# Registry Protocol TED-R13-002

# A Prospective, Multi-center Registry for Patients with Short Bowel Syndrome



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**Final v2.0 (EU)**

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## 2 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| CI | Confidence interval |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ER | Emergency room |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| FDA | US Food and Drug Administration |
| GI | Gastrointestinal |
| IBD | Inflammatory bowel disease |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IV | Intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDI | National Death Index |
| NPS | NPS Pharmaceutical, Inc. |
| PN | Parenteral nutrition |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System software |
| SBS | Short bowel syndrome |
| SEER | Surveillance Epidemiology and End Results |
| SMR | Standardized Morbidity Ratio |

# 3 RESPONSIBLE PARTIES

The principle investigator, coordinating investigators, and study centers with their contact information will be included in a stand-alone document in Annex 1 as these responsible parties are identified.

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# 4 ABSTRACT

| | |
|---|---|
| **Title** | A prospective, multi-center registry for patients with Short Bowel Syndrome |
| **Registry Number** | TED-R13-002 |
| **Date** | 11 March 2014 |
| **Main Author** | PPD , DO, MPH, PhD<br>NPS Pharmaceuticals, Inc. |
| **Planned Duration**<br>**Start of Data Collection (FPI):**<br>**Database Hard Lock:**<br>**Final Study Report:** | 5 years of enrollment with at least 10 years of follow-up per patient<br><br>Q1/2014<br>Q4/2029<br>Q2/2031 |
| **Research Question and Objectives** | • Primary: To evaluate the long-term safety profile for patients with short bowel syndrome (SBS) who are treated with teduglutide in a routine clinical setting. The primary safety outcome is the occurrence of colorectal cancer in SBS patients with a remnant colon taking teduglutide.<br>• Secondary: To evaluate long-term clinical outcomes in patients with SBS |
| **Study Design** | This is a single-group, prospective, observational, multi-center (ie, world-wide) registry designed to collect data on long-term safety and clinical outcomes in SBS patients.<br><br>This registry permits interested SBS patients and SBS-treating health care providers to participate. Patients exposed and not exposed to teduglutide will be recruited. A select set of data will be collected at baseline, and these data will then be recollected, as available, on an ongoing basis and solicited at least twice annually.<br><br>The primary outcome will be diagnosis of colorectal cancer in SBS patients, with any remnant colon, who were treated with teduglutide. The observed incidence of colorectal cancer in these patients will be compared with the incidence of colorectal cancer in the US population obtained from the most recent SEER (Surveillance Epidemiology and End Results) incidence rates at the time of analysis. For other regions of the world comparable local cancer data sources, when available, will be used for comparison to colorectal cancer rates seen in SBS patients with remnant colons who are treated with teduglutide in other countries.<br><br>In patients treated and not treated with teduglutide, this registry will also evaluate other clinically meaningful outcomes. |
| **Treatment Regimens** | Treatment regimens will be determined for each individual SBS patient by the physician according to usual clinical practice. |
| **Rationale and Background** | SBS is an orphan condition caused by a reduction in intestinal surface area, leading to inadequate absorption of fluid and nutrients. SBS is usually a consequence of major surgical resection of the small intestine; rarely does it occur secondarily to congenital intestinal abnormality or underlying intestinal disease. SBS patients are extremely heterogeneous in their clinical presentation, treatment needs, and natural progression of disease. Therefore, further insights into associated long-term comorbidities are warranted.<br><br>Current management strategies for SBS entail a combination of specialized diets, anti-diarrheal agents, anti-secretory agents, and parenteral nutrition (PN)/ intravenous (IV) fluids. Most SBS patients require initial PN/IV support, and many ultimately require long-term PN/IV therapy. |

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| **Rationale and Background (continued)** | In addition, other concomitant therapies are utilized in SBS patients to treat their underlying etiology for intestinal disease (eg, immunosuppressive and/or biological therapies for Crohn's disease).<br>The first long-term, targeted treatment currently approved in the US and EU for adult SBS patients is teduglutide, an analog of naturally occurring human glucagon-like peptide-2. Although the teduglutide development program provided the largest clinical dataset for SBS to date, a total of only 173 subjects were included in the marketing application from the Phase 3 pivotal trials, with 148 subjects receiving teduglutide for 24 weeks, 111 subjects treated for at least 12 months, 88 subjects treated for 24 months, and 14 treated subjects in the 36 month follow-up study. Further information is needed to characterize the safety profile and clinical outcomes of the SBS patient population, with a variety of underlying etiologies and associated comorbidities, who may or may not be treated with teduglutide in the post-marketing approval setting.<br>Based on mechanism of action and results of nonclinical studies, teduglutide has the potential to cause hyperplastic changes, including neoplasia, in the gastrointestinal (GI) tract. Phase 3 studies with teduglutide reported the occurrence of colorectal polyps, intestinal obstruction / stenosis, cholecystitis, cholangitis, cholelithiasis, and pancreatitis.<br>In addition, the increased intestinal absorption of fluids promoted by teduglutide could lead to fluid overload, resulting in heart failure, in patients with cardiovascular disease.<br>Therefore, this registry will collect data on clinical outcomes and potential risks of teduglutide in the real-world setting. |
| **Duration of Study** | This is a long-term registry planned for 5 years of enrollment with at least 10 years of follow-up per patient. |
| **Patient Population and Key Selection Criteria** | • Male and female patients, of any age, with a diagnosis of SBS.<br>• Signed informed consent and medical records release by the patient or a legally acceptable representative. |
| **Outcome Variables and Assessments** | |
| **Primary Outcome Variable:** | **Safety:**<br>• Occurrence of colorectal cancer |
| **Secondary Outcome Variables:** | **Other Safety Outcomes such as:**<br>• Occurrence of other malignancy<br>• Occurrence of benign neoplasia of the gastrointestinal tract, hepatobiliary system, and pancreas<br>• Occurrence of colorectal polyps<br>• Occurrence of intestinal obstruction<br>• Occurrence of pancreatic and biliary disease<br>• Occurrence of heart failure and other manifestations of volume overload<br>• Occurrence of allergic/hypersensitivity reaction to teduglutide<br>**Effectiveness Outcomes such as:**<br>• Actual volume change in parenteral support<br>• Percentage volume change in parenteral support |

