

# Incorporating Caregiver Burden in Japan’s Cost-Effectiveness Evaluation: A Case Study of Teduglutide for Pediatric Short Bowel Syndrome

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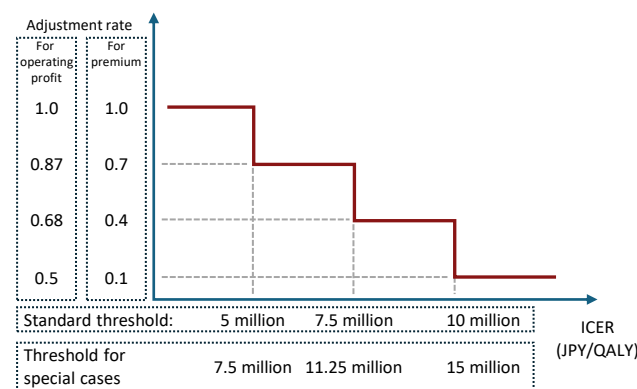
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## Background

### The Current Status of Cost-Effectiveness Evaluation in Japan

- In Japan, cost-effectiveness evaluation has been introduced to adjust the prices of new drugs after reimbursement. Under this framework, as shown in **Fig 1**, prices are mechanically adjusted based solely on the range that corresponds to the single point estimate of the ICER (incremental cost-effectiveness ratio) calculated from the cost-effectiveness model.
  - 1. If a product's ICER is less than ¥5 million per QALY, its price is not adjusted.
  - 2. When the ICER falls between ¥5 million and ¥7.5 million per QALY, the price adjustment rate increases stepwise. Basically, usefulness premium portion is adjusted following the rule. For cases with cost-plus method, operation profit portion can be adjusted if the disclosure rate of cost details such as manufacturing is below 50%.
  - 3. Finally, if the ICER is over ¥10 million per QALY, the price is adjusted at the maximum rate.
- For some special cases such as oncology products, the ICER threshold is set at 1.5 times the standard threshold, resulting in adjusted values of ¥7.5 million, ¥11.25 million, and ¥15 million per QALY, respectively.

**Fig 1.** Rate of price adjustments for usefulness premiums and operating profits (adapted from Reference 1).



ICER incremental cost-effectiveness ratio, JPY Japanese yen, QALY quality-adjusted life-year

- Decision making as price adjustment is always based on cost-effectiveness analysis results from public healthcare payer's perspective. As a result, the analysis often focuses solely on patient outcomes, overlooking caregiver burden in diseases requiring long-term care, potentially underestimating treatment value.
  - The perspective of properly evaluating the burden associated with caregiving and home care is not incorporated into actual price adjustments.
- On the other hand, the importance of incorporating broader values of new drugs, such as reducing caregiver burden, has been increasingly proposed and discussed.

### Overview of Short Bowel Syndrome (SBS) and Issues in Pediatric Patients

- SBS is a rare disease in which impaired intestinal absorption makes it difficult to maintain nutrition through oral intake alone, requiring long-term parenteral support (PS).<sup>2,3</sup>
- Particularly in pediatric patients, home management of PS places a significant caregiving burden on caregivers and requires careful attention to complications such as IF-associated liver disease (IFALD) and central venous catheter infections.<sup>4,5</sup>

### Reduction of Parenteral Support (PS) Dependency with Teduglutide

- Teduglutide has been shown in clinical trials to reduce the need for PS in patients with SBS and is expected to mitigate the risk of complications and ease the burden of home care<sup>6-8</sup>.
- However, when evaluating its cost-effectiveness, a key challenge is how to incorporate the burden on caregivers, including quality of life (QOL) and productivity loss.

