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## AGENDA

<table>
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| 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

- DEXILANT
- Lialda
- Amitiza

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

Global Brands
# 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\(^1\) (Generic name Teduglutide)
  - First and only approved GLP-2 analog for SBS treatment
  - Clinical Trials

1. Brand name for Japan is Revestive
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."¹

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."²

---

*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.

- **Proximal Small Intestine**:
  - ✓ Fat
  - ✓ Sugars
  - ✓ Peptides/AAs
  - ✓ Iron
  - ✓ Folate
  - ✓ Calcium
  - ✓ Water
  - ✓ Electrolytes

- **Middle Small Intestine**:
  - ✓ Sugars
  - ✓ Peptides/AAs
  - ✓ Calcium
  - ✓ Water
  - ✓ Electrolytes

- **Colon**:
  - ✓ Water
  - ✓ Electrolytes
  - ✓ MCTs
  - ✓ AAs

- **Distal Small Intestine**:
  - ✓ Bile salts
  - ✓ Vitamin B₁₂
  - ✓ Water
  - ✓ Electrolytes

AA: amino acid; MCT: medium-chain triglyceride
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\(^1,2\)

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

**Adult**
- Crohn’s diseases
- Superior mesenteric artery embolism
- Strangulated ileus
- Radiation enteritis

**Child**
- Congenital small intestinal atresia
- Midgut volvulus
- Hirschsprung disease and allied disorders of Hirschsprung’s disease*  
- Gastrochisis
- Necrotizing enterocolitis

---

*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\(^3\)

Epidemiology: Prevalence estimates of SBS

The exact prevalence of SBS is unknown and may vary per geographic region\(^1\)
SBS is a rare disease with a prevalence that appears to be increasing

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

*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

### Symptoms and Burden on Daily Life: Clinical symptoms and the mechanisms

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

<table>
<thead>
<tr>
<th>Clinical features of SBS(^1,2)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td>Fatty stools</td>
<td></td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanisms leading to SBS(^3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced absorptive mucosal surface</td>
<td></td>
</tr>
<tr>
<td>Increased intestinal losses of fluids and electrolytes</td>
<td></td>
</tr>
<tr>
<td>Restricted oral/enteral nutrition</td>
<td></td>
</tr>
<tr>
<td>Disease-related hypophagia</td>
<td></td>
</tr>
<tr>
<td>Lack of adaptive hyperphagia</td>
<td></td>
</tr>
<tr>
<td>Accelerated GI transit time</td>
<td></td>
</tr>
<tr>
<td>Small bowel bacterial overgrowth</td>
<td></td>
</tr>
</tbody>
</table>

### Key points:
- SBS primarily results from loss of intestinal absorptive capacity\(^1\text{-}^3\)
- Characterized by inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance with conventional diet\(^4\)
- Severity of clinical features varies from patient to patient\(^1,2\)

---

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.

- Comorbidity by long-term parenteral nutrition
- Restriction of activities during drip infusion
- Sleep disorder (interruption)
- Disturbance in travel, leisure activities and social life
- Decreased sexual desire and function
- Depression
- Fatigue and feebleness
- Feeling of being others’ burden
- Dry mouth
- Diarrhea

QoL component affected by SBS

QoL: Quality of Life

Symptoms and Burden on Daily Life: SBS Patient’s Voice

VIDEO
Symptoms and Burden on Daily Life: Survival rate of adult patients with SBS

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

Patient population: From January 1980 to April 2006, all consecutive adult patients with a SBS (remnant small intestine length of ≤ 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)

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

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

HPN: home parenteral nutrition

SBS: short bowel syndrome

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

Management and treatment of benign Chronic Intestinal Failure (CIF)

- Home parenteral nutrition (HPN)
- Intestinal rehabilitation
- Intestinal transplantation
- Complications of HPN

Management of HPN

Components of HPN

Venous catheters of HPN

- Management of HPN
- Components of HPN
- Venous catheters of HPN

Diet

- Medical
- Surgery

Special cases

CIPO

Radiation enteritis

Catheter related

- Occlusion thrombosis
- Liver disease
- Cholelithiasis
- Renal Failure/stones
- Bone disease

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

- **Medical treatment: Management of GI symptoms** and Growth factor therapies
  - Antisecretory agents
  - Antimotility/antidiarrheal drugs
  - Antibiotics
  - GLP-2 analog (teduglutide)
  - Growth hormone (somatropin)

- **Surgical options**
  - Nontransplant surgery
  - Intestinal transplantation

**Treatment goal: Adults**
To wean patients off parenteral nutrition, by promoting intestinal adaptation

**Treatment goal: Children**
To achieve intestinal adaptation while maintaining proper growth and development

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

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

Non-nutrient factors $^{3,4}$

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

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

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

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). This single amino-acid substitution resists degradation by DPP-IV, 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.