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| **Study Procedures** | Patients will be enrolled at previous clinical trial study sites and, as feasible, also will be recruited through treatment clinics and through centers that have access to claims and/or electronic medical records to identify additional SBS patients. Patients who participated in previous teduglutide trials are also eligible for entry into this registry. Baseline for these patients will be their baseline in the clinical trial at the start of teduglutide treatment. Patients enrolled will have a select set of data collected at baseline, and these data will then be recollected on an ongoing basis and solicited twice annually, if not spontaneously reported. Data collected during any pertinent healthcare visits will be solicited. All data will come from the prescriber/health care professional medical record.<br><br>Comprehensive demographic and baseline data are mandatory, if available, for enrollment in the registry, but any additional investigations that are outside normal clinical practice at the registry sites will not be required for participation in the registry. No predetermined follow-up requirements will apply; however, investigators will be prompted to update patient data in the registry based upon patients' visits to the physician. Investigators will be reminded to update the registry at least twice annually, although it is expected that patients will visit their physician more frequently for clinical follow-up. Female patients are requested to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy. |
| **Registry Outcome Committee** | A review committee will be established to review collected data at least on an annual basis. This committee will be subject matter experts comprising GI oncologists, SBS experts, a statistician, and an epidemiologist. |
| **Data Collection Procedures** | Data will be collected using electronic data capture. All data collected will be stored and evaluated in accordance with Good Pharmacoepidemiology Practices (GPP) and applicable guidance for electronic records. |
| **Baseline Data Collected at Study Enrollment** | Following the signing of the Informed Consent Form data will be collected, if available, such as:<br>• Demographics<br>• SBS background<br>• Significant medical history<br>• Significant past imaging studies of interest<br>• Significant past laboratory tests<br>• Treatments for SBS within the past 12 months<br>• Other Concomitant Medications within the past 12 months<br>• Pregnancy history |
| **Prospective Data Collected After Study Enrollment** | Since last visit or last data entry into the registry, data will be collected, if available, such as:<br>• Significant new medical history and clinical outcomes<br>• Results of imaging studies<br>• Significant laboratory tests (in the setting of other clinical outcomes including adverse events)<br>• Current treatments for SBS<br>• Other Concomitant Medications<br>• Pregnancy, outcome, neonatal characteristics |
| **Statistical Methods** | Detailed statistical analysis methods will be conducted as described in the statistical analysis plan (SAP) for this study. Data will be summarized with tabulated descriptive statistics: n, minimum, maximum, mean, median, standard deviation, and range for continuous variables; and counts and percentages for categorical variables. In addition, graphical data displays will be used to summarize selected data. Person-years of follow-up and incidence rates of prospective events will be calculated. |

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| **Sample Size** | This registry is to enroll as many SBS patients as possible. The primary safety analysis will focus on the SBS patients, with any remnant colon, who were treated with teduglutide. The projected numbers of patients to receive teduglutide in the US/EU for the 5 years of registry enrollment is used to determine sample size and power calculations. The goal is to enroll at least 655 SBS patients of whom 393 will have any remnant colon treated with teduglutide who are at risk for colorectal cancer. Assuming an annual attrition rate of 15% this study will provide 80% power to rule out an increased risk of colorectal cancer of 3.1 associated with teduglutide.<br><br>In addition, a target enrollment of at least 655 SBS adult patients 18 years and older dependent on parental support (patients for whom teduglutide is indicated) but not treated with teduglutide will be attempted for an internal comparison group. |
| **Analysis Populations** | All analyses will be based upon the enrolled population. The teduglutide-treated population will be defined as patients who received at least one dose of teduglutide. |
| **Outcome Data** | The primary safety analysis will focus on SBS patients, with any remnant colon, who were treated with teduglutide.<br>• Incidence rates of colorectal cancer in these patients will be calculated by dividing the number of incident colorectal cancer cases by the total number of person-years observed since beginning treatment with teduglutide. Person-years of observation will continue to accrue for teduglutide patients who discontinue teduglutide use for the duration of follow-up. Other calculations of colorectal cancer incidence rates using different groupings of person-years (eg, person-years restricted to teduglutide exposure, categorizing person-years to take account of treatment cross-over such as entering the registry not on teduglutide but later starting teduglutide) will be discussed in the SAP.<br>• The risk of colorectal cancer as a function of cumulative exposure to teduglutide will also be estimated. Kaplan-Meier curves will be used to graphically depict the occurrence of colorectal cancer as a function of time since the beginning of teduglutide treatment.<br>• Incidence rates and Kaplan-Meier curves will also be stratified by age at enrollment and gender and by underlying comorbid conditions that may impact cancer incidence, including the presence of inflammatory bowel disease.<br>• Incidence rates will be similarly calculated for the secondary outcomes, such as other malignancies, benign neoplasia of the gastrointestinal tract, hepatobiliary system and pancreas, colorectal polyps, bowel obstruction, pancreatic and biliary disease, heart failure and other manifestations of volume overload, and allergic/hypersensitivity reactions to teduglutide.<br>• The incidence of colorectal cancer in the teduglutide patients, with any remnant colon, will be compared and tested against the US population using standardized morbidity ratios (SMRs), defined as the ratio of the observed number of cases of colorectal cancer to the expected number of cases of colorectal cancer.<br>• The expected number of cases of colorectal cancer will be calculated by applying the latest available US SEER colorectal cancer incidence rates to the age, gender, and length of follow-up distributions of all teduglutide-treated patients with remnant colons. In addition, a sub-analysis will be done where only US patients will be compared to SEER data. For SBS patients from other regions of the world, comparable local cancer data sources, when available, will be used for comparison of colorectal cancer rates.<br>• The SMRs will be tested for significance by calculating exact one-sided 95% confidence intervals, assuming that the distribution of cases follow a Poisson distribution. |

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| **Outcome Data (cont.)** | • Descriptive statistics for teduglutide-treated and teduglutide non-treated patients will be made on safety and effectiveness outcomes. For non-confirmatory analyses, comparisons between the treated and non-treated groups on safety and effectiveness outcomes will be made. | |
| **Milestones** | Start of data collection (FPI) | Q1/2014 |
| | Planned end of recruitment | Q4/2018 |
| | End of data collection | Q4/2028 |
| | Database hard lock | Q4/2029 |
| | Planned completion of final study report | Q2/2031 |
| | Interim study reports | Annually beginning Q4/2014 |

## 5 AMENDMENTS AND UPDATES

None

## 6 STUDY MILESTONES

Study milestones are outlined in Table 1 below along with their estimated time of completion.

**Table 1 Study Milestones and Timelines**

| Milestone | Estimated Completion Date |
|---|---|
| Start of data collection (FPI) | Q1/2014 |
| Planned end of recruitment | Q4/2018 |
| End of data collection | Q4/2028 |
| Database hard lock | Q4/2029 |
| Planned completion of final study report | Q2/2031 |
| Interim study reports | Annually beginning Q4/2014 |



## 7 BACKGROUND AND RATIONALE

### 7.1 Background

Short bowel syndrome (SBS) results from surgical resection, congenital defect, or disease-associated loss of intestinal absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet (O'Keefe et al, 2006). Patients with SBS are highly prone to malnutrition, diarrhea, and dehydration due to their reduced intestinal capacity (Dudrick et al, 1991; Nightingale, 1999; Rombeau and Rolandelli, 1987; Shanbhogue and Molenaar, 1994; Vanderhoof and Langnas, 1997; Wilmore et al, 1997). Additional potential consequences of SBS include gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, diarrhea, small bowel bacterial overgrowth, and weight loss (Hollwarth, 1999; Nightingale and Woodward, 2006; O'Keefe et al, 2006). Suboptimal treatment of SBS can ultimately lead to severe malnutrition, impaired cardiac, hepatic, and renal functions, fluid retention, intestinal mucosa atrophy, loss of intracellular minerals (zinc, magnesium, phosphorus), osteoporosis, diminished cell-mediated immune function, increased risk of infections, and eventually death. The severity of the condition is illustrated by the shortened life-span in patients with moderate to severe disease (Buchman et al, 2003). In a 12-year study in SBS patients (Messing et al, 1999), survival probabilities were 94%

(confidence interval [CI] = 90 to 98) at 1 year, 75% (CI = 67 to 83) at 5 years, and 60% (CI = 49 to 71) at 10 years of follow-up.

