more than the same amount of bone marrow tissue)
- Expansion speed is faster than bone marrow-derived stem cells, thus ensuring easier requirements

# Product characteristics of ALOFISEL



- Takeda's first cell therapy product combined with minimally invasive surgical procedure, containing adipose-derived stem cells (eASC\*) developed for the treatment of complex perianal fistulas in patients with inactive or mild active Crohn's disease
- Takeda obtained marketing approval of ALOFISEL (generic name: darvadstrocel) in Europe in 2018 and has since been approved in 35 countries as of Feb 2022
- Preparation procedures include vigorous curettage of the fistula tract and suturing of the internal openings
- ALOFISEL is injected by trained surgeons around the internal openings and along the fistula tract wall



# Characteristics: Mechanism of Action

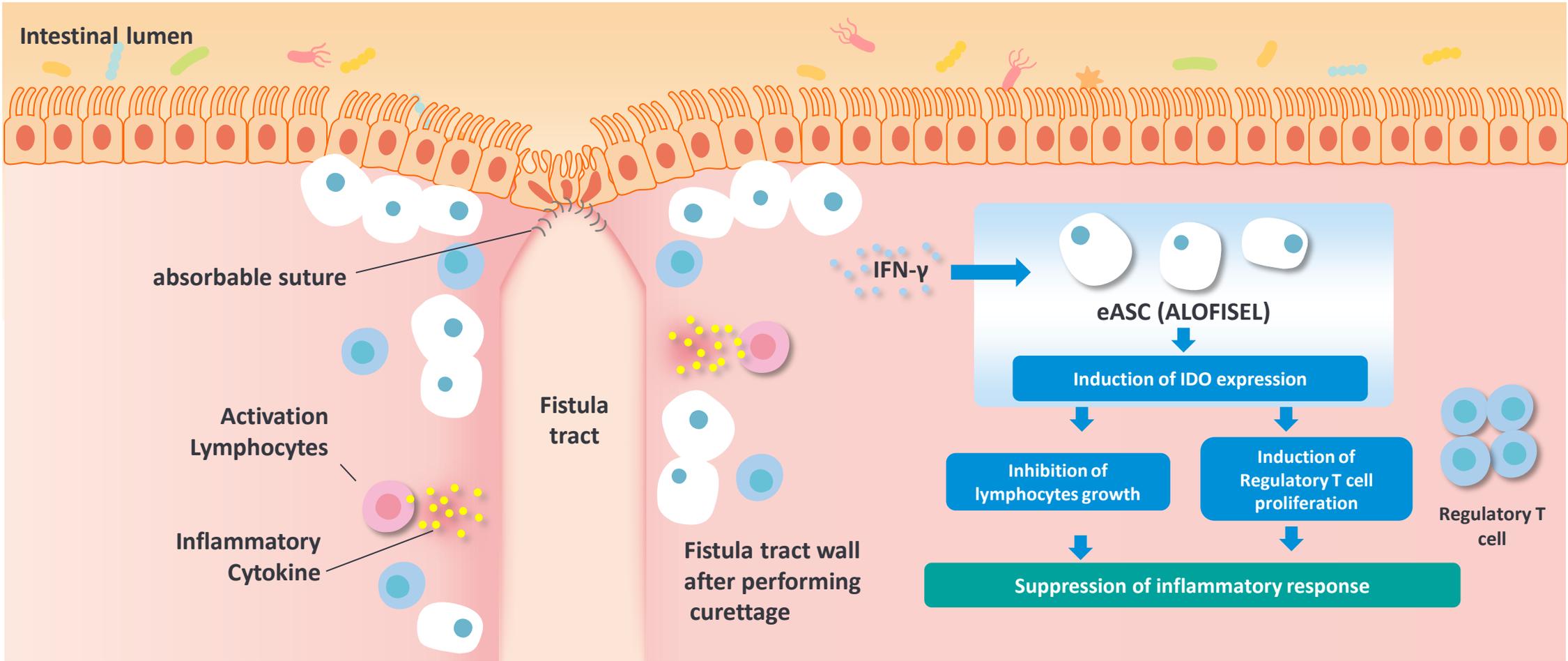


VIDEO

# Characteristics: Proposed immunomodulatory mechanism of action of ALOFISEL



Local injection of ALOFISEL may regulate inflammatory processes and allow tissue repair



eASC: human (allogeneic) adipose-derived stem cells; IDO: indoleamine-2,3-dioxygenase; IFN- $\gamma$ : interferon gamma

# Clinical trials: Development of ALOFISEL in Europe



- ALOFISEL has been approved in Europe based on the ADMIRE-CD pivotal study
- ALOFISEL was superior to control group in achieving combined remission at weeks 24 and 52

## Key overseas clinical study

### Phase 3: Cx601-0302 (ADMIRE CD)

Design: A multicenter, two arm, randomized, double-blind, placebo-controlled clinical trial.