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
Clinical Trials: GATTEX/REVESTIVE Phase 3 study with adult SBS patients (STEPS study)

**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)

**Study design**
- **PS optimization**
  - 0 - 8 weeks
  - n=43
- **PS stabilization**
  - 4 - 8 weeks
  - n=43
- **Placebo**
  - 24 weeks
  - n=43

**GATTEX/REVESTIVE 0.05 mg/kg/day**

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

SBS: short bowel syndrome; PS: parenteral support (parenteral nutrition and/or intravenous fluids)
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 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.

Mean (SE) absolute reduction in PS

Mean (SE) PS Volume Change From Baseline, (L/Week)

Weeks: 4, 8, 12, 16, 20, 24

GATTEX/REVESTIVE 0.05 mg/kg/day (n=43)
Placebo (n=43)

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.


PS: parenteral support (parenteral nutrition and/or intravenous fluids)
**Clinical Trials: STEPS Results – Adverse Events**

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

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

*None considered serious
**Deemed related to study drug (acute cholecystitis and small intestinal stenosis) and both resolved

AE: adverse event; TEAE: treatment emergent adverse event; TESAE: 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

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

* 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


TEAE: treatment emergent adverse event
Clinical Trials:
GATTEX/REVESTIVE Phase 3 study with pediatric SBS patients (TED-C14-006 study)

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

Study design

Screening period

2 weeks minimum

n=24

GATTEX/REVESTIVE 0.025 mg/kg/day subcutaneously (SC) + SOC

n=26

GATTEX/REVESTIVE 0.05 mg/kg/day SC + SOC

n=9

SOC only

24 weeks

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

Follow-up period

Randomization 1:1

Pediatric data

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

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

![Graph showing the proportion of patients (n=24) receiving 0.025 mg/kg/day of GATTEX/REVESTIVE with 54.2% reduction, and n=26 receiving 0.05 mg/kg/day with 69.2% reduction, compared to SOC with 11.1% reduction.]

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

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.

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

- **GATTEX/REVESTIVE 0.025 mg/kg/day** (n = 24): 8.3%
- **GATTEX/REVESTIVE 0.05 mg/kg/day** (n = 26): 11.5%
- **SOC** (n = 9): 0%

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

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

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

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.

SBS: Short Bowel Syndrome; QoL: Quality of Life; GLP-2: glucagon-like peptide-2
## Agenda

<table>
<thead>
<tr>
<th>Agenda</th>
<th>Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Takeda’s Initiatives in Gastroenterology (GI) Therapeutic Area</td>
<td>Mitsuhiro Shikamura&lt;br&gt;Senior Clinical Science Director, Therapeutic Area Strategy Unit (GI)</td>
</tr>
<tr>
<td>2. Short Bowel Syndrome</td>
<td>Masakazu Miyamoto&lt;br&gt;Manager, Marketed Product Group, Therapeutic Area Strategy Unit</td>
</tr>
<tr>
<td>3. Complex Crohn’s Perianal Fistulas</td>
<td>Tomoko Tanaka&lt;br&gt;Associate Medical Director, Therapeutic Area Strategy Unit (GI)&lt;br&gt;Takayoshi Yamaguchi&lt;br&gt;Manager, Therapeutic Area Strategy Unit (GI)</td>
</tr>
<tr>
<td>4. Q&amp;A Session</td>
<td>Q&amp;A Panelists</td>
</tr>
</tbody>
</table>
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 1st 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
  - 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
  - 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).

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)∗

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

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

Perianal fistula/abscess

- Shallow
- Single

- Deep
- Multiple secondary openings
- Multiple fistulas

Lay open or Seton drainage

- Resolve
- Observation
  - Continuous seton drainage + Biological drugs
    - Recurrent complex multiple fistula
    - Severe anal stricture
    - Vaginal fistula/urethral fistulas
    - Cancer
    - Severely damaged QoL

- Stoma

- Recurrence
  - Delayed healing complex lesions
    - With rectal lesions
    - Without rectal lesions
    - Stabilized
      - Continuous seton drainage
      - Resolve
      - Continuous treatment

Continuous treatment

Clinical Practice Guidelines for Anorectal Diseases (Hemorrhoids, Anal Fistulas, Anal Fissures) and Rectal Prolapses 2020, 45, 2020; Lichtenstein, 2018
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

CPF: Crohn’s perianal fistulas; QOL: quality of life; ASA: amino salicylic acid

Supervisor: Dr. Kenichi Takahashi, Head of Department of Colorectal Surgery, Head of IBD center, Tohoku Rosai Hospital
Symptoms and Burden on Daily Life: CPF Patient’s Voice

VIDEO
Characteristics: What are stem cells?