The extent of malnutrition suffered by the SBS patient is largely dependent upon the extent of residual intestine and colon, presence of an ileal segment, and the degree of adaptation following resection. A large proportion of SBS patients require the use of parenteral nutrition (PN) to supplement and stabilize their nutritional needs. Patients retaining their colon may absorb enough fluid but insufficient nutrition through the oral route and require PN/intravenous (IV) support. Patients without a colon and with only a short functional jejunum may require further supplementation with intravenous fluids and electrolytes (O'Keefe et al, 2006).

Although PN/IV support is vital for stabilizing the nutrition and hydration requirements of SBS patients, its use is associated with high cost and numerous potentially life-threatening metabolic and infectious complications. Insertion site, tunnel and catheter-related blood stream infections may lead to bacteremia and septicemia, central venous thrombosis, and even embolism (Buchman et al, 2003). Total parental nutrition has been shown to induce immunosuppression (Alverdy and Burke, 1992). Liver dysfunction in patients who receive PN is one of its most devastating complications. The development of PN-associated liver disease predisposes patients to an increased incidence of sepsis, higher mortality rates and the potential to develop irreversible liver injury (Tazuke and Teitelbaum, 2009). Parenteral constituents and chronic dehydration may contribute to PN/IV-associated liver and renal disease, and eventually, to organ failure (Goulet et al, 2009; Lauverjat et al, 2006). Use of PN/IV support is also associated with reduced quality of life due to the time required for, and consequences of, frequent access to an IV pump and complications such as catheter-related sepsis (DeLegge et al, 2007).



A significant clinical benefit for patients requiring PN nutrition would result from reduction in the amount of constituents delivered and/or decrease in the number of days that patients required PN. Consequently, increasing the absorptive capacity of the remaining intestine in order to decrease or obviate SBS patients' dependence on PN support is a rational therapeutic goal. However, reducing the PN/IV fluid volume must be done in a manner that does not negatively affect the patients' nutritional balance, which has been calibrated during years of PN support by the treating physician and the SBS patient.

Historically, clinical care of SBS patients has mainly focused on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, and anti-diarrheal and anti-secretory agents. Although surgical procedures such as bowel lengthening surgery or intestinal transplantation have been suggested as potential treatments, both options are associated with significant morbidity and mortality, and are therefore considered only in selected patients (Mardini and Villiers, 2008). Intestinal transplantation is limited to patients

who have developed life-threatening complications attributable to their intestinal failure and/or long-term PN/IV use (DeLegge et al, 2007). Problems associated with small bowel transplantation include the need for immunosuppression and risk for intestinal rejection and lymphoproliferative disease. In addition, the risk of intestinal stricture and small bowel obstruction increases with repeated surgical interventions.

The first long-term, targeted treatment approved for improving remnant intestinal function in SBS patients is teduglutide (known as Gattex® in the US and Revestive® in the EU), an analog of naturally occurring human glucagon-like peptide-2. Gattex received US marketing authorization on 21 December 2012 and Revestive received EU marketing approval on 30 August 2012.

## 7.2 Rationale for the Registry

Although the teduglutide development program provided the largest clinical dataset for SBS to date, a total of 173 subjects were included in the marketing application from the Phase 3 pivotal trials, with 148 subjects receiving teduglutide for 24 weeks, and 111 subjects treated for at least 12 months, 88 subjects treated for 24 months, and 14 treated subjects in the 36 month follow-up study. Further information is needed to characterize the safety profile and clinical outcomes of the SBS patient population with a variety of underlying etiologies and associated comorbidities who may or may not be treated with teduglutide in the post-marketing setting.



Based on mechanism of action and results of nonclinical studies, teduglutide has the potential to cause hyperplastic changes, including neoplasia, in the gastrointestinal (GI) tract. Phase 3 studies with teduglutide reported the occurrence of colorectal polyps, intestinal obstruction / stenosis, cholecystitis, cholangitis, cholelithiasis, and pancreatitis. Therefore, treatment with teduglutide has the following safety concerns:

- Potential acceleration of neoplastic growth and enhanced growth of colorectal polyps
- Potential gastrointestinal obstruction
- Potential gall bladder, biliary tract, and pancreatic disease

In addition, in patients with cardiovascular disease, the increased intestinal absorption of fluids promoted by teduglutide could lead to fluid overload, resulting in heart failure.

Therefore, this registry will collect data in the real-world setting on the occurrence of the following primary and secondary outcome variables in patients treated with teduglutide: 1) primary safety outcome of colorectal cancer, and 2) secondary safety outcomes such as other malignancies, benign neoplasia of the gastrointestinal tract, hepatobiliary system and pancreas, colorectal polyps, intestinal obstruction, pancreatic and biliary disease, and heart failure. This registry also will collect secondary outcome data on effectiveness of teduglutide

in the real-world setting by, as an example, evaluating changes in parenteral support over time required by patients treated with teduglutide.

To reduce risk with use of teduglutide, as part of the overall Risk Management Plan strategy, NPS Pharmaceuticals will use the local prescribing information (Contraindications, Warnings & Precautions and language describing screening/and follow-up testing) along with an SBS registry and a teduglutide US Risk Evaluation and Mitigation Strategy program, which will focus on communicating the product's potential risks to prescribers.

# 8 RESEARCH QUESTION AND OBJECTIVES

## 8.1 Primary Objective

The primary objective of this registry is to evaluate the long-term safety profile for patients with short bowel syndrome (SBS) who are treated with teduglutide in a routine clinical setting. The primary safety outcome is the occurrence of colorectal cancer in SBS patients with any remnant colon taking teduglutide.



## 8.2 Secondary Objectives

The secondary objective of this registry is to characterize long-term clinical outcomes in patients with SBS.

## 8.3 Variables

### 8.3.1 Primary Outcome Variable

- Occurrence of colorectal cancer

### 8.3.2 Secondary Outcome Variables

**Other Safety Outcomes such as:**

- Occurrence of other malignancy
- Occurrence of benign neoplasia of the gastrointestinal tract, hepatobiliary system, and pancreas
- Occurrence of colorectal polyps
- Occurrence of intestinal obstruction
- Occurrence of pancreatic and biliary disease
- Occurrence of heart failure and other manifestations of volume overload
- Occurrence of allergic/hypersensitivity reaction to teduglutide

**Effectiveness Outcomes such as:**

- Actual volume change in parenteral support
- Percentage volume change in parenteral support

# 9 RESEARCH METHODS

## 9.1 Overall Design of the Study

This is primarily a single-group, prospective, observational, multi-center (ie, world-wide) registry designed to collect data on long-term safety and clinical outcomes in SBS patients. SBS patients treated and not treated with teduglutide will be enrolled.

The primary outcome will be diagnosis of colorectal cancer in SBS patients, with any remnant colon, who were treated with teduglutide. The observed incidence of colorectal cancer for these patients will be compared with the incidence of colorectal cancer in the US population obtained from the most recent SEER (Surveillance Epidemiology and End Results) incidence rates at the time of analysis. The study is powered (80%) to rule out an increased risk of 3.1 for colorectal cancer in teduglutide patients with remnant colons relative to the SEER incidence rates, taking into account the age and gender distribution of the enrolled patients, the length of follow-up, and the composition of teduglutide patients with respect to inflammatory bowel disease (IBD). In addition, a sub-analysis will be done where only US patients will be compared to SEER data. For SBS patients from other regions of the world, comparable local cancer data sources, when available, will be used for comparison of colorectal cancer rates.



