22 February 2024
EMA/CHMP/33643/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Revestive

(Teduglutide)

Procedure no: EMEA/H/C/002345/P46/014

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 10 November 2023, the MAH submitted a completed paediatric study for Revestive, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study TAK-633-4003: Post Authorization Study to Monitor Efficacy, Effectiveness, and Safety of Teduglutide (Revestive®) in Adult and Pediatric Patients with Short Bowel Syndrome in Argentina, is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Powder and solvent for solution for injection.

2.3. Clinical aspects

2.3.1. Introduction

As described in the clinical study report, Revestive (Teduglutide) is a recombinant, degradation-resistant, longer-acting glucagon-like peptide 2 analog. Glucagon-like peptide 2 is a peptide secreted primarily in the distal intestine known to increase intestinal and portal blood flow, increasing absorptive capacity, and inhibiting gut motility and secretion (Parrish and DiBaise 2017).

The European Medicines Agency and the United States Food and Drug Administration approved teduglutide for treatment of adult patients with SBS in 2012 and pediatric patients (1 year of age and older) with SBS in 2016 and 2019, respectively. In June 2023, the European Commission approved the extension of pediatric indication to include patients aged 4 months (by corrected gestational age) and above with SBS.

According to the MAH, in Argentina, teduglutide was approved on 16 Oct 2019 for the treatment of adult and pediatric patients with SBS. A post-authorization study to monitor the safety, efficacy, and effectiveness of teduglutide in the context of routine clinical practice was requested by the Argentinean Health Authority (National Administration of Drugs, Food and Medical Devices [ANMAT]), and is part of the drug's risk management plan for Argentina.

With this submission the final results from the Study TAK 663-4003, a noninterventional real-world data study designed to investigate the safety and effectiveness of teduglutide in 2 observational cohorts (adult and pediatric populations) of subjects with SBS who are dependent on parenteral nutrition (PN)/intravenous (IV) support according to currently approved indications in routine clinical practice settings in Argentina is provided. The primary objective was to assess the safety profile of teduglutide in adult and pediatric subjects with SBS in the real-world setting of routine clinical practice in Argentina. The secondary objective was to study the effectiveness of teduglutide in the real-world setting of routine clinical practice in Argentina. This final report summarized the data analysis of all included subjects between 02 Nov 2020 (start of data collection) and 05 Jun 2023 (study completion). The data collected during this study showed reductions in PN/IV support with teduglutide in both adult and pediatric populations treated in a real-world setting.

The MAH submitted a final report(s) for:

- Study TAK663-4003, a noninterventional real-world data study designed to investigate the safety and effectiveness of teduglutide in 2 observational cohorts (adult and pediatric populations) of subjects with SBS who are dependent on parenteral nutrition (PN)/intravenous (IV) support according to currently approved indications in routine clinical practice settings in Argentina

Based on the study results, it is the MAH's position that there is no change to the benefit-risk profile of the product and no updates are necessary for the prescribing information or product label.

Assessor's comments

According to the MAH, in Argentina, teduglutide was approved on 16 Oct 2019 for the treatment of adult and paediatric patients with SBS. The age-limits for the paediatric age-group approved in Argentina are not specified in this report (the Argentine product information is not included), but it is assumed the age-limits correspond to the paediatric age-group included in the present PASS study TAK-633-4003, i.e. paediatric patients with Short Bowel Syndrome aged one year through 17 years. The data collection in the study started on 02 November 2020 and completed on 05 June 2023. It was in June 2023 the European Commission approved the extension of paediatric indication to include patients aged 4 months (by corrected gestational age) and above with SBS. Therefore, this EU age-group extension would not have affected the inclusion criteria on age in the present study in Argentina.

2.3.2. Clinical study

Clinical study number and title: Study TAK-663-4003, a noninterventional real-world data study designed to investigate the safety and effectiveness of teduglutide in 2 observational cohorts (adult and pediatric populations) of subjects with SBS who are dependent on parenteral nutrition (PN)/intravenous (IV) support according to currently approved indications in routine clinical practice settings in Argentina.

Methods

Objectives

The primary objective of this post-authorization study was to assess the safety profile of teduglutide in adult and pediatric patients with SBS in the real-world setting of common clinical practice in Argentina. The secondary objective was to study the effectiveness of teduglutide in the real-world setting of common clinical practice in Argentina.

Study Design

This is a non-interventional real-world data study that was designed to investigate the safety and effectiveness of teduglutide in two observational cohorts (adult and pediatric populations) of patients with SBS who were dependent on parenteral support according to currently approved indications in routine clinical practice settings in Argentina.

This study included patients who received treatment with teduglutide after marketing authorization in Argentina (de novo patients) and patients who had received treatment before marketing authorization (legacy patients) under the expanded access type of compassionate program use.

Patients were treated, followed, and monitored by their physicians according to local clinical practice and there were no specific visits planned as per the protocol. However, baseline and follow-up data were gathered from the medical records at the moment of inclusion in the study and approximately 12 week intervals up to 24 weeks from the start of treatment.

Data collection was both prospective and/or retrospective, depending on the time of data recording in the source documents and the inclusion of each patient in the study (de novo or legacy patients). Patients included in the study were followed for 24 weeks unless treatment discontinuation or lost to follow-up.

Setting

This study was carried out by 15 specialized physicians in their outpatient clinics in Argentina. All physicians prescribing teduglutide were informed of this study and invited to participate in this mandatory additional pharmacovigilance study.

Subjects and Study Size

Subjects: Eligibility criteria for each patient in this study were:

- Adult patients (≥18 years) or pediatric (≥1 year and <18 years) with a diagnosis of SBS who were dependent on parenteral support.
- Have received at least 1 dose of teduglutide according to the approved indications.
- Signed the mandatory consent that was agreed with the national regulatory authorities (ANMAT) as applicable.