- 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

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

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)


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

- 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

- Clinical trials of MSCs have been conducted for **various immune-mediated inflammatory diseases**
  - Demyelinating neuropathy (multiple sclerosis)
  - Systemic lupus erythematosus
  - Crohn's disease

---

MSCs: mesenchymal stem cell

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

*eASC: expanded human allogeneic Adipose-derived mesenchymal Stem Cell, extracted from adipose tissue of healthy adults
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

**Intestinal lumen**

- Absorbable suture
- Activation Lymphocytes
- Inflammatory Cytokine

**Fistula tract**

- Fistula tract wall after performing curettage

**eASC (ALOFISEL)**

- Induction of IDO expression
- Induction of T cell proliferation
- Inhibition of lymphocytes growth

**Suppression of inflammatory response**

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

References:

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

<table>
<thead>
<tr>
<th></th>
<th>Darvadstrocel (n=103)</th>
<th>Control (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs (all grade)</td>
<td>76.7%</td>
<td>72.5%</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>24.3%</td>
<td>20.6%</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Japanese clinical studies</th>
<th>Overseas clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1/2</strong></td>
<td><strong>Phase 1/2</strong></td>
</tr>
<tr>
<td>Extrapolation of Study Cx601-0101</td>
<td>Extrapolation of Study Cx601-0302 (ADMIRE-CD)</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td><strong>Phase 3</strong></td>
</tr>
<tr>
<td>Study Darvadstrocel-3002 (open-label, uncontrolled study) Patients with complex perianal fistulising Crohn’s disease (n=22) [Evaluation data]</td>
<td>Study Cx601-0302 (ADMIRE-CD) (placebo-controlled study) Patients with complex perianal fistulising Crohn’s disease (n=211; ITT population) [Evaluation data]</td>
</tr>
</tbody>
</table>

Extrapolation of Study Cx601-0101

Extrapolation of Study Cx601-0302 (ADMIRE-CD)

Extrapolation

Comparison of similarity

Use of overseas study data

n: planned sample size

PMDA: Pharmaceuticals and Medical Devices Agency
Clinical trials: Development of ALOFISEL in Japan

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

Japanese phase 3 study

**Phase 3: Darvadstrocel-3002**
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)**
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-3002^1

<table>
<thead>
<tr>
<th></th>
<th>W24</th>
<th>W52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darvadstrocel (n=22)</td>
<td>59.1 (13/22)</td>
<td>68.2 (15/22)</td>
</tr>
</tbody>
</table>

ADMIRE-CD^2,3

<table>
<thead>
<tr>
<th></th>
<th>W24</th>
<th>W52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darvadstrocel (n=107)</td>
<td>49.5 (53/107)</td>
<td>54.2 (58/107)</td>
</tr>
<tr>
<td>Control (n=105)</td>
<td>34.3 (36/105)</td>
<td>37.1 (39/105)</td>
</tr>
</tbody>
</table>

ITT 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

<table>
<thead>
<tr>
<th>Group</th>
<th>Darvadstrocel (N=22)</th>
<th>Darvastrocel (N=107)</th>
<th>Control (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion (%[N])</td>
<td>23.1 (3/13)</td>
<td>25.0 (13/52)</td>
<td>44.1 (15/34)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.2, 46.0]</td>
<td>[13.2, 36.8]</td>
<td>[27.4, 60.8]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Darvadstrocel-3002¹</th>
<th>ADMIRE CD Study²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darvadstrocel (N=22)</td>
<td>Darvadstrocel (N=103)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Subjects (%)</th>
<th>Number of Subjects (%)</th>
<th>Number of Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Emergent AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Related</td>
<td>20 (90.9)</td>
<td>79 (76.7)</td>
</tr>
<tr>
<td>Related</td>
<td>18 (81.8)</td>
<td>71 (68.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (9.1)</td>
<td>21 (20.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (54.5)</td>
<td>57 (55.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (27.3)</td>
<td>54 (52.4)</td>
</tr>
<tr>
<td>Leading to Study Discontinuation</td>
<td>2 (9.1)</td>
<td>10 (9.7)</td>
</tr>
<tr>
<td>Treatment-Emergent Serious AEs</td>
<td>4 (18.2)</td>
<td>25 (24.3)</td>
</tr>
<tr>
<td>Not Related</td>
<td>3 (13.6)</td>
<td>19 (18.4)</td>
</tr>
<tr>
<td>Related</td>
<td>1 (4.5)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Leading to Study Discontinuation</td>
<td>0 (0.0)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

[Summary of ALOFISEL safety profiles in Japanese population]

- TEAEs occurring at an incidence of ≥ 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