Secondary outcomes will include occurrence of other safety concerns such as other malignancies, benign neoplasia of the gastrointestinal tract, hepatobiliary system and pancreas, colorectal polyps, intestinal obstruction, pancreatic and biliary disease, heart failure and other manifestations of volume overload, occurrence of allergic/hypersensitivity reaction to teduglutide, and long-term effectiveness in patients treated with teduglutide.

Progress updates of registry patient accrual and a demographic summary will be provided at least annually. Registry safety data will be subject to ongoing pharmacovigilance assessment, as appropriate, and provided in periodic safety reports. Recipients of these updates and reports include registry stakeholders such as regulatory agencies, the Registry Outcome Committee, investigators, and internal NPS staff.

This registry permits interested SBS patients and SBS-treating health care providers to participate. A select set of data will be collected at baseline, and these data will then be recollected on an ongoing basis and solicited at least twice annually, as indicated in Table 2.

## 9.2 Study Duration

This study is planned for 5 years of enrollment with at least 10 years of follow-up for each SBS patient.

## 9.3 Patient Recruitment and Follow-up

### 9.3.1 Patient Recruitment

Patient recruitment is global. The Investigators are encouraged to consecutively enroll all patients who consent and meet the selection criteria, regardless of treatment or health status. Teduglutide patients may enroll in this registry if they participated in past teduglutide trials or other registries.

The number of patients invited and declined to participate in the registry will be tracked in order to assess participation rates. Basic information, such as age, gender, diagnosis, and reason for declining, will be collected, as allowed by local data privacy laws, to assess selection bias.



### 9.3.2 Patients Follow-Up

During the inform consent process and as allowed by local data privacy laws, the patient will be asked to supply personal contact and identifiable (eg, social security number) information, permission to contact new treating physicians, and permission to search the US National Death Index (NDI) and/or other available health status databases to ascertain their vital status, all procedures to reduce loss to follow-up.

Specifically, the patients will be asked for their contact information and to identify an alternate “contact” person so that the sponsor and/or designee or investigator can contact the patient (or alternate contact person) as needed for registry follow-up.

It is expected that some patients will transfer their medical care to a new physician over the course of their participation in the study. If this occurs, contact information for the new treating physician will be requested, and the new treating physician may be invited to participate in the study. If the new treating physician is not willing to participate in the study, the patient will be asked to sign a medical release form requesting and permitting the new treating physician to provide copies of the patient’s medical records for abstraction of study data.

The sponsor/designee will search the US NDI and other available health status databases in order to ascertain the vital status and cause of death of US patients who are lost to follow-up. Likewise, for SBS patients from other regions of the world ascertainment of vital status will be done where similar vital status databases exist.

## 9.4 Registry Outcome Committee

A Registry Outcome Committee will be established to review collected data on an annual basis. This committee will be subject matter experts comprising gastrointestinal oncologists, SBS experts, a statistician, and an epidemiologist.

It is the mandate of this committee to identify any potential safety signals that may arise in the registry or provide input if further additional data collection may be warranted.

## 9.5 Subject Selection and Participation

### 9.5.1 Number of Subjects

This registry is to enroll as many SBS patients as possible. For the primary outcome of occurrence of colorectal cancer the goal is to enroll at least 655 SBS patients of whom 393 will have any remnant colon (ie, at risk for colorectal cancer) and be treated with teduglutide; the primary analytic analysis of cancer occurrence in the exposed teduglutide group will be to compare it to cancer registry incidence data (i.e., a standardized morbidity ratio analysis). In addition, a target enrollment of at least 655 SBS adult patients 18 years and older dependent on parental support (patients for whom teduglutide is indicated) but not treated with teduglutide also will be attempted for an internal comparison group. Recognizing recruiting this number of non-teduglutide exposed SBS patients might be difficult, NPS will recruit non-teduglutide exposed SBS adults for two years and then reevaluate with the regulatory agencies the success of recruiting these patients for use as an internal control group. The internal control group will be for descriptive and comparative (not confirmatory) purposes.



### 9.5.2 Inclusion Criteria

1. Male and female patients, of any age, with a diagnosis of SBS.
2. Signed informed consent and medical records release by the patient or a legally acceptable representative.

### 9.5.3 Exclusion Criteria

None

### 9.5.4 Subject Withdrawal Criteria

Patients may participate as long as the registry is active and may withdraw at any time for any reason. If a patient withdraws, the reason should be documented in the electronic case report form (eCRF). Patients who withdraw from the registry will be allowed to re-enter.

## 9.6 Treatments and Treatment Plan

Treatment regimens will be determined for each individual SBS patient by the physician according to usual clinical practice.

## 9.7 Study Evaluations and Procedures

### 9.7.1 Study Procedures

This registry is designed to permit interested SBS-treating health care providers and/or interested SBS patients to participate. Patients will be enrolled at previous clinical trial study sites and, as feasible, also will be recruited through treatment clinics and through centers that have access to claims and/or electronic medical records to identify additional SBS patients. Patients who participated in previous teduglutide trials are eligible for registry entry. Baseline for these patients is their baseline in the clinical trial at the start of teduglutide treatment. Patients enrolled will have a select set of data collected at baseline, and these data will then be recollected on an ongoing basis and solicited twice annually, if not spontaneously reported, as indicated in Table 2 . Data collected during any pertinent healthcare visits will be solicited. All data will come from the prescriber/health care professional medical record.



Comprehensive demographic and baseline data are mandatory, if available, for enrollment in the registry, but any additional investigations that are outside normal clinical practice at the registry sites will not be required for participation in the registry. No predetermined follow-up requirements will apply; however, investigators will be prompted to update patient data in the registry based upon patients' visits to the physician. Investigators will be reminded to update the registry at least twice annually, although it is expected that patients will visit their physician more frequently for clinical follow-up. Female patients are requested to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy.

### 9.7.2 Schedule of Evaluations and Procedures

The schedule for data collection is summarized in Table 2.

**Table 2 Schedule for Data Collection**

| | Baseline Data[a] | Prospective Data (at Least Twice Annually)[b] |
|---|---|---|
| Informed consent and medical records release | X | |
| Inclusion criteria | X | |
| Demographic information | X | |
| SBS background | X | |
| Significant medical history | X | |
| Significant past/current imaging studies of interest | X | X |
| Significant past/current laboratory tests | X | X |
| Past/current treatments for SBS | X[d] | X |
| Other Concomitant Medications | X[d] | X |
| Clinical outcomes (SBS-comorbidities, other new comorbidities, and teduglutide-related events) | | X |
| Pregnancy, outcome, neonatal characteristics | X | X |
| US National Death Index and other vital status database searches | | X[c] |

SBS = short bowel syndrome; US = United States

[a] Mandatory baseline data to be entered as available. No additional measures or tests will be mandated or required.