## Methods

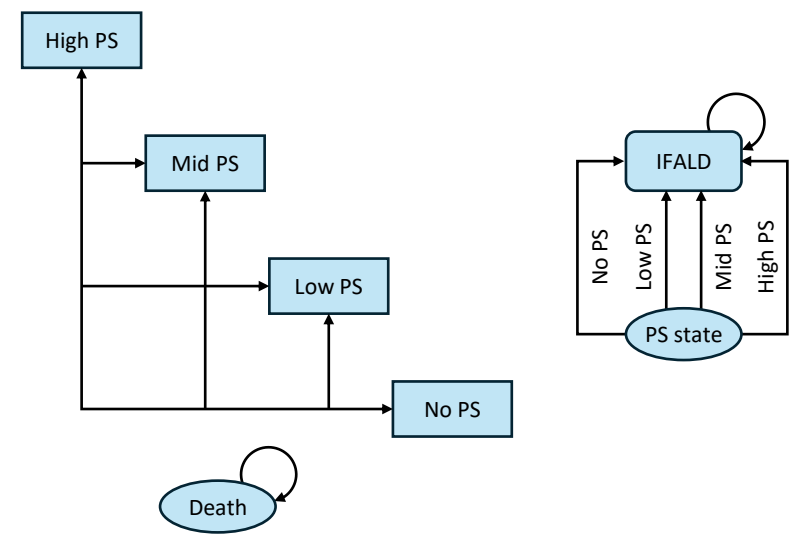
### Overview

- Target population:** pediatric patients with SBS in Japan (An average starting age for treatment of 6 years)
- Target product:** Teduglutide (0.05 mg/kg/day)
- Comparator:** Standard of care (SOC) which aims to alleviate symptoms through optimization of residual intestinal function using PS and enteral nutrition.
- Markov model:**
  - 1. Cycle length: 1 month
  - 2. Analysis period: lifetime
- Discount rate:** 2% per annum for both costs and effect (in accordance with Guideline for Cost-Effectiveness Evaluation in Japan)<sup>9</sup>
- Perspective**
  - Public healthcare payer's perspective: consider only medical cost
  - Public healthcare and long-term care payer's perspective: additional consideration of caregiver utility
  - Societal perspective: additional consideration of caregiver utility and productivity loss

### Model Structure

- Health state:** patients could transfer reversibly between PS states (**Fig. 2**)
  - No PS: without PS–PS withdrawal state
  - Low PS: PS required 1–3 days per week
  - Mid PS: PS required 4–5 days per week
  - High PS: PS required 6–7 days per week
  - Death
- IFALD:** this model also considered the occurrence of IFALD as a complication of PS, assuming irreversible progression to liver fibrosis and cirrhosis.<sup>10</sup>

**Fig 2.** Markov model structure.



PS parenteral support, IFALD intestinal failure-associated liver disease

### Utilities

#### Patient utility

- Each PS state: set using mean scores from a UK adult study due to the lack of reported utility data for pediatric SBS patients based on PS days.<sup>11</sup>
  - No PS, 0.820; Low PS, 0.717; Mid PS, 0.545; High PS, 0.385
- IFALD: set using weighted averages of chronic hepatitis and liver cirrhosis utilities for hepatitis B and C.<sup>12</sup>

#### Caregiver utility

- Each PS state: set using caregiver utility derived from EQ-5D survey results of UK SBS patient caregivers.<sup>13</sup>
- Based on expert opinions, the assumed number of caregivers per patient:
  - <18 years: 1.5 caregivers, ≥18 years: 0.8 caregivers
- The utility for caregivers in the “No PS”, “Low PS”, “Mid PS”, and “High PS” patient states was accumulated over the analysis period

### Costs

#### Direct costs

- The medication cost of teduglutide (one vial per day, based on the list price), management fee for self-injection at home, Colonoscopy costs, IFALD treatment cost, AE treatment cost in 2024
- The cost for each PS state was calculated on the basis of results of a medical resource consumption survey (targeting physicians who treat patients with SBS)<sup>14</sup>, and according to the medical service fee point summary and drug price standard.<sup>15,16</sup>

#### Productivity Loss (Societal perspective)

- Productivity loss for pediatric patients with SBS was not considered, but caregiver productivity loss was included.
- The probability of caregivers being full-time employees, part-time employees, or full-time stay-at-home was estimated based on domestic statistics.<sup>17-20</sup>
- Caregiver productivity was calculated using data from a Work Productivity and Activity Impairment (WPAI) survey conducted in the UK<sup>13</sup>, considering the PS state of the care recipient.