Patients: Treatment-refractory complex Crohn's perianal fistulas (n=211; ITT population)

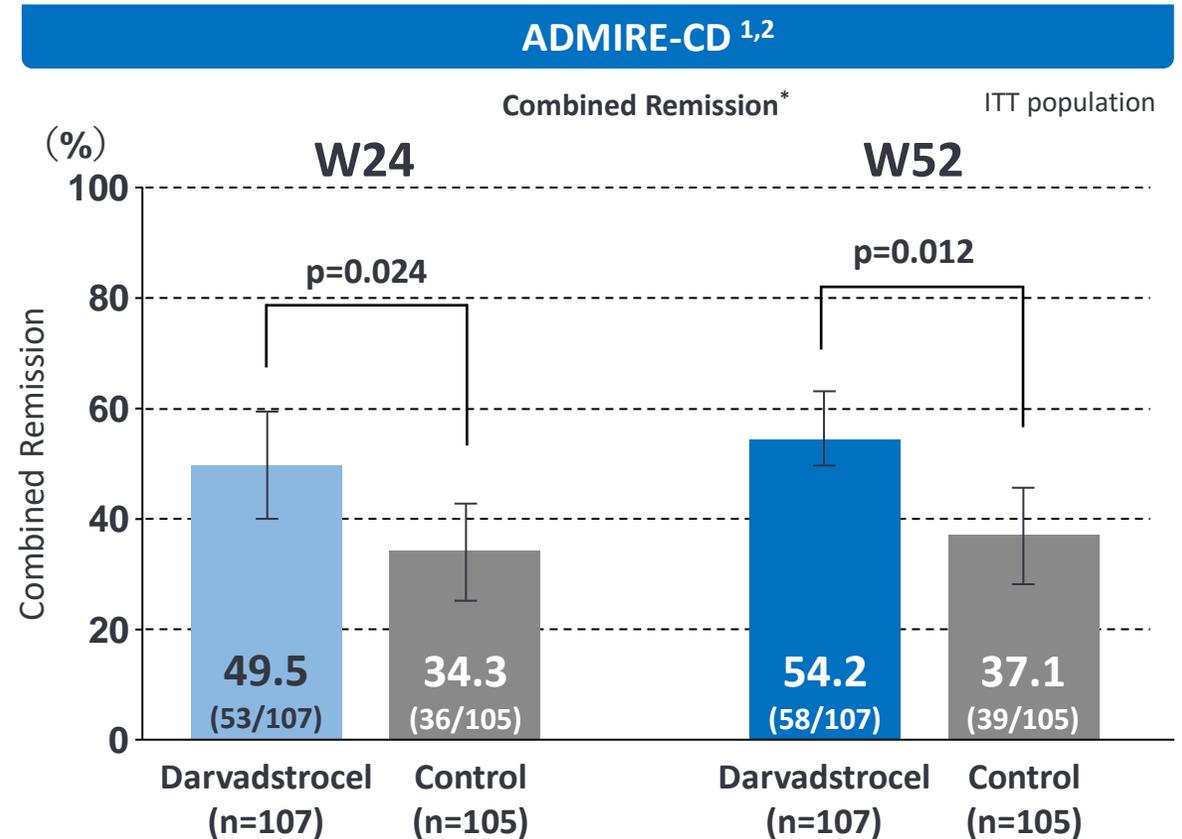
Primary endpoint: Combined remission rate at Week 24

## Safety profile of ADMIRE-CD study at W52

	Darvadstrocel (n=103)	Control (n=102)
TEAEs (all grade)	76.7%	72.5%
Serious TEAEs	24.3%	20.6%

\*Combined remission:

Defined as the clinically confirmed closure of all treated external openings that were draining at the screening despite gentle finger compression, and absence of collections >2 cm in the treated fistulas which is confirmed by the central MRI assessment.