[b] Investigators will be prompted to enter comprehensive information according to the patient's visit to the clinic and other pertinent health care visits. It is expected that patients will visit their physician more frequently for follow-up, eg, changes in pharmacological treatment. Data to be entered from since the last visit or last registry data entry.

[c] Search intervals to be determined

[d] Within past 12 months



## 9.8 Data Collection Procedures

### 9.8.1 Baseline Data Collection

Data such as the following will be recorded at the time of study enrollment:

- Demographics
  - Birth date
  - Gender
  - Ethnicity
  - Race
  - Level of education and employment status
  - Height and weight

- SBS background
  - Age at onset/diagnosis
  - Cause of major intestinal resection
  - Intestinal anatomy (small bowel remnant, intact colon, colon remnant)
  - Years of PN/IV
- Significant medical history (time interval will be age-dependent)
  - Cancer
  - Benign neoplasia of the gastrointestinal tract, hepatobiliary system, and pancreas
  - Colorectal polyps with histological diagnosis when available
  - Intestinal obstruction
  - Pancreatic disease including relevant laboratory/enzyme tests
  - Biliary disease including relevant laboratory/enzyme tests
  - Heart failure
  - PN-associated liver disease
  - Repeat intestinal surgery
  - Systemic infections (within the past 12 months)
  - Transplant history
  - Hospitalizations or emergency room (ER) visits (within the past 12 months)
  - Other, eg, cardiovascular disease, renal insufficiency, diabetes, liver disease, allergies
- Significant past imaging studies of interest
  - Upper endoscopy
  - Colonoscopy
  - Imaging including abdominal ultrasound, x-radiography, endoscopic retrograde cholangiopancreatography (ERCP), etc.
- Results of clinically significant laboratory tests (in the setting of other clinical outcomes)
- Treatments for SBS (within the past 12 months)
  - Parenteral support (L/week and days/week)
  - Teduglutide, growth hormone, glutamine
  - Other SBS concomitant medications
- Other Concomitant Medications (within the past 12 months)
- Pregnancy
  - History

### 9.8.2 Follow-up Data Collection

Data such as the following will be recorded at clinic visits, or at least twice annually.

Since the last visit or last registry data entry:

- Clinical Outcomes
  - Cancer (cancer adjudication will require a positive biopsy report in the medical record)
  - Benign neoplasia of the gastrointestinal tract, hepatobiliary system, and pancreas
  - Colorectal polyps with histological diagnosis when available
  - Intestinal obstruction
  - Pancreatic disease including relevant laboratory/enzyme tests
  - Biliary disease including relevant laboratory/enzyme tests
  - Heart failure and other manifestations of volume overload
  - PN-associated liver disease
  - Repeat intestinal surgery
  - Allergic/hypersensitivity reactions to teduglutide
  - Systemic infections
  - Hospitalization or ER visits
  - Other, eg, cardiovascular disease, renal insufficiency, diabetes, liver disease, allergies
  - Death
- Results of imaging studies
  - Upper endoscopy
  - Colonoscopy
  - Imaging, including abdominal ultrasound, x-radiography, ERCP, etc.
- Results of clinically significant laboratory tests (in the setting of other clinical outcomes and adverse events [AEs])
- Current treatments for SBS
  - Parenteral support (L/week and days/week)
  - Other concomitant medications (eg, antidiarrheal motility, antisecretory agents, narcotics, anxiolytics, ursodeoxycholic acid, biologics, immunosuppressives)
  - Teduglutide, growth hormone, glutamine
- Other Concomitant Medications and AEs associated with increased absorption of them due to teduglutide

- Pregnancy
  - Delivery date
  - Outcome
  - Neonatal characteristics

## 9.9 Data Management

### 9.9.1 Data Collection

All data collected will be stored and evaluated in accordance with GPP, local regulatory requirements and applicable guidance for electronic records.

### 9.9.2 Method of Data Collection

Electronic case report forms will be used. Data will be abstracted from the patient's medical record and entered into the electronic data capture (EDC) system according to the schedule presented in Table 2. Patients will be identified by use of the ID number assigned to them when they enroll in the registry. This ID will consist of a 4 digit site number plus a 4-digit patient number (xxxx-xxxx). If the patient has previously been enrolled in an NPS-sponsored Gattex study, the same ID should be assigned to the patient.

Before the first patient's medical record is abstracted, the sponsor/designee will meet with the Investigator and the study center's personnel to train them on recording the data on the eCRFs using the EDC system.



### 9.9.3 Electronic Case Report Forms and Data Capture System

Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with instructions from the sponsor/designee. Each Investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner. Data collected during the study will be recorded in the patient's eCRF by study center personnel or sponsor/designee. The investigator center personnel or sponsor/designee will keep records of the patient's visit, eg, medical records, research charts, etc, as source documents for the patient.

On-line logic checks will be built into the system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study center and answered electronically by that study center's personnel. The identifying information (assigned user name, date, and time), for both the originator of the query and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on the data, will be collected.

The Investigator will be responsible for reviewing eCRFs, resolving data queries generated by the sponsor/designee via the system, providing missing or corrected data, approving all

changes performed on the patient data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature. A 10% random sample of sites will be visited for quality control and source data verification of eCRFs. Additional site monitoring may be done based on the periodic review of data.

### 9.9.4 Record Retention

The investigators will maintain medical records, copies of eCRFs, laboratory records, including but not limited to signed patient consent documents, for at least 15 years from registry termination/completion or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor. Records will be retained according to local regulations. The sponsor/designee will retain study related documents and data according to applicable sponsor's record retention schedules, local regulations, or 15 years from registry termination/ completion whichever is longer.

## 9.10 Statistical Methodology and Sample Size

Detailed statistical analysis methods will be conducted as described in the statistical analysis plan (SAP) for this study. Statistical Analysis Software (SAS) will be used for data analysis. Data will be summarized with tabulated descriptive statistics: n, minimum, maximum, mean, median, standard deviation, and range for continuous variables; and counts and percentages for categorical variables. In addition, graphical data displays will be used to summarize selected data. Person-years of follow-up and incidence rates of prospective events will be calculated.



### 9.10.1 Demographic and Baseline Variables

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Disposition, baseline, and demographic data will be summarized with descriptive statistics and presented in listings.

### 9.10.2 Pharmacologic Treatments/Medications

Medications will be coded using the World Health Organization Drug Dictionary with regard to drug class and drug name. The number and percentage of patients with specific medications will be summarized with descriptive statistics.

### 9.10.3 Outcome Variables

Tabulated descriptive statistics and graphical data displays will be used to summarize the data.

The primary safety analysis will focus on SBS patients, with any remnant colon, who were treated with teduglutide.