### Sensitivity analysis

- For the societal perspective, the most comprehensive analysis, a **deterministic sensitivity analysis (DSA)** and a **probabilistic sensitivity analysis (PSA)** were performed.

### Scenario analysis

- Two different scenario analyses were conducted for the public healthcare and long-term care payer perspective.
  - The decrement method: A scenario in which the caregiver's "negative utility" is subtracted based on the patient's survival duration, (assuming that the caregiver's utility decreases as the patient's life is prolonged).
  - Delphi panel method: A scenario where caregiver's state-specific utility is derived from expert consensus, reflecting the burden associated with each patient condition.

## Results

### Base-Case Analysis

- Incorporating caregiver utility contributed an additional 5.12 QALYs to the incremental QALYs, reducing the ICER from 8,468,372 JPY to 5,628,147 JPY per QALY and thereby improving the cost-effectiveness of teduglutide (**Table 1**).

**Table 1.** Results of the base-case analysis

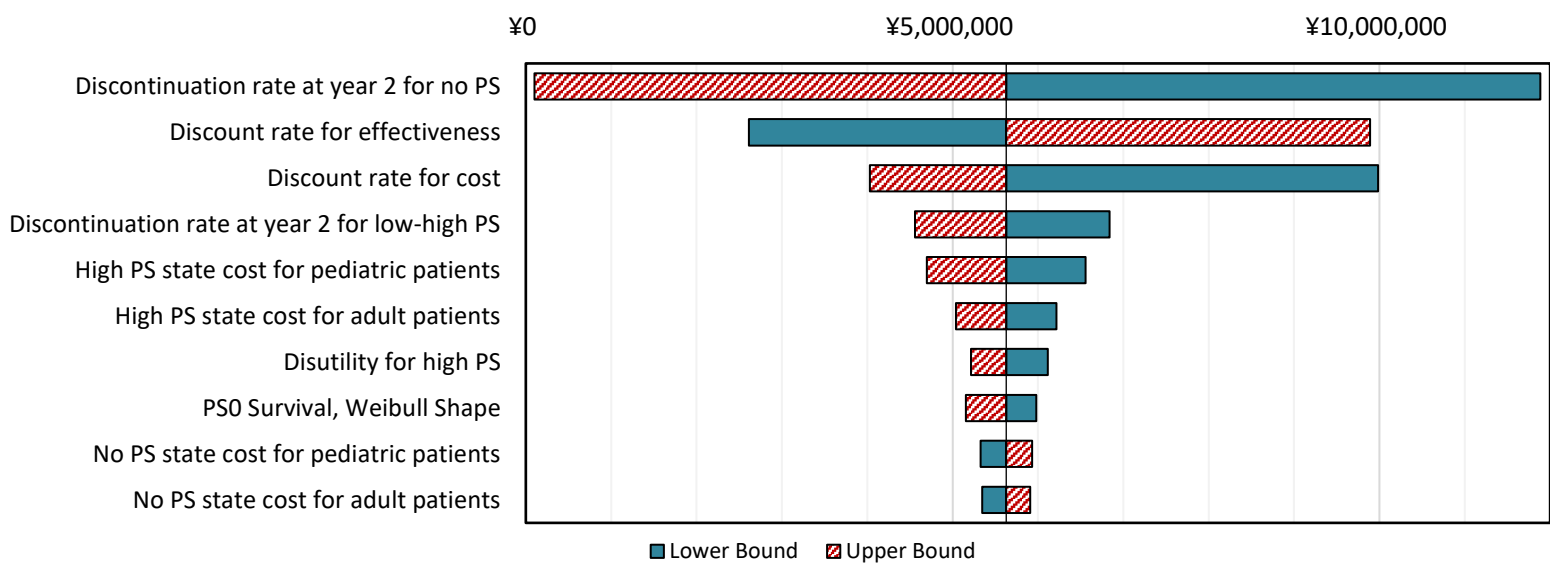
Strategy	Cost (JPY)	Incremental cost (JPY)	QALY	Incremental QALY	ICER (Cost/QALY)
Perspective 1: public healthcare payer					
Teduglutide	243 750 194	85 974 012	22.42	10.15	8 468 372
SOC	157 776 182	–	12.27	–	–
Perspective 2: public healthcare and long-term care payer					
Teduglutide	243 750 194	85 974 012	55.02	15.28	5 628 147
SOC	157 776 182	–	39.74	–	–
Perspective 3: societal					
Teduglutide	281 144 996	42 810 787	55.02	15.28	2 802 537
SOC	238 334 209	–	39.74	–	–