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Patients</th>
<th>Enrollment</th>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Cx601-0303 (ADMIRE-CD II) NCT03279081</td>
<td>Complex perianal fistula(s) in subjects with inactive or mildly active CD</td>
<td>554</td>
<td>Phase 3</td>
<td>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</td>
</tr>
<tr>
<td>Study Darvadstrocel-3002 NCT03706456</td>
<td>Complex perianal fistula(s) in Japanese adult subjects with inactive or mildly active CD</td>
<td>22</td>
<td>Phase 3</td>
<td>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</td>
</tr>
<tr>
<td>Study Darvadstrocel-3003 NCT04075825</td>
<td>Complex perianal fistula in subjects with CD who have participated in the Cx601-0303 study</td>
<td>150</td>
<td>A follow-up of Phase 3</td>
<td>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</td>
</tr>
<tr>
<td>Darvadstrocel-3004 NCT04701411</td>
<td>Pediatric subjects with CD between 4 and &lt;18 years of age with complex perianal fistula</td>
<td>20</td>
<td>Phase 3</td>
<td>An open-label, pediatric study to assess the safety and efficacy of darvadstrocel in pediatric subjects between 4 and &lt;18 years of age with complex perianal fistula (A part of the pediatric investigation plan (PIP) endorsed by the EMA pediatric committee)</td>
</tr>
<tr>
<td>Alofisel-4001 NCT04118088</td>
<td>Complex perianal fistula(s) in subjects with inactive or mildly active CD</td>
<td>50</td>
<td>Phase 4</td>
<td>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)</td>
</tr>
</tbody>
</table>

CD: Crohn's disease; PASS: Post-authorization safety studies; EMA: European Medicines Agency
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.

GDP: Good Distribution Practice
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.

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.)
Take-home Messages

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\(^1,2,3\)

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

<table>
<thead>
<tr>
<th>Agenda</th>
<th>Presenters</th>
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</thead>
<tbody>
<tr>
<td>1. Takeda’s Initiatives in Gastroenterology (GI) Therapeutic Area</td>
<td>Mitsuhiro Shikamura</td>
</tr>
<tr>
<td></td>
<td>Senior Clinical Science Director, Therapeutic Area Strategy Unit (GI)</td>
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<tr>
<td>2. Short Bowel Syndrome</td>
<td>Masakazu Miyamoto</td>
</tr>
<tr>
<td></td>
<td>Manager, Marketed Product Group, Therapeutic Area Strategy Unit</td>
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<td>3. Complex Perianal Fistulas in Crohn’s Disease</td>
<td>Tomoko Tanaka</td>
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<td></td>
<td>Associate Medical Director, Therapeutic Area Strategy Unit (GI)</td>
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<td></td>
<td>Takayoshi Yamaguchi</td>
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<td></td>
<td>Manager, Therapeutic Area Strategy Unit (GI)</td>
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<tr>
<td>4. Q&amp;A Session</td>
<td>Q&amp;A Panelists</td>
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</table>
## Q&A Session

### Q&A Panelists

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
<tr>
<td>Mitsuhiro Shikamura</td>
<td>Senior Clinical Science Director, Therapeutic Area Strategy Unit (GI)</td>
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<td>Masakazu Miyamoto</td>
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<td>Tomoko Tanaka</td>
<td>Associate Medical Director, Therapeutic Area Strategy Unit (GI)</td>
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<tr>
<td>Takayoshi Yamaguchi</td>
<td>Manager, Therapeutic Area Strategy Unit (GI)</td>
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<tr>
<td>Emiko Koumura</td>
<td>Japan Site Head, Marketed Products Group, Therapeutic Area Strategy Unit</td>
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<tr>
<td>Taisuke Kondo</td>
<td>Medical Director, Marketed Products Group, Therapeutic Area Strategy Unit</td>
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APPENDIX
# Two Innovative GI Therapies Approved in Japan in 2021

<table>
<thead>
<tr>
<th>GATTEX/REVESTIVE (teduglutide)</th>
<th>ALOFISEL (darvadstrocel)</th>
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<tr>
<td><strong>Indication</strong></td>
<td>Short Bowel Syndrome (SBS)</td>
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<tr>
<td><strong>Approval Status</strong></td>
<td>Approved in <strong>47 countries</strong> including;</td>
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<tr>
<td>[Approval Date]</td>
<td>US [Dec 2012 (adults), May 2019 (pediatrics(^1))]</td>
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<tr>
<td></td>
<td>EU [Aug 2012 (adults), Jun 2016 (pediatrics(^1))]</td>
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<tr>
<td></td>
<td>Japan [Jun 2021 (adults, pediatrics, infants)]</td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Glucagon-like peptide 2 receptor analog (GLP-2 RA)</td>
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<tr>
<td><strong>What’s New for Patients, family and HCPs?</strong></td>
<td>First and only GLP-2 approved for helping to improve the absorptive capacity of the small intestine in SBS</td>
</tr>
<tr>
<td></td>
<td><strong>First cell therapy for Takeda</strong></td>
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Manufacturing ALOFISEL

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.