- Incidence rates of colorectal cancer in these patients will be calculated by dividing the number of incident colorectal cancer cases by the total number of person-years observed since beginning treatment with teduglutide. Person-years of observation will continue to accrue for teduglutide patients who discontinue teduglutide use for the duration of follow-up. Other calculations of colorectal cancer incidence rates using different groupings of person-years (eg, person-years restricted to teduglutide exposure, categorizing person-years to take account of treatment cross-over such as entering the registry not on teduglutide but later starting teduglutide) will be discussed in the SAP.
- The risk of colorectal cancer as a function of cumulative exposure to teduglutide will also be estimated. Kaplan-Meier curves will be used to graphically depict the occurrence of colorectal cancer as a function of time since the beginning of teduglutide treatment.
- Incidence rates and Kaplan-Meier curves will also be stratified by age at enrollment and gender and by underlying comorbid conditions that may impact cancer incidence, including the presence of IBD.
- Incidence rates will be similarly calculated for the secondary outcomes, such as other malignancies, benign neoplasia of the gastrointestinal tract, hepatobiliary system and pancreas, colorectal polyps, intestinal obstruction, pancreatic and biliary disease, heart failure and other manifestations of volume overload, and allergic/hypersensitivity reactions to teduglutide.
- The incidence of colorectal cancer in the teduglutide patients, with any remnant colon, will be compared and tested against the US population using standardized morbidity ratios (SMRs), defined as the ratio of the observed number of cases of colorectal cancer to the expected number of cases of colorectal cancer.
- The expected number of cases of colorectal cancer will be calculated by applying the latest available US SEER colorectal cancer incidence rates to the age, gender, and length of follow-up distributions of all the teduglutide-treated patients with remnant colons. In addition, a sub-analysis will be done where only US patients will be compared to SEER data. For SBS patients from other regions of the world, comparable local cancer data sources, when available, will be used for comparison of colorectal cancer rates.

The effect of the length of follow-up is important to consider, because the expected incidence rates of colorectal cancer rapidly increase in magnitude above age 50. Therefore, patients this age and older who are followed for a maximum of 15 years will experience a marked change in their background colorectal cancer risk during the course of the registry. To take into account the duration of follow-up, the accrual of person-years will be tracked for each of the

age groups used in reporting the SEER incidence rates. The gender-specific person-years totals for each age group will then be applied to the SEER incidence rates to arrive at estimates of expected numbers of cases.

- The SMRs will be tested for significance by calculating exact one-sided 95% confidence intervals (CIs), assuming that the distribution of cases follow a Poisson distribution.

Descriptive statistics for teduglutide-treated and teduglutide non-treated patients will be made on safety and effectiveness outcomes. For non-confirmatory analyses, comparisons between the treated and non-treated internal comparison groups on safety and effectiveness outcomes will be made as described in the SAP.

### 9.10.4 Analysis Population

All analyses will be based upon the enrolled population. The teduglutide-treated population will be defined as patients who received at least one dose of teduglutide.

### 9.10.5 Statistical/Analytical Issues

#### 9.10.5.1 Adjustments for Covariates

SMRs will be calculated based on the age, gender, and follow-up distribution of the teduglutide-treated SBS patients with remnant colons.

#### 9.10.5.2 Handling of Dropouts or Missing Data

No missing values will be imputed.

#### 9.10.5.3 Examination of Subgroups

For SMR analyses, a sub-analysis will be done where only US patients will be compared to SEER data. For SBS patients from other regions of the world, comparable local cancer data sources, when available, will be used for comparison of colorectal cancer rates. Specifically, a US-only, non-US, and a total world analysis of cancer SMRs will be attempted. Further subgroup analyses (if any) will be discussed in the SAP.

### 9.10.6 Determination of Sample Size

This registry is to enroll as many SBS patients as possible. The primary safety analysis will focus on the SBS patients, with any remnant colon, who were treated with teduglutide. The projected numbers of patients to receive teduglutide in the US/EU for the 5 years of registry enrollment is used to determine sample size and power calculations (Annex 2). The US SEER cancer registry is used to calculate the expected number of colorectal cancer occurrences for the patients in the registry, applying these data to both patients from the US and from other regions of the world. Given these caveats, the goal is to enroll at least 655 SBS patients treated with teduglutide world-wide of whom 393 will have a remnant

colon. With this sample size this study will provide 80% power to rule out a 3.1 fold increased risk of colorectal cancer associated with teduglutide.

The required sample size was estimated using a simulation approach. See Annex 2 for a table of simulation study results. For the simulation study, the following assumptions were made.

- Five years of enrollment and a minimum of 10 years of follow-up for each SBS patient.
- Annual attrition follows an exponential distribution.
- Enrollment follows a uniform distribution within each year of the five-year enrollment.
- Approximately 60% of new teduglutide patients will have any remnant colon and be at risk for colorectal cancer.
- Approximately one-third of SBS patients will have IBD and experience double the risk of colorectal cancer as the general population. Overall, this means that the newly treated teduglutide population will have approximately one-third greater risk than the general population.
- The age distribution of patients entering the registry will be similar to the age distribution of the teduglutide clinical studies. The age distribution of SBS patients was 31.4%, 53.5%, and 15.1% for ages <45, 45-65, and >65 years, respectively. To simulate this age distribution, a scaled beta distribution was used with parameters a=3.3 and b=3.3.

Based on these assumptions, the rate of annual attrition (5%, 10%, 15 %, 25%, and 50%) and the percent of new teduglutide patients that will enroll in the registry (20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90%) were varied. For each scenario, the following calculations were performed:

- The expected number of person-years accrued
- The expected background incidence of colorectal cancer, based on SEER 2005-2009 colorectal cancer rates
- The expected number of colorectal cancer patients, based on the background SEER incidence and person-years accrued
- The relative risk that could be ruled out with 80% power
- The minimum number of colorectal cancer cases that would be required to conclude increased risk

The results of the simulation study are presented in Annex 2.

Based on these calculations, it is estimated that enrolling 30% of new teduglutide patients with any remnant colon (n = 393) and an annual attrition of 15% will yield a total of 2072 person-years of exposure and a background risk for colorectal cancer of 120.1 cases per

100,000 person-years. This study would provide 80% power to rule out a 3.1 fold increased risk of colorectal cancer for teduglutide-exposed patients who have remnant colons.

### 9.10.7 Changes to Planned Statistical Analyses

Deviations from the SAP (if any) will be described and justified in the final study report.

## 9.11 Study limitations

Potential limitations of the study are:

- Participation in the registry is voluntary for patients and doctors. Difficulty in recruiting patients may occur with consequently smaller sample sizes, reduced statistical power, and limited generalizability of results. NPS is addressing this by making the registry open to all SBS patients, and not limiting patient recruitment to centers that participated in teduglutide clinical trials. NPS will compare patients that participate in the registry to those that do not on a few key variables (eg, age, gender, and where allowed by law and regulation) to evaluate for patient selection bias.
- Following patients over 10 years may be difficult with subsequent lost to follow-up of patients. This lost to follow-up can reduce the statistical power of the study and result in a selection bias in those that are followed for 10 years. The latter can limit the generalizability of study findings. Section 9.3.2 of the protocol details how NPS will minimize this risk. NPS will also use in the statistical analysis all person-years of follow-up a patient contributes until they are lost to follow-up.
- Like all observational studies, unmeasured patient and clinical variables related to both teduglutide use and study outcomes may confound the study results. An example of this is factors leading to confounding by indication. This study depends on patient information in the investigators medical records; the medical records are assumed to be a valid source of data and no validation of the information in the medical records will be done. To the extent that the medical record validity assumption is true will dictate the degree of potential information bias in the registry; the direction and degree of this information bias is not known.
- The internal comparison group, if sample size is large enough as described above, is a non-teduglutide exposed cohort of SBS adult patients on parenteral support with no other restrictions, including treatment, for registry eligibility. The comparator group will be treated mainly by parental support although some patients will receive Zorbtive or glutamine. Intestinal surgery such as small bowel transplantation may be seen in a few patients. Therefore, the comparator group will consist of a mix of therapies. (Note that Zorbtive is not approved in Europe and its labeled duration of treatment is one month so the number of patient-years exposed to Zorbtive will likely be small.) The main focus of

the registry is to collect additional safety data of teduglutide. The registry is not designed to be a comparative effectiveness evaluation of SBS treatments. No matter the final composition or size of the internal comparator group, the registry is observational and due to influences such as confounding by indication, the teduglutide and non-teduglutide groups will not be comparable in many factors. We will attempt to control for these differences by collecting relevant demographic and clinical data and using multivariate statistical modeling.