ICER incremental cost-effectiveness ratio, JPY Japanese yen, QALY quality-adjusted life-year, SOC standard of care

### Sensitivity Analysis

- The ICER was highly sensitive to the treatment discontinuation rate and discount rate, whereas the medical cost of PS had only a minor influence (**Fig 3**).

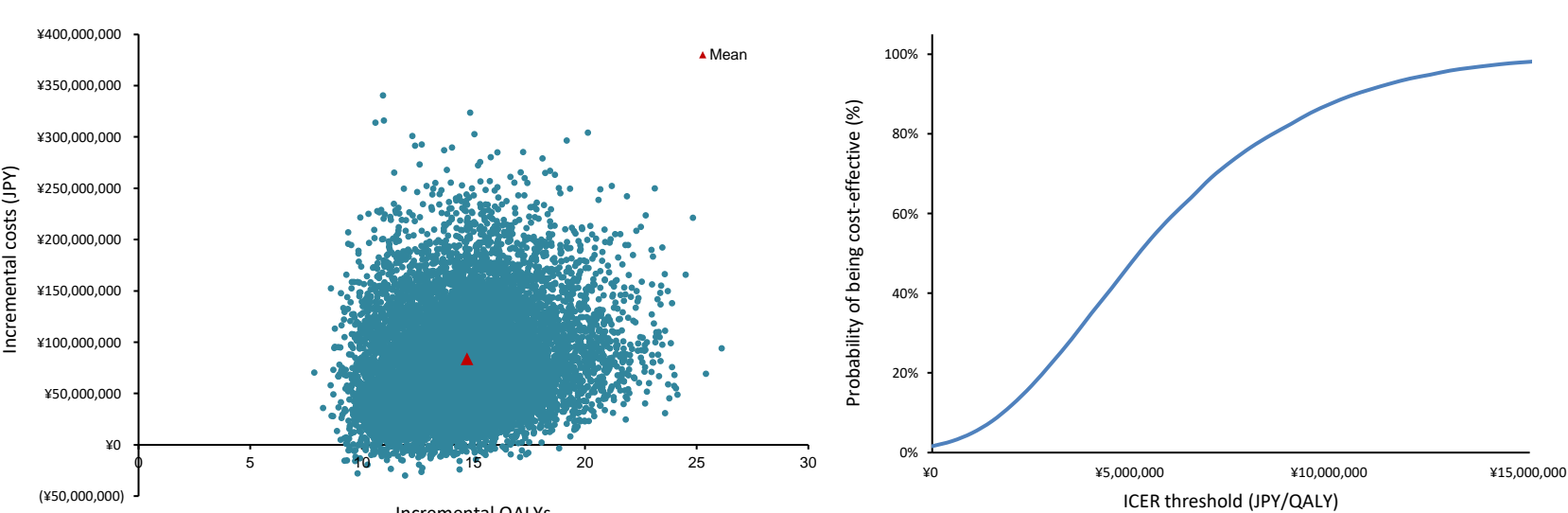
**Fig 3.** Results of deterministic sensitivity analysis (societal perspective)