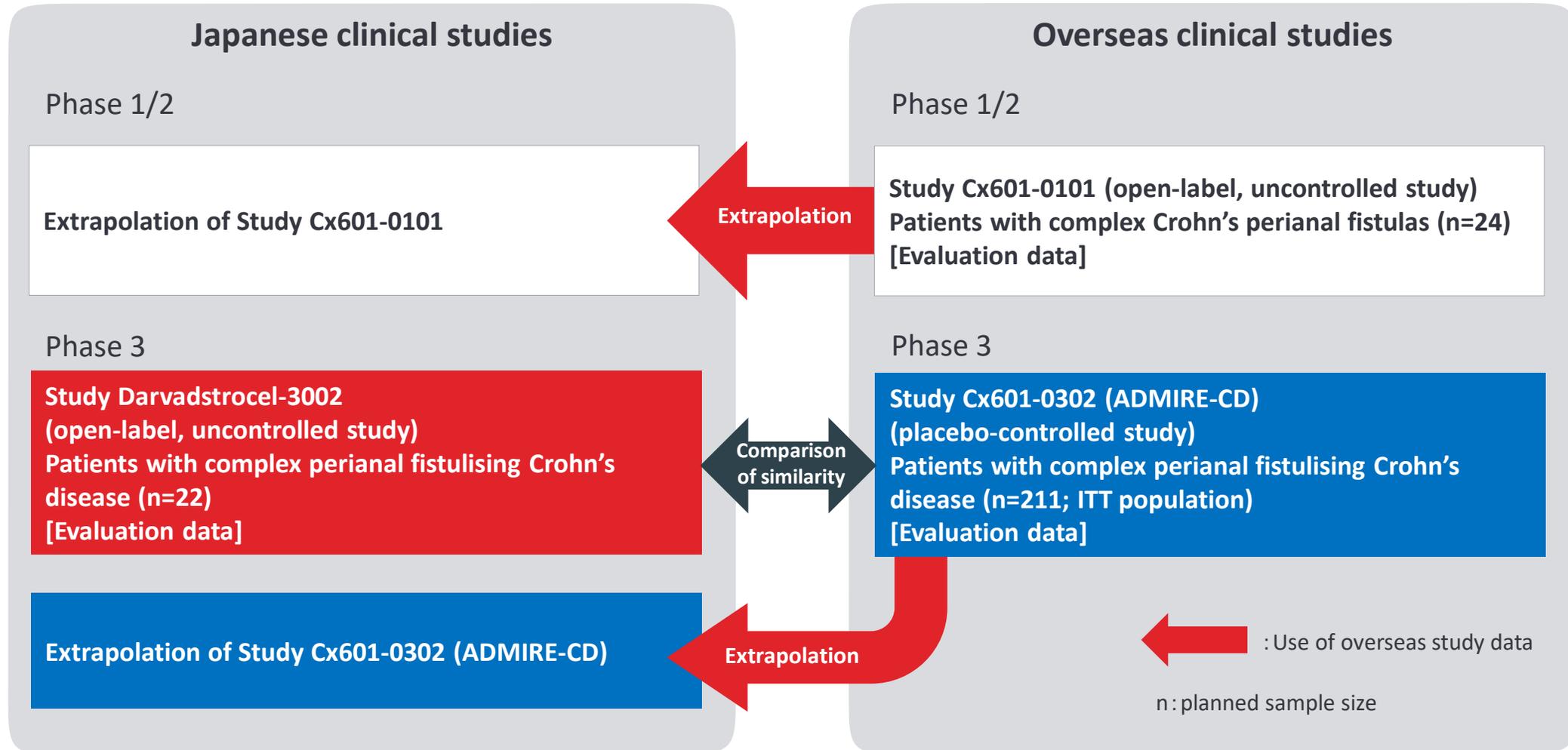


P-value; as determined by Cochran-Mantel-Haenszel test, adjusted for randomization strata (concomitant use of anti-TNFs and concomitant use of immunomodulators).

# Clinical trials: Development strategy in Japan (clinical data package)



This clinical data package was discussed in consultation with PMDA and aligned



Investigate the comparison of similarity between Darvadstrocel-3002 and ADMIRE-CD

## Japanese phase 3 study

### Phase 3: Darvadstrocel-3002<sup>1</sup>

Complex Crohn's perianal fistulas (n=22; ITT population)

Design: Open-Label, Uncontrolled, Multicenter Study

## Overseas phase 3 study

### Phase 3: Cx601-0302 (ADMIRE-CD)<sup>2,3</sup>

Complex Crohn's perianal fistulas (n=211; ITT population)

Design: Randomized, double blind, two arm ,  
placebo controlled, multicenter study

Countries: Austria, Belgium, France, Germany, Israel,  
Italy, The Netherlands and Spain