# 10 ADMINISTRATIVE AND PROTECTION OF HUMAN SUBJECTS

## 10.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the internationally recognized code of Good Pharmacoepidemiology Practices as described by the International Society for Pharmacoepidemiology.

In accordance with guidelines, the protocol, any advertisements and ICFs will be reviewed and approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The sponsor will supply relevant material for the investigator to submit to the IRB/IEC for the protocol's review and approval. Written and dated verification of the IRB/IEC approval of the protocol and the written ICF will be forwarded to the sponsor/designee.

The investigator or sponsor/designee will inform the IRB/IEC of subsequent protocol amendments (and any safety results due to an unanticipated problem). Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator or sponsor/designee will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a study summary report following the completion or discontinuation of the study, if requested.



## 10.2 Patient Information and Consent

In accordance with GPP and applicable guidelines, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the patient before entry into the registry. A consent form model will be provided by the sponsor/designee and adapted by the investigator to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the patient the nature of the study. The patient will be informed that participation is voluntary and that he or she can withdraw from the study at any time, without prejudice to their current or subsequent care.

## 10.3 Patient Data Protection

Patients should be informed in writing that their data will be stored and analyzed, with confidentiality maintained, including personal health information de-identified in datasets used for statistical analyses and that may be accessible to non-study personnel, in accordance with GPP, national, and local legislation. Center-specific information must be added to the ICF as appropriate.

Patients also should be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records which are relevant to the study, including medical history, for data collection and verification purposes.

The investigator is responsible for keeping a patient identification list of all patients screened and enrolled which includes the following information: patient number, full name, and a secondary unique identifier (ie, hospital/clinic number). A list of patients with a very limited set of data, as allowed by local data privacy laws, who declined participation must also be maintained and be available for inspection.

For US patients lost to follow-up during the course of the registry, the sponsor/designee will conduct a search of the US NDI and other available health status databases to ascertain their vital status, and in the case of a participant's death, the cause of death. Likewise, for SBS patients from other regions of the world ascertainment of vital status will be done where similar vital status data sources exist.



To facilitate this vital status search, patients will be asked to provide personal identifiable information (ie, social security number) at the time of enrollment along with their permission to do the search. Patients who decline this permission will be permitted to enroll with no consequence or change to their registry participation. All personal contact information will be maintained in a secure, password protected file and will be destroyed at the conclusion of the registry. Only the patient ID number, the outcome of the search, and cause of death will be reported. Where possible, the study site personnel will be requested to perform the vital status search without disclosure of any patient identifying information.

## 10.4 Changes to the Protocol

No change in the study procedures shall be effected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments, or as a revised protocol. Changes to the protocol may require notification to or approval by the IRB/IEC and the regulatory authorities before implementation. GPP and local regulatory requirements must be followed.

The sponsor/designee is responsible for the distribution of protocol amendment(s) to the investigators and those concerned with the conduct of the study. The investigator is responsible for the distribution of all amendments to the IRB/IEC and all staff concerned at his/her center.

### 10.5 Investigator Obligations

Each investigator must provide the following, at minimum, to the sponsor/designee prior to the start of the study:

- A current (within 2 years) signed and dated curriculum vitae for the investigator, including a current office address.
- A copy of the original approval for conducting the study from the IRB/IEC. Renewals must be submitted at yearly intervals if the study is ongoing, or as required by the institution.
- A Statement of Investigator (ie, FDA-1572 Form)
- A copy of the IRB/IEC-approved ICF
- Financial disclosure for the investigator
- IRB/IEC membership list or Department of Health and Human Services General Assurance Number, which must be maintained current during the study

The "Investigator Registry Protocol Agreement Page" of this protocol must be signed and dated by the investigator.



### 10.6 Confidentiality/Publication of the Study

Any information shared by the sponsor regarding this registry, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this registry are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion and/or for submission to regulatory agencies. In addition, the sponsor reserves the right to review data from this study relative to the potential release of proprietary information 30 days prior to submission to any publication or for any presentation.

### 10.7 Registry Discontinuation

The sponsor reserves the right to discontinue the registry at any time in consultation and agreement with regulatory agencies.

# 11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

NPS will follow the EMA's Guideline on Good Pharmacovigilance Practices, Module VIII – Post-authorisation Safety Studies (April 2013). NPS proposes a two-part approach for pharmacoviligance reporting for teduglutide from the SBS registry. First, the registry will query for a select group of potential clinical outcomes/AEs (Section 9.8.2). For reported events NPS will collect additional information to meet the objectives of the registry. Also, the NPS Pharmacovigilance Department/designee will have real time access to the data about these events and will process them, including if needed additional data collection for pharmacovigilance reporting, and for the EU according to NPS pharmacovigilance procedures as described in the current Pharmacovigilance System Master File (Annex 1).

Second, the registry will ask if the health care provider is aware of other AEs (ie, non-select) that are possibly related to teduglutide. If so, the registry will prompt the health care provider to complete AE forms within the registry system which will then be forwarded in real time to the sponsor's Pharmacovigilance Department/designee for pharmacovigilance processing and for the EU as described in the current Pharmacovigilance System Master File (Annex 1).

All teduglutide safety-related data – AEs, Adverse Drug Reactions, Serious AEs, select and non-select – on study patients collected in the registry and AEs reported to NPS according to normal procedures for marketed drugs (ie, outside of the registry) will be analyzed and/or summarized in the registry study reports and/or Periodic Safety Update Reports. Adverse event will be coded using MedDRA.



# 12 PLANS FOR DISSEMINATION AND COMMUNICATING STUDY RESULTS

Confidential site-specific and aggregate reports will be provided to participating investigators and/or regulatory authorities on a periodic basis. Patient specific data will be anonymized. Annual reports will include, but not be limited to accrual rates; summary demographic, and clinical data; and total person-years of follow-up. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate. Publications on findings from this registry will be prepared as appropriate per sponsor publication policies and procedures.