\*The sensitivity analysis range was based on the 95% CI. #Values assume 1.5 caregivers for patients <18 years and 0.8 for those ≥18. The 2.5% and 97.5% points of the Dirichlet distribution set the lower and upper limits. CI confidence interval, OWI overall work impairment, TED teduglutide

- Based on the threshold for cost-effectiveness evaluation of teduglutide for pediatric patients with SBS in Japan (7.5 million JPY per QALY<sup>1</sup>), the probability that the cost-effectiveness of teduglutide is favorable from a societal perspective was 59.3%. (**Fig. 4**)

**Fig 4.** Results of deterministic sensitivity analysis (societal perspective)



Data show (A) scatter plots of incremental costs and incremental QALYs and (B) the cost-effectiveness acceptability curve.

### Scenario analysis

- In the decrement method, the cumulative decline in caregiver utility due to patient survival leads to a slightly higher ICER of 7,111,167 JPY per QALY (**Table 2**).
- In both scenarios, incorporating caregiver burden reduced the ICER from the base-case value of 8,468,372 JPY to 7,111,167 JPY per QALY in Scenario 1 and 4,676,567 JPY per QALY in Scenario 2 (**Table 2**).

**Table 2.** Results of the scenario analyses

Strategy	Cost (JPY)	Incremental cost (JPY)	QALY	Incremental QALY	ICER (Cost/QALY)
Perspective 2: public healthcare and long-term care payer					
Scenario 1. Decrement method					
Teduglutide	243 750 194	85 974 012	20.81	12.09	7 111 167
SOC	157 776 182	–	8.72	–	–
Scenario 2. Delphi panel					
Teduglutide	243 750 194	85 974 012	52.21	18.38	4 676 567
SOC	157 776 182	–	33.82	–	–

ICER incremental cost-effectiveness ratio, JPY Japanese yen, QALY quality-adjusted life-year, SOC standard of care

## Discussion

### Significance of Including Caregiver utility in the Analysis

- Diseases such as pediatric SBS, which require long-term home management, impose a significant burden on caregivers, greatly affecting their QoL and social activities.
- Measuring not only patient utility but also caregiver utility helps visualize the actual burden and enables a more comprehensive assessment of the value of treatment introduction.

### Interpretation of Results and Limitation

- The results vary depending on the method used to calculate caregiver utility (e.g., EQ-5D survey, Decrement method, Delphi panel method).
- However, irrespective of the method used, it is evident that caregiver burden cannot be overlooked.
- As a limitation, transition probabilities, utilities, and WPAI scores were derived from non-Japanese sources, which may not fully reflect the Japanese context. However, SBS pathology and causes are generally consistent across countries.

### Implications for Japan's Cost-Effectiveness Evaluation System

- Currently, decision-making is based solely on the public healthcare payer's perspective. However, in Japan, where a well-established long-term care exists, it is essential to consider healthcare and long-term care together to capture broader values of new drugs.
- In future evaluations of diseases with a high caregiver burden, analyses that incorporate the caregiver perspective should be presented and discussed.

## Conclusion

- This study aimed to evaluate and discuss the integration of caregiver burden into cost-effectiveness evaluations within Japan's healthcare system, using teduglutide and its clinically demonstrated benefits for PS dependence, as a case study.
- For the evaluation of pharmaceuticals for diseases such as pediatric SBS, which require long-term home management and impose a heavy burden on families, a comprehensive approach that considers both patient and caregiver perspectives is essential.
- In Japan, incorporating not only medical costs but also long-term care costs will be a critical challenge for future policy decisions regarding diseases with a significant caregiver burden.

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## Disclosure

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