## ● Primary Objective

To evaluate the efficacy of Darvadstrocel for the treatment of complex Crohn's perianal fistulas in adult patients over 24 weeks

## ● Endpoints

- Primary: Proportion of subjects with combined remission\* at Week 24
- Secondary: Includes proportion of subjects with combined remission\* at Week 52

\*Combined remission:

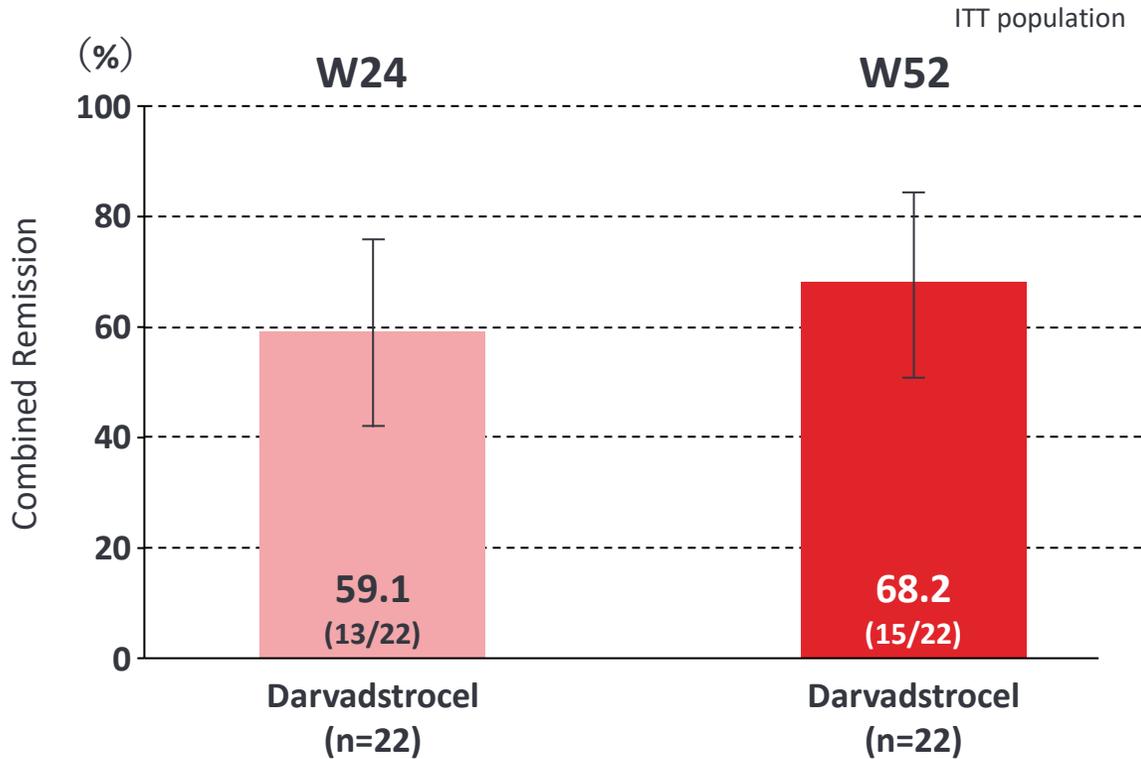
Defined as the clinically confirmed closure of all treated external openings that were draining at the screening, despite gentle finger compression, and absence of collections >2 cm in the treated fistulas which is confirmed by the central MRI assessment.