Study size and dropouts: As local national authorities (ANMAT) requested this study, the study size was based on all consecutive patients who received (de novo patients) or had previously received (legacy patients) teduglutide in the usual practice setting.

Assessor's comments

It is understood that the initial protocol version 1.0 included only de novo patients with prospective data collection. The addition of legacy patients was a later amendment, see the following list of protocol versions and amendments.

8.0 AMENDMENTS AND UPDATES

Following is a summary of protocol versions and amendments

Version Number	Date	Section of study protocol	Amendment or update	Reason
1.0	29-Jul-2020	NAP	NAP	Initial version
2.0	25-Sep-2020	9.1; 9.2.2; 9.4; 9.5*	Amendment #1	Include retrospective legacy patients based on MOH request

*The following sections were amended in the synopsis and protocol: Section 9.1-Study design; 9.2.2-Inclusion criteria; 9.4-Data sources, and 9.5-Study size.

It is noted that the data collection started on 02 November 2020, when protocol version 2.0 with amendment #1 was in force (25 September 2020).

It means that data collection was both prospective and retrospective from the start of data collection.

The legacy patients with retrospective data collection included patients who had received previous treatment before marketing authorization (16 Oct 2019) under expanded access type of compassionate program use, see section 9.1 Study design in the Clinical Study Report.

The retrospective data collection in a legacy patient was done at 3 and 6 months from the date of the first dose. The entire 24 weeks treatment period thus evaluated may have been in the past.

An example:

Patient ID: [redacted]. Date of first dose: [redacted]. Date of 3 months data: [redacted]. Date of 6 months data: [redacted].

Source: Listing 1 (TAK-633-4003-List_1_Study Population and Final Disposition) in Module 5,

Although this patient, and other legacy patient might have continued treatment beyond the 6 months data collection time point, and data from such continued treatment would have been available in the records at the time of data collection, only the first 6 months data was collected retrospectively. The same time period was used for the prospective data collection in the de novo patients, i.e. 3 and 6 months, respectively, from the date of the first dose.

In the overall perspective, with only 24 weeks follow-up from the initial dose, this PASS study is considered a short-term safety observation study only, but this was the observation time required by the Argentine regulatory authority.

It is stated that *"the study size was based on all consecutive patients who received (de novo patients) or had previously received (legacy patients) teduglutide in the usual practice setting."*

For the prospective data collection in de novo patients, consecutive inclusion of all eligible patients would have minimized potential selection bias in that patient group.

For the retrospective data collection in legacy patients, including all patients who had previously received teduglutide in the usual practice setting would have minimized selection bias in that patient group.

Unfortunately, it is not described in practical details how a strict consecutive inclusion of de novo patients, and complete inclusion of all legacy patients was achieved. For example, since all legacy patients included appears to have had least 6 months data available, a more detailed description could have added reassurance that no legacy patients with shorter treatment durations had been excluded. However, this is a rare disease, so, the total number of legacy patients in the aforementioned compassionate use program is assumed to have been small. Furthermore, should a legacy patient have been excluded because of too short treatment duration, any adverse event leading to early discontinuation of treatment in such patient is expected to have been captured through routine pharmacovigilance regardless of this PASS. Therefore, this potential issue is not likely to change the overall conclusions of the present PASS study with respect to the benefit-risk assessment or the product information, and it will not be pursued further.

It is noted that 2 de novo patients, i.e. patient IDs [redacted] were late enrollers with first dose on [redacted], respectively, and 3 months data collection on [redacted], respectively. See Listing 1 Module 5. As the data collection was completed on [redacted], no 6 months data are available for these 2 patients. This is as expected with strict consecutive inclusion.

In conclusion, the study design and subject selection in the given setting is accepted.

Endpoints

<u>The primary endpoint variables were:</u>

- Incidence of adverse events of special interest (AESI) such as Biliary disorders and cholecystitis; Pancreatic disease; Cardiovascular adverse events associated with fluid overload; Intestinal obstruction; Stoma complications; Malignancy; Gastrointestinal neoplastic growth, including colorectal polyps and small bowel neoplasia; Adverse Events associated with increased absorption of concomitant oral medications; Anxiety, Injection site reactions and suspected immunogenic reactions (like hypersensitivity or other reactions); Embryo-fetal toxicity (assessed through follow up of all pregnancies).

- Incidence of all other adverse events (AEs; serious and non-serious).

The secondary endpoint variables were:

- The proportion of patients showing clinical response after 12 and 24 weeks of treatment. Clinical response was defined as a 20% or more reduction in weekly parenteral support volume. Change in weekly parenteral support volume after 12 and 24 weeks of treatment. Parenteral support volume was assessed at baseline (before treatment), 12 and 24 weeks.
- Change in the number of days per week requiring parenteral support after 12 and 24 weeks of treatment. The number of days requiring parenteral support was assessed at baseline (before treatment), 12 and 24 weeks.

Assessor's comments

The definition of the primary endpoint variables includes the phrase: *"incidence of adverse events of special interest (AESI) such as …"*

The phrase *"such as"* seems to indicate that the list is not complete, which is confusing.

However, as it is assumed that the AESI tables below reflect all observed AESIs, whether on the above list or not, this confusion has little impact and will not be pursued further.

Apart from that, the primary and secondary endpoints are accepted.