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# ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

| Number | Document Reference Number | Date | Title |
|---|---|---|---|
| 1 | MFL5055 | 27 February 2014 | Pharmacovigilance System Master File for NPS Pharmaceuticals |
| 2 | TBD | TBD | Principle Investigator, Coordinating Investigators, and Study Centers Contact Information |
| | | | |

## ANNEX 2 ADDITIONAL INFORMATION

**Simulation Study Results of the Registry Power Analysis**[a] (The proposed design is highlighted in blue.)

| Percent of New Teduglutide Patients Enrolling in the Registry[b] | Total Enrollment After 5 Years | Annual Attrition | Total Person-years Observed at the End of Follow-up | Background Risk of CRC Based on SEER CRC Rates for 2005-2009[c] | Expected Number of CRC Cases Assuming SEER Background Rate Holds True | Detectable RR with 80% Power | Minimum Number of CRC Cases to Conclude Increased Risk |
|---|---|---|---|---|---|---|---|
| 90 | 1180 | 5.0% | 10620 | 130.6 | 13.9 | 1.7 | 21 |
| 90 | 1180 | 10.0% | 8048 | 125.2 | 10.1 | 1.9 | 17 |
| 90 | 1180 | 15.0% | 6222 | 120.1 | 7.5 | 2.1 | 13 |
| 90 | 1180 | 25.0% | 3963 | 111.3 | 4.4 | 2.5 | 9 |
| 90 | 1180 | 50.0% | 1700 | 98.9 | 1.7 | 3.7 | 5 |
| | | | | | | | |
| 80 | 1049 | 5.0% | 9441 | 130.6 | 12.3 | 1.8 | 19 |
| 80 | 1049 | 10.0% | 7154 | 125.2 | 9.0 | 2.0 | 15 |
| 80 | 1049 | 15.0% | 5532 | 120.1 | 6.6 | 2.2 | 12 |
| 80 | 1049 | 25.0% | 3523 | 111.3 | 3.9 | 2.7 | 8 |
| 80 | 1049 | 50.0% | 1511 | 98.9 | 1.5 | 4.0 | 5 |
| | | | | | | | |
| 70 | 918 | 5.0% | 8262 | 130.6 | 10.8 | 1.9 | 17 |
| 70 | 918 | 10.0% | 6261 | 125.2 | 7.8 | 2.1 | 14 |
| 70 | 918 | 15.0% | 4841 | 120.1 | 5.8 | 2.3 | 11 |
| 70 | 918 | 25.0% | 3083 | 111.3 | 3.4 | 2.8 | 8 |
| 70 | 918 | 50.0% | 1323 | 98.9 | 1.3 | 4.2 | 4 |
| | | | | | | | |
| 60 | 787 | 5.0% | 7083 | 130.6 | 9.2 | 2.0 | 15 |
| 60 | 787 | 10.0% | 5367 | 125.2 | 6.7 | 2.2 | 12 |
| 60 | 787 | 15.0% | 4150 | 120.1 | 5.0 | 2.4 | 10 |
| 60 | 787 | 25.0% | 2643 | 111.3 | 2.9 | 3.0 | 7 |
| 60 | 787 | 50.0% | 1134 | 98.9 | 1.1 | 4.7 | 4 |

| Percent of New Teduglutide Patients Enrolling in the Registry[b] | Total Enrollment After 5 Years | Annual Attrition | Total Person-years Observed at the End of Follow-up | Background Risk of CRC Based on SEER CRC Rates for 2005-2009[c] | Expected Number of CRC Cases Assuming SEER Background Rate Holds True | Detectable RR with 80% Power | Minimum Number of CRC Cases to Conclude Increased Risk |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| 50 | 656 | 5.0% | 5094 | 130.6 | 7.7 | 2.0 | 14 |
| 50 | 656 | 10.0% | 4474 | 125.2 | 5.6 | 2.2 | 11 |
| 50 | 656 | 15.0% | 3459 | 120.1 | 4.2 | 2.6 | 9 |
| 50 | 656 | 25.0% | 2203 | 111.3 | 2.5 | 3.1 | 6 |
| 50 | 656 | 50.0% | 945 | 98.9 | 0.9 | 5.1 | 4 |
| | | | | | | | |
| 40 | 524 | 5.0% | 4716 | 130.6 | 6.2 | 2.2 | 12 |
| 40 | 524 | 10.0% | 3574 | 125.2 | 4.5 | 2.5 | 9 |
| 40 | 524 | 15.0% | 2763 | 120.1 | 3.3 | 2.8 | 7 |
| 40 | 524 | 25.0% | 1759 | 111.3 | 2.0 | 3.5 | 6 |
| 40 | 524 | 50.0% | 756 | 98.9 | 0.7 | 6.1 | 3 |
| | | | | | | | |
| 30 | 393 | 5.0% | 3537 | 130.6 | 4.6 | 2.5 | 9 |
| 30 | 393 | 10.0% | 2680 | 125.2 | 3.4 | 2.7 | 8 |
| 30 | 393 | 15.0% | 2072 | 120.1 | 2.5 | 3.1 | 6 |
| 30 | 393 | 25.0% | 1319 | 111.3 | 1.5 | 4.0 | 5 |
| 30 | 393 | 50.0% | 567 | 98.9 | 0.6 | 6.8 | 3 |
| | | | | | | | |
| 20 | 262 | 5.0% | 2358 | 130.6 | 3.1 | 2.8 | 7 |
| 20 | 262 | 10.0% | 1787 | 125.2 | 2.2 | 3.1 | 6 |
| 20 | 262 | 15.0% | 1382 | 120.1 | 1.7 | 3.5 | 5 |
| 20 | 262 | 25.0% | 879 | 111.3 | 1.0 | 4.9 | 4 |
| 20 | 262 | 50.0% | 378 | 98.9 | 0.4 | 8.2 | 3 |

| Percent of New Teduglutide Patients Enrolling in the Registry[b] | Total Enrollment After 5 Years | Annual Attrition | Total Person-years Observed at the End of Follow-up | Background Risk of CRC Based on SEER CRC Rates for 2005-2009[c] | Expected Number of CRC Cases Assuming SEER Background Rate Holds True | Detectable RR with 80% Power | Minimum Number of CRC Cases to Conclude Increased Risk |
|---|---|---|---|---|---|---|---|
| CRC = colorectal cancer; IBD = inflammatory bowel disease; RR = risk ratio; SEER = Surveillance Epidemiology and End Results<br>[a] The projected numbers of patients to receive teduglutide in the US/EU for the 5 years of registry enrollment is used to determine sample size and power calculations.<br>[b] Assuming that only 60% of new teduglutide patients have any remnant colon<br>[c] Assumes 1/3 of Gattex patients will have IBD and experience double the risk of CRC; rates per 100,000 person-years | | | | | | | |

## INVESTIGATOR REGISTRY PROTOCOL AGREEMENT PAGE

## Protocol TED-R13-002

I agree:

To assume responsibility for the proper conduct of this registry at this center and to conduct the study in compliance with this registry protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Pharmacoepidemiologic Practices, International Society for Pharmacoepidemiology standards, and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol and any amendments thereof, written informed consent or updates thereof, patient recruitment procedures (eg, advertisements), and any other written information to be provided to the patients, before initiating this natural history registry,

Not to implement any changes to, or deviations from the registry protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the patient participants, or when change(s) involves only logistical or administrative aspects of the natural history registry,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the natural history registry in order to conduct the study properly, ethically, and safely,



To ensure that all persons assisting in this study are adequately informed about the protocol and their natural history registry-related duties and functions,

To maintain copies of medical records, electronic case report forms, and study records, including but not limited to signed patient consent documents, for at least 15 years from registry termination/completion or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

| Investigator (Print Name) | Date (DD MMM YYYY) |
|---|---|

Investigator (Signature)