# Clinical trials: Combined remission at Week 24 and 52

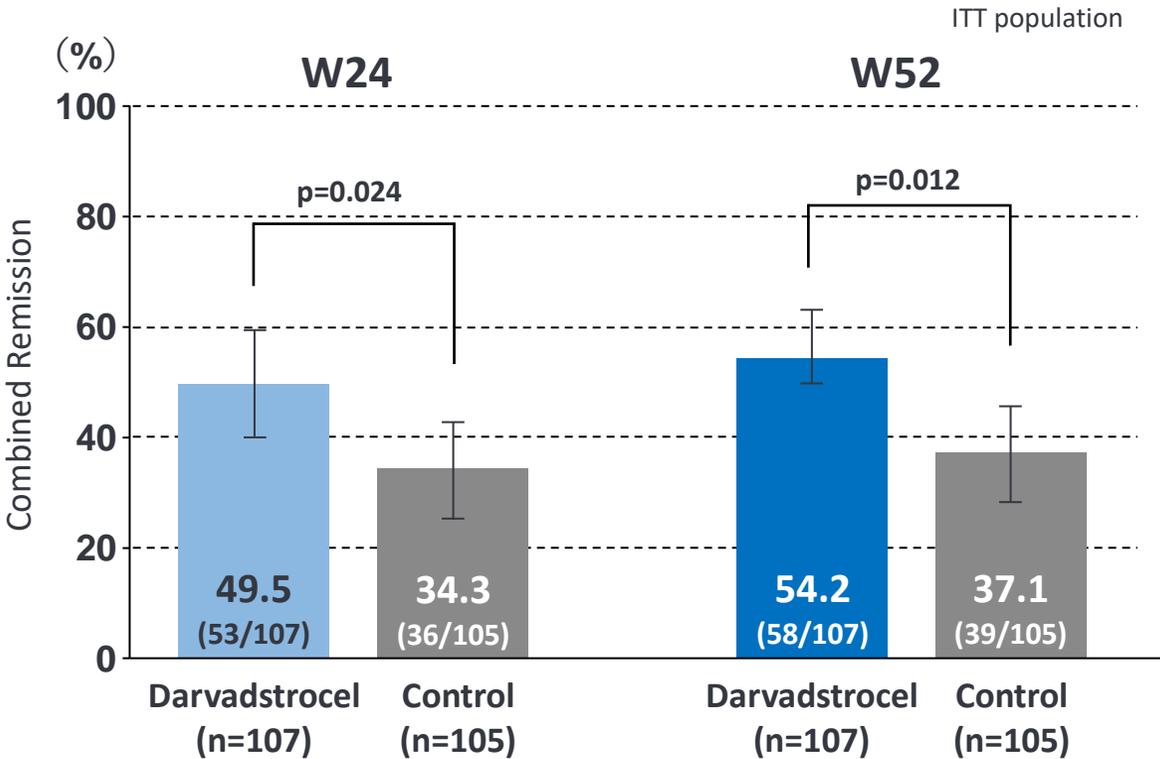


Efficacy in Japanese patients was similar compared to ADMIRE-CD

## Darvadstrocel-3002<sup>1</sup>



## ADMIRE-CD<sup>2,3</sup>



IITT population, in case of missing clinical assessment at Week 52, LOCF from the latest earlier post-baseline visit (including an Early Termination Visit prior to Week 52, if applicable) applied.  
 p: determined by Cochran-Mantel-Haenszel test adjusted for randomization strata (use of anti TNF agents or immunosuppressants at randomization)

# Clinical trials: Relapse at W52



- Efficacy in Japanese patients was similar compared to ADMIRE-CD
- Results suggest maintenance of efficacy after W24 in Japanese patients

ITT population

	Darvadstrocel-3002 <sup>1,2</sup>	ADMIRE-CD <sup>1,3</sup>	
Group	Darvastrocel (N=22)	Darvastrocel (N=107)	Control (N=105)
Proportion (%[N])	23.1 (3/13)	25.0 (13/52)	44.1 (15/34)
95% CI	[0.2, 46.0]	[13.2, 36.8]	[27.4, 60.8]

**【Relapse】** Defined as the clinically confirmed reopening of any of the treated external openings with active drainage, or the development of a collection >2 cm in the treated fistulas confirmed by central MRI assessment.

# Clinical trials: Overview of Adverse Events



## Similar trends in percentage and type of TEAEs between Darvadstrocel-3002 and ADMIRE CD

	Darvastrocel-3002 <sup>1</sup>	ADMIRE CD Study <sup>2</sup>	
	Darvastrocel (N=22)	Darvastrocel (N=103)	Control (N=102)
	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
<b>Treatment-Emergent AEs</b>	<b>20 (90.9)</b>	<b>79 (76.7)</b>	<b>74 (72.5)</b>
Not Related	18 (81.8)	71 (68.9)	69 (67.6)
Related	2 (9.1)	21 (20.4)	27 (26.5)
Mild	12 (54.5)	57 (55.3)	59 (57.8)
Moderate	6 (27.3)	54 (52.4)	52 (51.0)
Severe	2 (9.1)	10 (9.7)	12 (11.8)
Leading to Study Discontinuation	0 (0.0)	9 (8.7)	9 (8.8)
<b>Treatment-Emergent Serious AEs</b>	<b>4 (18.2)</b>	<b>25 (24.3)</b>	<b>21 (20.6)</b>
Not Related	3 (13.6)	19 (18.4)	16 (15.7)
Related	1 (4.5)*	7 (6.8)	7 (6.9)
Leading to Study Discontinuation	0 (0.0)	6 (5.8)	7 (6.9)
<b>Deaths</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>