Data sources:

Data collection was both prospective and/or retrospective, depending on the time of data recording in the source documents and the inclusion of each patient in this study (de novo or legacy patients). The investigator collected historical data (demographic and clinical characteristics) from medical records and treatment-related data during visits that took place in routine practice for de novo patients. The investigators completed the electronic case report form (eCRF) based on the routine medical care data that was collected in the medical records. The patients were followed as per routine medical practice and there were no visits planned by the protocol. Baseline and follow-up data were gathered from the medical records at the nearest routine visit after every 12 weeks from the start of treatment up to the 24 weeks of follow-up. Adverse events, AESI, and special situation data were collected as they occurred in the de novo patients and documented in the medical records and entered in the appropriate eCRF pages for reporting according to internal sponsor and local regulatory requirements. For legacy patients, adverse events were collected retrospectively from the review of the medical records. Adverse events were collected from the first dose of medication moving forward.

Assessor's comments

The prospective and retrospective data collection method has been discussed above. This method is accepted. More details on the data sources are provided here. These data sources are accepted.

Statistical methods:

Descriptive statistics were used in the analysis. Analyses were performed separately for each of the patient cohorts (adult and pediatric). The 2 main populations for the previous interim analysis were the safety population and the per-protocol population. The safety population included all patients who had received at least 1 dose of teduglutide. The per-protocol population included all patients in the safety population who had at least 1 evaluation of efficacy and effectiveness after treatment. At the end of the study, both the safety and per-protocol populations were equivalent because all patients that received at least 1 dose of teduglutide had at least 1 effectiveness evaluation after treatment, and therefore are described in the results of this final report as "study population".

Assessor's comments

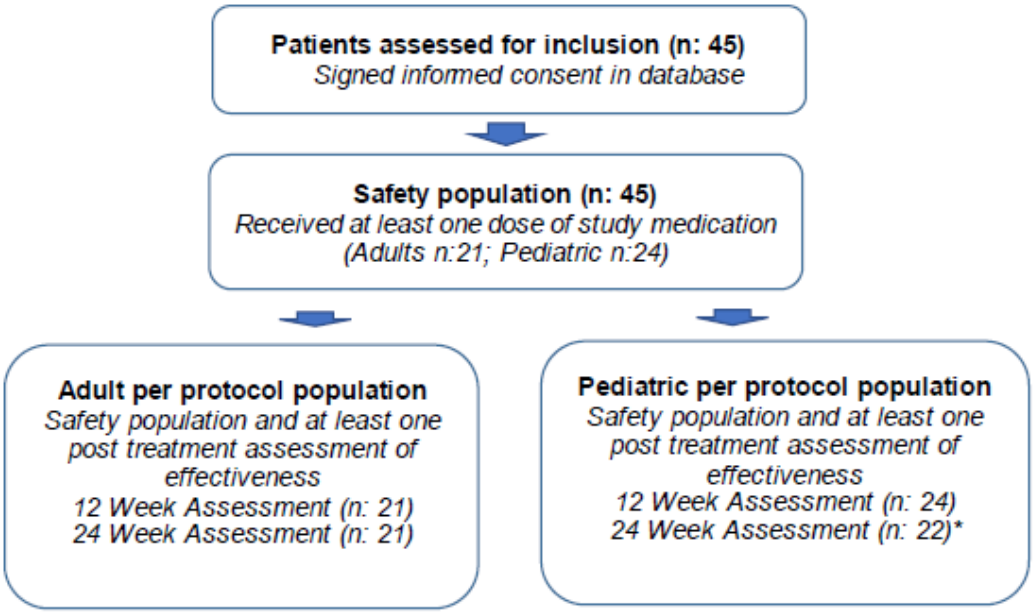
This is a non-interventional, uncontrolled, observational study. Using descriptive statistical methods only is acceptable.

Results

Participant flow

Between 02 Nov 2020 to 05 June 2023 a total of 45 patients were included in this study (21 adult patients, and 24 pediatric patients).

Figure 1. Patient Flow Chart and Disposition



*Ref.: *2 patients did not reach the 24-week assessment because of late enrollment*

Baseline data

The overall study population (n:45) included 21 adult patients with a mean age of 42.9 ±17.6 years and 24 pediatric patients (aged less than 18 years at first dose) with a mean age of 9.7 ±4.6 years. The most frequent cause of SBS was vascular disease in the adult population (42.9%) and volvulus or intestinal atresia in the pediatric population (58.4%). Table 1 summarizes the baseline characteristics of the included patients.

Table 1. Baseline Patient Characteristics

	Adults (n: 21)	Pediatric (n: 24)
Age (years)		
-Mean (SD)	42.9 (17.6)	9.7 (4.6)
-Range (Min-Max)	(19-75)	(3-17)
Sex, n (%)		
-Female	11 (52.4%)	5 (20.8%)
-Male	10 (47.6%)	19 (79.2%)
Etiology, n (%)		
-Vascular disease	9 (42.9%)	0 (0%)
-Volvulus	3 (14.3%)	7 (29.2%)
-Intestinal atresia	1 (4.8%)	7 (29.2%)
-Gastroschisis	0 (0%)	5 (20.8%)
-Injury/Traumatic	2 (9.5%)	1 (5.6%)
-Necrotizing enterocolitis	0 (0%)	1 (4.2%)
-Other or not available	6 (28.6%)	3 (12.5%)
Colon in continuity, n (%)		
-Yes	19 (90.5%)	22 (91.7%)
-No	2 (9.5%)	2 (8.3%)
Remanent colon, n (%)		
>0-25%	2 (9.5%)	2 (8.3%)
>25-50%	13 (61.9%)	6 (25%)
>50-75%	0 (0%)	6 (25%)
>75-100%	6 (28.6%)	9 (37.5%)
-Other or not available	0 (0%)	1 (4.2%)
Remanent small bowel length in cm		
-Mean (SD)	48.2 (40.6)	43 (39.8)
Ostomy, n (%)		
-Colostomy	0 (0%)	2 (8.3%)
-Jejunostomy	1 (4.8%)	1 (4.2%)
-Ileostomy	1 (4.8%)	0 (0%)

Source: TAK-633-4003-List_2_Demography and baseline

The treatment dose of teduglutide was 0.05mg/kg/day dose in 95.2% of adult patients and in all pediatric patients. The initial number of treatment days per week was 7 in all adult patients and 83.3% of pediatric patients. Four pediatric patients (16.7%) started treatment 6 days per week.