[Summary of ALOFISEL safety profiles in Japanese population]

Safety analysis set

- TEAEs occurring at an incidence of  $\geq 10\%$  were proctalgia (27.3%), nasopharyngitis (22.7%), and anal fistula (18.2%).
- Most were mild or moderate in severity. No TEAEs leading to discontinuation of the study, No deaths occurred after study product administration.
- Treatment-related TEAEs were Crohn's disease, diarrhea, and blood bilirubin increased each in 1 subject.
- Serious TEAEs were Crohn's disease, intestinal obstruction, intestinal anastomosis complication, calculus urinary, and tubulointerstitial nephritis each in 1 subject. Of these, Crohn's disease was the only treatment-related TEAE.

# Clinical trials: Ongoing Clinical studies



**ALOFISEL is also being investigated globally, including in the U.S., and for expanded usable target/indication**

Trial Name	Patients	Enrollment	Phase	Description
<b>Study Cx601-0303 (ADMIRE-CD II)</b> NCT03279081	Complex perianal fistula(s) in subjects with inactive or mildly active CD	554	Phase 3	A double-blind study to assess efficacy and safety of darvadstrocel for the treatment of complex perianal fistula(s) in subjects with inactive or mildly active CD over a period of 24 weeks and a follow-up period up to 52 weeks
<b>Study Darvadstrocel-3002</b> NCT03706456	Complex perianal fistula(s) in Japanese adult subjects with inactive or mildly active CD	22	Phase 3	An open label study to assess the efficacy and safety of darvadstrocel in the treatment of complex perianal fistula(s) in Japanese adult subjects with inactive or mildly active CD over a period of 24 weeks and a follow-up period up to 156 weeks
<b>Study Darvadstrocel-3003</b> NCT04075825	Complex perianal fistula in subjects with CD who have participated in the Cx601-0303 study	150	A follow-up of Phase 3	A follow-up study to evaluate the long-term safety and efficacy of darvadstrocel in the treatment of complex perianal fistula in subjects with CD who have participated in the Cx601-0303 study
<b>Darvadstrocel-3004</b> NCT04701411	Pediatric subjects with CD between 4 and <18 years of age with complex perianal fistula	20	Phase 3	An open-label, pediatric study to assess the safety and efficacy of darvadstrocel in pediatric subjects between 4 and <18 years of age with complex perianal fistula (A part of the pediatric investigation plan (PIP) endorsed by the EMA pediatric committee)
<b>Alofisel-4001</b> NCT04118088	Complex perianal fistula(s) in subjects with inactive or mildly active CD	50	Phase 4	A phase 4, PASS to assess the repeat administration of darvadstrocel. (Initiated at the request of the EMA to provide further evidence on the safety and efficacy of darvadstrocel repeat administration)

# Manufacturing and Supply of ALOFISEL



## Lead the transformation as state-of-the art manufacturing facilities

Implemented at the cell therapy manufacturing facilities:

- Rapid sterilization technology
- Advanced cell-based testing and rapid testing methods & lab equipment
- Manufacturing Execution System (MES) and big-data analysis



## Supply Chain Management (SCM)

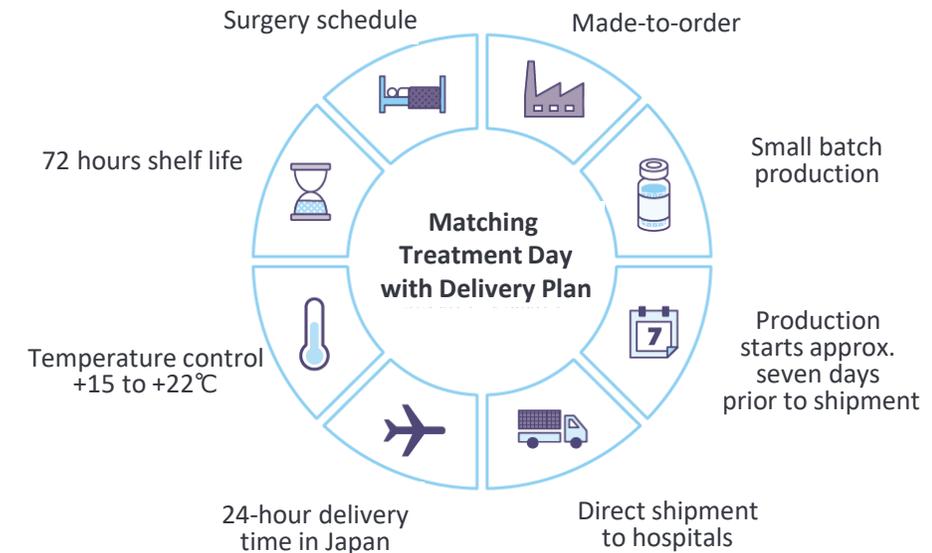
ALOFISEL is supplied using a made-to-order model as the product's shelf-life is just 72 hours. To successfully treat the patient as planned, ALOFISEL is delivered directly from the plant to the hospital under strict transport management.

### SCM System

End-to-end supply chain visibility with cloud-based system built specifically for ALOFISEL in collaboration with a transport service partner. It enables not only Takeda but also hospitals to track the package from the moment it leaves the plant.

### Transport management

Strict temperature control until surgery starts using a passive packaging system and transport risk is minimized in line with GDP using real time temperature and GPS monitoring.



# Efforts in Logistics

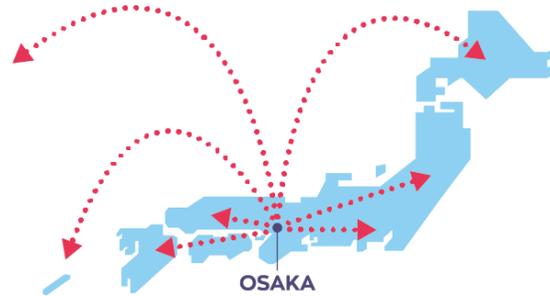


## Japan

Osaka, which is centrally located in Japan and provides excellent convenience for shipping by both land and air, is very geographically advantageous. With the plant based in Osaka, Takeda can quickly deliver cellular pharmaceuticals with a high level of quality guaranteed through the use of state-of-the-art technology to patients in Japan.



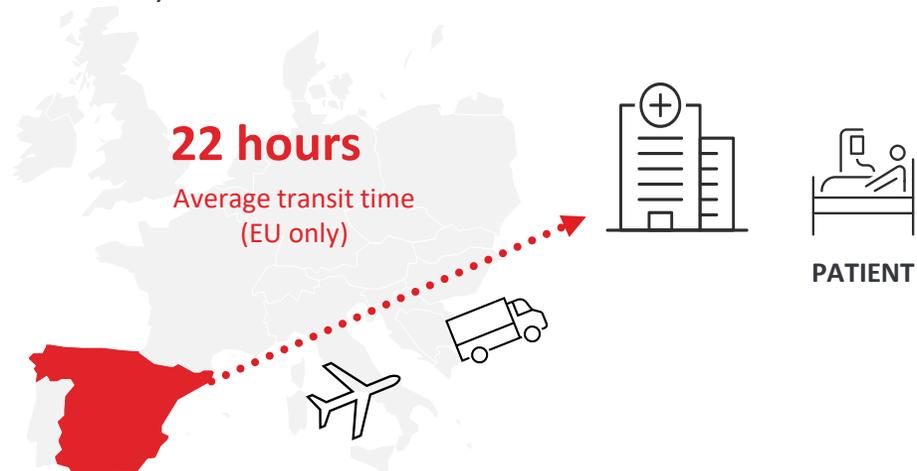
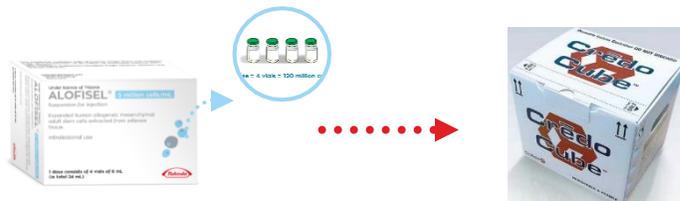
Truck transportation within the main island, Shikoku and Kyushu.



Air transport to Hokkaido and Okinawa.

## Europe

Deliveries are made direct from the manufacturing site to the hospital and into the hands of a named and trained recipient without further local release or wholesaler interaction. Approximately 500 patients across 19 countries have received ALOFISEL from Madrid plant as of December 2021. (Deliveries from Grange Castle plant is planned to start in Feb 2022.)