There was 1 reported pregnancy, from the adult cohort, that resulted in a full-term live birth

Assessor's comments

The baseline patient characteristics are as would be expected.

Results

The study outcomes were reported in each interim analysis based on protocol-predefined study populations (safety and per-protocol; see Figure 1) which at the end of the study coincided because all of the 45 included patients (21 adults and 24 pediatric patients) had at least 1 effectiveness assessment, and therefore are referred to as "study population" in this final report.

Patients included in the study were followed up to 24 weeks or until treatment discontinuation, whichever occurred first. Effectiveness and safety outcomes were analyzed separately in each of the primary patient cohorts (adult and pediatric population). See Figure 1 for patient disposition.

Efficacy

A total of 45 patients were included in the study population (21 adults and 24 pediatric patients).

The proportion of adult patients showing clinical response (defined as a 20% or more reduction in weekly parenteral support volume) after 12 and 24 weeks of treatment was 57.1% (95% CI: 34-78.1%), and 90.4% (95% CI: 69.6-98.8%), respectively.

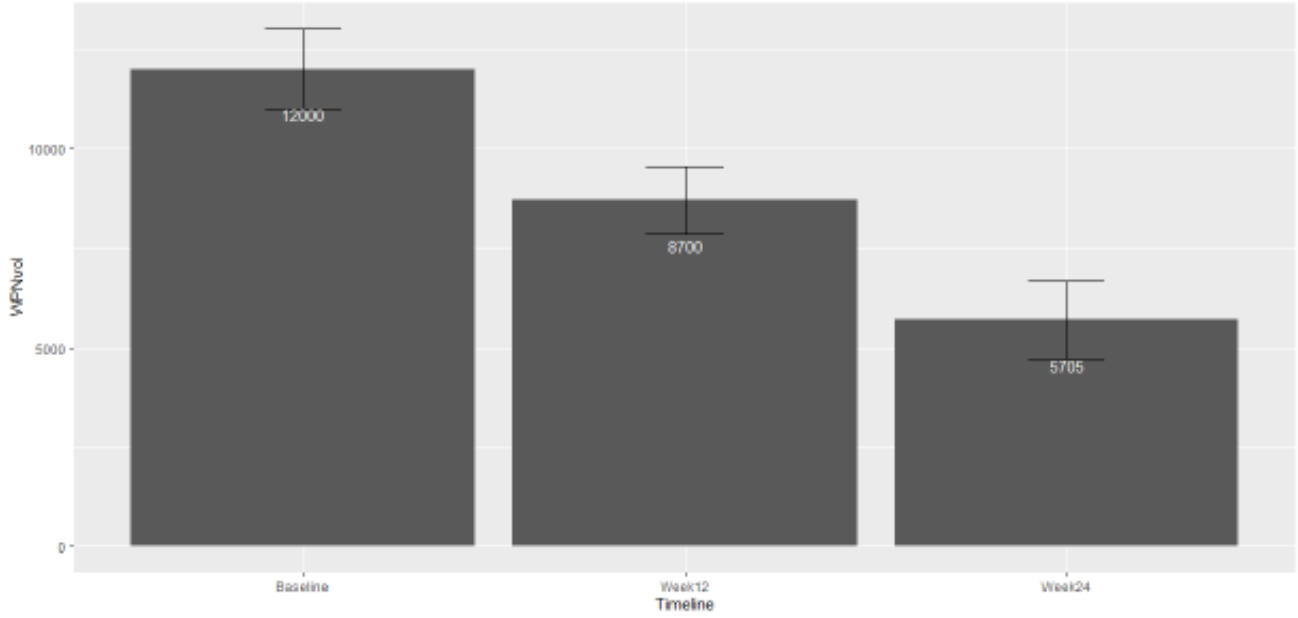
Adult patients showed significant reductions in weekly parenteral support volume after 12 (3.30 l/week; p= 0.00071) and 24 weeks (6.29 l/week; p=0.00014) of treatment compared with baseline, see Table 2 and Figure 2. Also, there were significant reductions in the number of days per week requiring parenteral support after 12 (p=0.00482) and 24 weeks (p=0.00019) of treatment compared with baseline.

Table 2. Effects on the reduction of parenteral support in the adult population

	Weekly PN Volume (ml)°	*p value°*	Number of Days Per Week with PN°	*p value°*
Baseline	12000 (4663)	*NA*	4 (4-7)	*NA*
Week 12	8700 (3884)	*0.00071*	4 (4-5)	*0.00482*
Week 24	5705 (4514)	*0.00014*	3 (0-4)	*0.00019*

°Reference: Weekly volume expressed as mean (SD); Number of days per week expressed as median (1st and 3rd quartile); P value calculated by non-parametric method for paired data versus baseline; NA: not applicable; Source: TAK-633-4003-List_4_Effectiveness

Figure 2. Reduction of weekly parenteral support in the adult population



Footnote: Error bars express SE of the mean. Source: TAK-633-4003-List_4_Effectiveness

The proportion of adult patients showing clinical response (defined as a 20% or more reduction in weekly parenteral support volume) after 12 and 24 weeks of treatment was 37.5% (95% CI: 18.7-59.4%), and 83.3% (95% CI: 62.6-95.2%), respectively.

Assessor's comments

The proportion of adult patients showing clinical response (defined as a 20% or more reduction in weekly parenteral support volume) after 12 and 24 weeks of treatment increases during the treatment period. This is reassuring, but the efficacy assessment is based on descriptive statistics in an uncontrolled observational study and should be interpreted with caution.