**22 hours**

Average transit time  
(EU only)

**4 hours**

minimum guaranteed

PATIENT



Crohn's perianal fistulas significantly impair patients' health-related quality of life (HRQoL) including physical, social and emotional well-being



Limited surgical and biological treatment options available, while up to 70% of patients receiving conventional treatments relapse<sup>1,2,3</sup>



ALOFISEL is a cell therapy product with an immunomodulatory and anti-inflammatory MOA administered by a minimally invasive surgical procedure



ALOFISEL provides a potential cell-mediated closure option for complex Crohn's perianal fistulas in patients with inactive or mildly active Crohn's Disease in Japan who have shown an inadequate response to at least one existing medicinal treatment

1. Panes J, Reinisch W, Rupniewska E, Khan S, et al. Burden and outcomes for complex perianal fistulas in Crohn's disease: Systematic review. *World J Gastroenterol.* 2018; 24(42): 4821–4834.  
2. Gold S, Cohen-Mekelburg S, Schneider Y, Steinlauf A. perianal fistulas in patients with Crohn's disease, Part 1: current medical management. *Gastroenterol Hepatol.* 2018;14(8):470-481.  
3. Lightner A. Cell-based therapy for Crohn's disease: time to consider optimization. *Nat Rev Gastroenterol Hepatol.* 2019;16(3):137-138.

## Agenda

## Presenters

### 1. Takeda's Initiatives in Gastroenterology (GI) Therapeutic Area

Mitsuhiro Shikamura  
Senior Clinical Science Director, Therapeutic Area Strategy Unit (GI)

### 2. Short Bowel Syndrome

Masakazu Miyamoto  
Manager, Marketed Product Group, Therapeutic Area Strategy Unit

### 3. Complex Perianal Fistulas in Crohn's Disease

Tomoko Tanaka  
Associate Medical Director, Therapeutic Area Strategy Unit (GI)  
Takayoshi Yamaguchi  
Manager, Therapeutic Area Strategy Unit (GI)

### 4. Q&A Session

### Q&A Panelists

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# APPENDIX



# Two Innovative GI Therapies Approved in Japan in 2021



## GATTEX/REVESTIVE (teduglutide)

## ALOFISEL (darvadstrocel)

Indication

Short Bowel Syndrome (SBS)

Complex Crohn's Perianal Fistulas (CPF)

Approval Status  
[Approval Date]

Approved in **47 countries** including;  
US [Dec 2012 (adults), May 2019 (pediatrics<sup>1</sup>)]  
EU [Aug 2012 (adults), Jun 2016 (pediatrics<sup>1</sup>)]  
Japan [Jun 2021 (adults, pediatrics, infants)]

Approved in **35 countries** including;  
EU<sup>2</sup> [Mar 2018]  
Japan<sup>2</sup> [Sep 2021]

Mode of Action

Glucagon-like peptide 2 receptor analog (GLP-2 RA)

Immunomodulatory and anti-inflammatory effects at inflammation sites

What's New for  
Patients, family and HCPs?

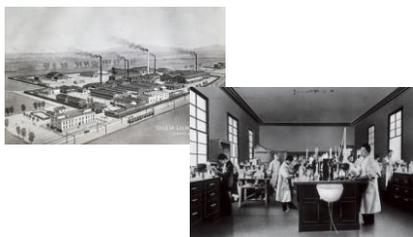
First and only GLP-2 approved for helping to improve the absorptive capacity of the small intestine in SBS

First stem cell therapy approved for treating complex CPF in patients with non-active or mildly active Crohn's Disease  
First cell therapy for Takeda

## Key Manufacturing Facilities in Japan and Europe

### Osaka Plant (Japan)

Established in 1915, the site is one of the plants with long history in Takeda manufacturing & supply network. Over 100 years of history, technology and capability in solid dosage, injections and sterile have been built. With expansion of the new facility as the product specific site for sterile/injection, Takeda has ensured that this historical site will remain globally competitive for years to come, implementing state-of-art technology



### Madrid Plant (Spain)

Following the acquisition of TiGenix in 2018, the Madrid Plant joined Takeda's manufacturing network and is the first manufacturing plant which started producing ALOFISEL. Since the approval of ALOFISEL by EMA in 2018, it has supplied ALOFISEL across 18 European countries. In September 2021, Madrid Plant tripled its production capacity of ALOFISEL to meet the increasing demand for this medicine.



### Grange Castle Plant (Ireland)

The site began operations in 2007 as Takeda's first overseas manufacturing center for active pharmaceutical ingredients. In October 2021, Takeda celebrated the opening of a cell therapy production facility at its Grange Castle Plant. The state-of-the-art commercial scale cell therapy production facility is the first of its kind in Ireland and is expected to play an important role in supplying European, U.S. and Canadian markets with a cell therapy treatment option for patients.