The error bars in Figure 2 express SE of mean. This is less informative than 95% confidence intervals. However, since efficacy assessment is not the primary objective of the PASS study, this issue will not be pursued further.

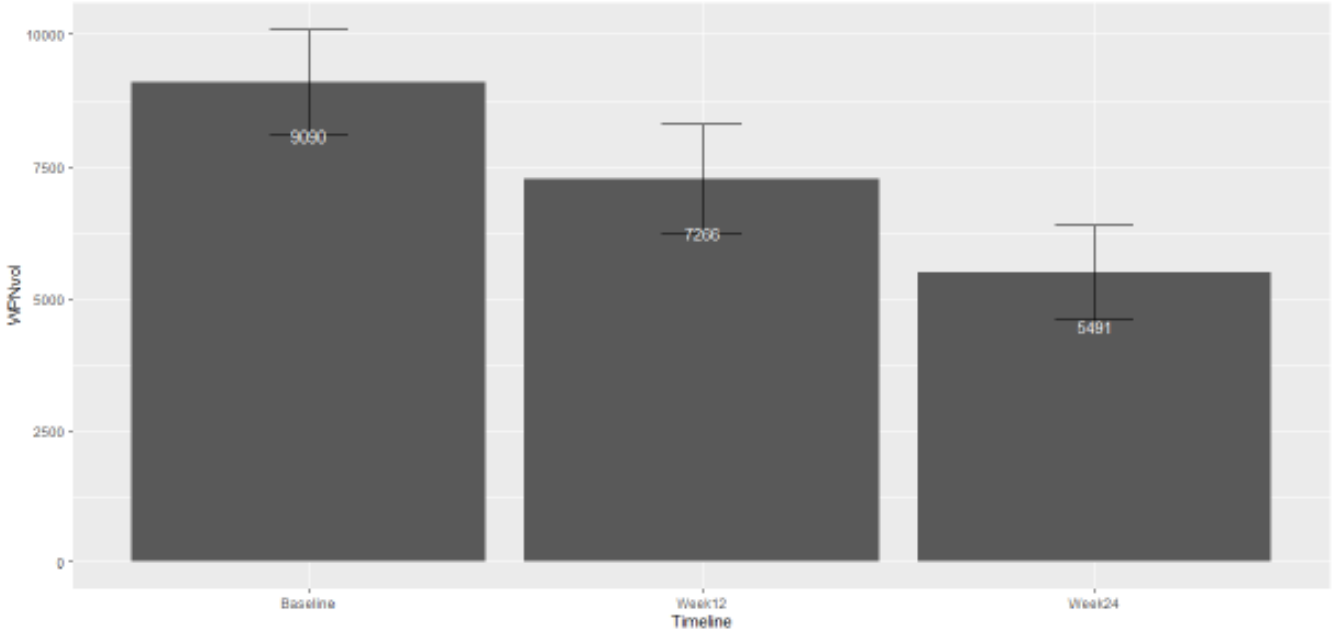
Pediatric patients showed significant reductions in weekly parenteral support volume after 12 (1.82 l/week; p=0.00044) and 24 weeks (3.59 l/week; p=0.00002) of treatment compared with baseline, see Table 3 and Figure 3. Also, there were significant reductions in the number of days per week requiring parenteral support after 12 (p=0.00143) and 24 weeks (p=0.00008) of treatment compared with baseline.

Table 3. Effects on the reduction of parenteral support in the pediatric population

	Weekly PN Volume (ml)°	*p value°*	Number of Days Per Week with PN°	*p value°*
Baseline	9090 (4954)	*NA*	6 (5-7)	*NA*
Week 12	7266 (5082)	*0.00044*	6 (4-6)	*0.00143*
Week 24	5491 (4433)	*0.00002*	5 (2-5)	*0.00008*

°Reference: Weekly volume expressed as mean (SD); Number of days per week expressed as median (1st and 3rd quartile); P value calculated by non-parametric method for paired data versus baseline; NA: not applicable; Source: TAK-633-4003-List_4_Effectiveness

Figure 3. Reduction of weekly parenteral support in the pediatric population



Footnote: Error bars express SE of the mean. Source: TAK-633-4003-List_4_Effectiveness

Assessor's comments

The proportion of paediatric patients showing clinical response (defined as a 20% or more reduction in weekly parenteral support volume) after 12 and 24 weeks of treatment increases during the treatment period. This is reassuring, but the efficacy assessment is based on descriptive statistics in an uncontrolled observational study and should be interpreted with caution.

The error bars in Figure 3 express SE of mean. This is less informative than 95% confidence intervals. However, since efficacy assessment is not the primary objective of the PASS study, this issue will not be pursued further.

Safety

Overall 19 patients (42.2%) in the study population experienced at least 1 TEAE. Five patients (23.8%) in the adult population and 14 patients (58.3%) in the pediatric population experienced at least 1 TEAE. A total of 41 (7 in adult, and 34 in the pediatric population) TEAE were reported.

The most commonly reported TEAEs were mild to moderate abdominal pain and abdominal distension (3 in the adult population, 14.2%; and 4 in the pediatric population, 16.6%), Table 4.

Table 4. Summary of Treatment-Emergent Adverse Events

	Adults (n: 21)		Pediatric (n: 24)	
	Mild-Moderate	Severe	Mild-Moderate	Severe
Infections and infestations				
-Catheter site infection	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-COVID-19	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Device-related infection	0 (0%)	0 (0%)	1 (4.1%)	1 (4.1%)
-Gastroenteritis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Herpangina	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Influenza	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Rhinovirus infection	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Overgrowth bacterial	1 (4.7%)	0 (0%)	0 (0%)	0 (0%)
-Upper respiratory tract infection	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)
-Vascular device infection	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Gastrointestinal disorders				
-Abdominal pain	1 (4.7%)	0 (0%)	4 (16.6%)	0 (0%)
-Abdominal distension	2 (9.5%)	0 (0%)	0 (0%)	0 (0%)
-Diarrhoea	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
General disorders and administration site conditions				
-Asthenia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Injection site pain	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Puncture site erythema	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Vascular device occlusion	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Metabolism and nutrition disorders				
-Decrease appetite	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Hypophosphatemia	1 (4.7%)	0 (0%)	0 (0%)	0 (0%)
-Hypoalbuminemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Lactic acidosis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Injury, poisoning, and procedural complications				
-Stoma complications	1 (4.7%)	0 (0%)	1 (4.1%)	1 (4.1%)
Hepatobiliary disorders				
-Cholestasis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Hyperbilirubinemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Skin and subcutaneous tissue disorders				
-Pruritus	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Rash	1 (4.7%)	0 (0%)	0 (0%)	0 (0%)
Blood and lymphatic system disorders				
-Anaemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)

Investigations				
-Liver function test abnormal	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Musculoskeletal and connective tissue disorders				
-Myalgia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Nervous system disorders				
-Seizure	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Renal and urinary disorders				
-Chromaturia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Vascular disorders				
-Poor venous access	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)

Source: TAK-633-4003-List_5_Safety_Unique Aes

Assessor's comments

The frequencies and types of treatment-emergent adverse events in adult and paediatric patients are as would be expected. However, the observation period is only 24 weeks from initial dosing. Long-term adverse events are not captured in this PASS. The results should, therefore, be interpreted with caution.

The treatment-emergent adverse events are presented by intensity categories only, i.e., mild-moderate and severe, but the total-category is missing. This is not appropriate. The intensity categories are entirely based in the individual investigator's judgement and are as such highly prone to bias. These intensity categories (not to be confused with the more objectively defined seriousness categories) are, therefore, of limited clinical and regulatory interest. When presenting all treatment-emergent adverse events, the total-categories of patients and events should always be presented as the primary observations. However, since the number of patients and events are small in the present study, the total-categories can easily be calculated from the displayed tables. These totals will not change the conclusion and this issue will not be pursued further.

Also, mild to moderate abdominal pain and abdominal distension were the most commonly reported related TEAEs (2 in the adult population, 9.5%; and 4 in the pediatric population, 16.6%), followed by mild to moderate metabolism and nutritional disorders (1 in the adult population, 4.7%; and 3 in the pediatric population, 12%), Table 5. None of the reported TEAEs or related TEAEs led to treatment discontinuation.

Table 5. Summary of Related Treatment-Emergent Adverse Events

	Adults (n: 21)		Pediatric (n: 24)	
	Mild-Moderate	Severe	Mild-Moderate	Severe
Gastrointestinal disorders				
-Abdominal pain	1 (4.7%)	0 (0%)	4 (16.6%)	0 (0%)
-Abdominal distension	1 (4.7%)	0 (0%)	0 (0%)	0 (0%)
Metabolism and nutrition disorders				
-Decrease appetite	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Hypophosphatemia	1 (4.7%)	0 (0%)	0 (0%)	0 (0%)
-Hypoalbuminemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Lactic acidosis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
General disorders and administration site conditions				
-Injection site pain	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Puncture site erythema	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Injury, poisoning, and procedural complications				
-Stoma complications	1 (4.7%)	0 (0%)	1 (4.1%)	0 (0%)
Hepatobiliary disorders				
-Hyperbilirubinemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Investigations				
-Liver function test abnormal	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Renal and urinary disorders				
-Chromaturia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Skin and subcutaneous tissue disorders				
-Pruritus	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)

Source: TAK-633-4003-List_5_Safety_Unique Aes

Assessor's comments

According to the ICH-E2A definitions, related treatment-emergent adverse events are also designated Adverse Drug Reaction (ADR). For these adverse events, a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

The types of related treatment-emergent adverse events are as would be expected, but the frequencies of in adult and paediatric patients are low.

It is understood that in the present study, the causal relationship between the drug and an adverse event is entirely based in the investigator's judgement. Therefore, some bias cannot be ruled out.

Furthermore, the observation period is only 24 weeks from initial dosing. Long-term adverse events are not captured in this PASS. The results should, therefore, be interpreted with caution.

As already mentioned above, the treatment-emergent adverse events are presented by intensity categories only, i.e., mild-moderate and severe, but the total-category is missing. This is not appropriate, but will not be pursued further, please see the previous Assessor's comments on this issue.

The most commonly reported AESI were injection site reactions (none in adults; and 2 in pediatrics 8.3%), and gastrointestinal stoma complications (1 adult, 4.7%; and 1 pediatric patient, 4.1%), representing overall 40% of patients with a stoma, followed by cholestasis (none in adults; and 1 in pediatrics 4.1%), see Table 6.

Table 6. Adverse Events of Special Interest

	Adults (n: 21)		Pediatric (n: 24)	
	Mild-Moderate	Severe	Mild-Moderate	Severe
General disorders and administration site conditions				
-Injection site pain	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Puncture site erythema	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Injury, poisoning, and procedural complications				
-Stoma complications	1 (4.7%)	0 (0%)	1 (4.1%)	0 (0%)
Hepatobiliary disorders				
-Cholestasis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)

Source: TAK-633-4003-List 5 Safety Unique Aes

Assessor's comments

The types of adverse events categorized as adverse events of special interest (AESI) are as would be expected. The frequencies are low.

It is noted that there are no incidences reported on the following AESIs: Malignancy; Gastrointestinal neoplastic growth, including colorectal polyps and small bowel neoplasia. This is reassuring.

However, as mentioned before, the observation period is only 24 weeks from initial dosing. Long-term adverse events are not captured in this PASS. The results should, therefore, be interpreted with caution.

As already mentioned above, the treatment-emergent adverse events are presented by intensity categories only, i.e., mild-moderate and severe, but the total-category is missing. This is not appropriate, but will not be pursued further, please see the previous Assessor's comments on this issue.

A total of 17 TEAEs were considered SAEs, and 6 TEAEs were considered serious and related to treatment with teduglutide (1 in adults, 4.7%; and 5 in pediatrics, 20.8%), Table 7, and Table 8. The most frequently reported serious and related TEAE was gastrointestinal stoma complications (1 adult, 4.7%; and 1 pediatric patient, 4.1%), Table 8. None of the SAEs led to treatment discontinuation. Also, there were no study deaths during the observational period.

Table 7. Serious Adverse Events

	Adults (n: 21)		Pediatric (n: 24)	
	Mild-Moderate	Severe	Mild-Moderate	Severe
Infections and infestations				
-Catheter site infection	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Device-related infection	0 (0%)	0 (0%)	1 (4.1%)	1 (4.1%)
-Influenza	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Rhinovirus infection	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Vascular device infection	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
General disorders and administration site conditions				
-Vascular device occlusion	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Metabolism and nutrition disorders				
-Hypoalbuminemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Lactic acidosis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Injury, poisoning, and procedural complications				
-Stoma complications	1 (4.7%)	0 (0%)	1 (4.1%)	1 (4.1%)
Hepatobiliary disorders				
-Cholestasis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Hyperbilirubinemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Blood and lymphatic system disorders				
-Anaemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Investigations				
-Liver function test abnormal	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Nervous system disorders				
-Seizure	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)

Source: TAK-633-4003-List_5_Safety_Unique Aes

Table 8. Serious and Related Adverse Events

	Adults (n: 21)		Pediatric (n: 24)	
	Mild-Moderate	Severe	Mild-Moderate	Severe
Metabolism and nutrition disorders				
-Hypoalbuminemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
-Lactic acidosis	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Injury, poisoning, and procedural complications				
-Stoma complications	1 (4.7%)	0 (0%)	1 (4.1%)	0 (0%)
Hepatobiliary disorders				
-Hyperbilirubinemia	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)
Investigations				
-Liver function test abnormal	0 (0%)	0 (0%)	1 (4.1%)	0 (0%)

Source: TAK-633-4003-List_5_Safety_Unique Aes

Assessor's comments

The types of serious adverse events and related serious adverse events are as would be expected. The frequencies are low, in particular for related serious adverse events.

It is noted that no fatal serious adverse events are reported.

As mentioned before, it is understood that in the present study, the causal relationship between the drug and an adverse event is entirely based in the investigator's judgement. Therefore, some bias of the causality cannot be ruled out.

Furthermore, the observation period is only 24 weeks from initial dosing. Long-term adverse events are not captured in this PASS. The results should, therefore, be interpreted with caution.

As already mentioned above, the treatment-emergent adverse events are presented by intensity categories only, i.e., mild-moderate and severe, but the total-category is missing. This is not appropriate, but will not be pursued further, please see the previous Assessor's comments on this issue.

2.3.3. Discussion on clinical aspects

The study is a post-authorization study to monitor the safety, efficacy, and effectiveness of teduglutide in the context of routine clinical practice was requested by the Argentinean Health Authority (National Administration of Drugs, Food and Medical Devices [ANMAT]), and is part of the drug's risk management plan for Argentina.

Methods

The study included adult patients (≥18 years) or paediatric (≥1 year and <18 years) with a diagnosis of SBS who were dependent on parenteral support. It is understood this the age-groups are defined according to the approved indications in adults and paediatric patients in Argentine.

The study design is non-interventional (i.e., teduglutide is administered as part of clinical practice), uncontrolled and observational.

The study included both de novo patients with prospective data collection and legacy patients with retrospective data collection.

The legacy patients with retrospective data collection included patients who had received previous treatment before marketing authorization (16 Oct 2019) under expanded access type of compassionate program use, see section 9.1 Study design in the Clinical Study Report.

The retrospective data collection in a legacy patient was done at 3 and 6 months from the date of the first dose. The entire 24 weeks treatment period thus evaluated may have been in the past.

An example:

Patient ID: [redacted]. Date of first dose: [redacted]. Date of 3 months data: [redacted]. Date of 6 months data: [redacted].

Source: Listing 1 (TAK-633-4003-List_1_Study Population and Final Disposition) in Module 5,

Although this patient, and other legacy patient might have continued treatment beyond the 6 months data collection time point, and data from such continued treatment would have been available in the records at the time of data collection, only the first 6 months data was collected retrospectively. The same time period was used for the prospective data collection in the de novo patients, i.e. 3 and 6 months, respectively, from the date of the first dose.

In the overall perspective, with only 24 weeks follow-up from the initial dose, this PASS study is considered a short-term safety observation study only, but this was the observation time required by the Argentine regulatory authority.

It is stated that "the study size was based on all consecutive patients who received (de novo patients) or had previously received (legacy patients) teduglutide in the usual practice setting."

For the prospective data collection in de novo patients, consecutive inclusion of all eligible patients would have minimized potential selection bias in that patient group.

For the retrospective data collection in legacy patients, including all patients who had previously received teduglutide in the usual practice setting would have minimized selection bias in that patient group.

Unfortunately, it is not described in practical details how a strict consecutive inclusion of de novo patients, and complete inclusion of all legacy patients was achieved. For example, since all legacy patients included appears to have had least 6 months data available, a more detailed description could have added reassurance that no legacy patients with shorter treatment durations had been excluded. However, this is a rare disease, so, the total number of legacy patients in the aforementioned compassionate use program is assumed to have been small. Furthermore, should a legacy patient have been excluded because of too short treatment duration, any adverse event leading to early discontinuation of treatment in such patient is expected to have been captured through routine pharmacovigilance regardless of this PASS. Therefore, this potential issue is not likely to change the overall conclusions of the present PASS study with respect to the benefit-risk assessment or the product information, and it will not be pursued further.

It is noted that 2 de novo patients, i.e. patient IDs [redacted] were late enrollers with first dose on [redacted], respectively, and 3 months data collection on [redacted], respectively. See Listing 1 Module 5. As the data collection was completed on [redacted], no 6 months data are available for these 2 patients. This is as expected with strict consecutive inclusion.

Overall, the study design and subject selection in the given setting is accepted.

The primary endpoint variables included incidence of adverse events of special interest (AESI), incidence of all other adverse events (AEs; serious and non-serious).

The secondary endpoint variables included the proportion of patients showing clinical response (20% reduction of parenteral support volume) after 12 and 24 weeks of treatment. Change in weekly parenteral support volume after 12 and 24 weeks of treatment. Change in the number of days per week requiring parenteral support after 12 and 24 weeks of treatment.

These endpoint variables are accepted.

The data sources included existing medical records only for legacy patients and both existing medical records and medical treatment-related data during visits that took place in routine practice for de novo patients. The data was transferred to eCRF pages. These data sources are accepted.

Only descriptive statistical methods were used. This is acceptable as this is a non-interventional, uncontrolled, observational study.

Results

The overall study population (n:45) included 21 adult patients with a mean age of 42.9 ±17.6 years and 24 pediatric patients (aged less than 18 years at first dose) with a mean age of 9.7 ±4.6 years. The most frequent cause of SBS was vascular disease in the adult population (42.9%) and volvulus or intestinal atresia in the pediatric population (58.4%).

The baseline patient characteristics are as would be expected.

Efficacy

The proportion of adult and paediatric patients showing clinical response (defined as a 20% or more reduction in weekly parenteral support volume) after 12 and 24 weeks of treatment increases during the treatment period. This is reassuring, but the efficacy assessment is based on descriptive statistics in an uncontrolled observational study and should, therefore, be interpreted with caution.

The error bars in the presented figures on efficacy express SE of mean. This is less informative than 95% confidence intervals. However, since efficacy assessment is not the primary objective of the PASS study, this issue will not be pursued further.

Safety

The frequencies and types of treatment-emergent adverse events in adult and paediatric patients are as would be expected. However, the observation period is only 24 weeks from initial dosing. Long-term adverse events are not captured in this PASS. The results should, therefore, be interpreted with caution.

The treatment-emergent adverse events are presented by intensity categories only, i.e., mild-moderate and severe, but the total-category is missing. This is not appropriate. The intensity categories are entirely based in the individual investigator's judgement and are as such highly prone to bias. These intensity categories (not to be confused with the more objectively defined seriousness categories) are, therefore, of limited clinical and regulatory interest. When presenting all treatment-emergent adverse events, the total-categories of patients and events should always be presented as the primary observations. However, since the number of patients and events are small in the present study, the total-categories can easily be calculated from the displayed tables. These totals will not change the conclusion and this issue will not be pursued further.

The types of related treatment-emergent adverse events are as would be expected, but the frequencies in adult and paediatric patients are low.

It is understood that in the present study, the causal relationship between the drug and an adverse event is entirely based in the investigator's judgement. Therefore, some bias cannot be ruled out.

The types of adverse events categorized as adverse events of special interest (AESI) are as would be expected. The frequencies are low.

It is noted that there are no incidences reported on the following AESIs: Malignancy; Gastrointestinal neoplastic growth, including colorectal polyps and small bowel neoplasia. This is reassuring.

The types of serious adverse events and related serious adverse events are as would be expected. The frequencies are low, in particular for related serious adverse events.

It is noted that no fatal serious adverse events are reported.

As mentioned before, it is understood that in the present study, the causal relationship between the drug and an adverse event is entirely based in the investigator's judgement. Therefore, some bias of the causality cannot be ruled out.

Furthermore, as mentioned before, the observation period is only 24 weeks from initial dosing. The results from all the sub-categories of adverse events reported, i.e., related treatment-emergent adverse events, adverse events of special interest, serious adverse events and related serious adverse events should, therefore, be interpreted with caution.

3. Rapporteur's overall conclusion and recommendation

This PASS study was conducted as part of the drug's risk management plan for Argentina. The study design and methods are overall accepted. Minor points of concerns regarding the retrospective data collection in legacy patients and the data presentation have been mentioned in the discussion, but since no impact on the conclusion and recommendations is foreseen, these points are not pursued further. In the overall perspective, with only 24 weeks follow-up from the initial dose, this PASS study is considered a short-term safety observation study only, but this was the observation time required by the Argentine regulatory authority. However, the short-term observation means that both the primary safety data and the secondary efficacy data should be interpreted with caution. In addition, the causal relationship between the drug and an adverse event is entirely based in the investigator's judgement. Therefore, some bias cannot be ruled out. With these limitations in mind, the safety data did not show any unexpected results. In particular, there was no fatal serious adverse events, and no incidences reported on the following AESIs: Malignancy; Gastrointestinal neoplastic growth, including colorectal polyps and small bowel neoplasia. This is reassuring. The secondary efficacy results were as would be expected, but these results are uncontrolled and observational only and should, therefore, be interpreted with caution.

In conclusion, it is agreed with the MAH's position that based on the study results, there is no change to the benefit-risk profile of the product and no updates are necessary for the prescribing information or product label.

☒ **Fulfilled:**

No regulatory action required