PASS Information

Title	A multicentre, European, observational, Drug Utilisation Study (DUS) of BLI800 (Eziclen®/Izinova®) as a bowel cleansing preparation
Protocol version identifier	Final: 13 August 2015 (including amendment N°1)
Date of last version of protocol	Final: 19 February 2015 (incorporating comments from the Pharmacovigilance Risk Assessment Committee (PRAC), 12 February 2015)
European Union electronic register of postauthorisation studies (EU PAS register) number	Study registered on ENCePP register (no number allocated)
Active substance	Sodium sulphate anhydrous Magnesium sulphate heptahydrate Potassium sulphate 06A - Laxatives
Medicinal product	BLI800 (Eziclen®/Izinova®)
Product reference	BLI800
Procedure number	FR/H/511/01/DC
Marketing authorisation holder (MAH)	Ipsen Pharma SAS
Joint PASS	No
Research question and objectives	The postapproval commitments for BLI800 (Eziclen®/Izinova®) in Europe included a request that Ipsen Pharma SAS conducts a DUS to assess drug utilisation in the real life setting in a representative sample of the European target population. The objectives of this DUS are: • Primary objective: to document the misuse of BLI800 (Eziclen®/Izinova®), defined as non-compliance in terms of insufficient liquid intake, during the postapproval period in the real life setting. • Secondary objective: to describe the safety profile of BLI800 (Eziclen®/Izinova®) in routine clinical practice, overall and in case of misuse defined as non-compliance in terms of insufficient liquid intake, and identify any immediate/acute adverse events associated with the use of BLI800 (Eziclen®/Izinova®) in special populations (i.e. the elderly and patients at risk of electrolyte shifts).
Country(ies) of study	The study will be conducted in the Czech Republic, Poland, Germany and the Netherlands, where BLI800 (Eziclen®/Izinova®) is already on the market, and potentially in two other European countries, where the product will be launched during the study period (i.e. in 2015 and 2016).
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Marketing Authorisation Holder(s)

MAH	Ipsen Pharma SAS
MAH contact person	PPD Ipsen Biopharm Limited 190, Bath Road Slough, Berkshire, United Kingdom Tel:PPD Serious Adverse Event (SAE) form(s) to be submitted to: PPD

PROTOCOL SIGNATURES

Investigator Signature

I have read and agree to the postauthorisation safety study (PASS)/drug utilisation study (DUS) protocol N° 8-79-58800-001 entitled "A multicentre, European, observational, Drug Utilisation Study (DUS) of BLI800 (Eziclen®/Izinova®) as a bowel cleansing preparation". I am aware of my responsibilities as an investigator under the guidelines of Good Pharmacoepidemiology Practices (GEP/GPP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____

TITLE: (Principal) Investigator: SIGNATURE: _____

DATE: _____

OFFICE: _____

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

On behalf of the Sponsor:

NAME: Hélène Mathiex-Fortunet

TITLE: VP Drug Development Primary Care SIGNATURE: _____

DATE: _____

OFFICE: _____

[SUMMARY OF CHANGES]

The current version of the protocol was released on 13 August 2015 and includes Amendment 1. For all protocol amendments, amendment forms were prepared and are provided in Appendix 4 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	13 August 2015	Appendix 4

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2 LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse Event
CI	Confidence Interval
CRO	Contract Research Organisation
CSR	Clinical Study Report
DUS	Drug Utilisation Study
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS register	European Union Electronic Register of Postauthorisation Studies
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP/GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intent To Treat
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Postauthorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
RMS	Reference Member State
SAE	Serious Adverse Event
SAS®	Statistical Analysis System

SD	Standard Deviation
SOC	System Organ Class
USA	United States of America
WHODRUG	World Health Organisation Drug Dictionary

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4 ABSTRACT

Title

Study Title:	A multicentre, European, observational, Drug Utilisation Study (DUS) of BLI800 (Eziclen®/Izinova®) as a bowel cleansing preparation
Protocol Version N°:	Final: 13 August 2015 (including amendment N°1)
Date of the Last Version of the Protocol:	Final, 19 February 2015 (incorporating comments from the Pharmacovigilance Risk Assessment Committee (PRAC), 12 February 2015)
Author:	Hélène Mathiex-Fortunet, VP Drug Development Primary Care, Ipsen Pharma SAS

Rationale and Background

Colonoscopy plays an important role in the diagnosis and management of colorectal diseases. This procedure remains the gold standard for the early detection of colorectal cancer. Bowel cleansing is a critical issue in the quality and diagnostic efficacy of this examination as well as for the potential therapeutic procedures.

In January 2013, the European registration procedure was successfully concluded for BLI800 (Eziclen®/Izinova®), an oral solution composed of the sulphate salts of sodium, potassium and magnesium. The postmarketing commitments that accompanied the approvability of this bowel oral preparation requested that Ipsen Pharma SAS conducts a DUS to assess drug utilisation in the real life setting in a representative sample of the European target population.

Research Question and Objectives

- Primary objective: to document the misuse of BLI800 (Eziclen®/Izinova®), defined as non-compliance in terms of insufficient liquid intake, during the postapproval period in the real life setting.
- Secondary objective: to describe the safety profile of BLI800 (Eziclen®/Izinova®) in routine clinical practice, overall and in case of misuse defined as non-compliance in terms of insufficient liquid intake, and identify any immediate/acute adverse events associated with the use of BLI800 (Eziclen®/Izinova®) in special populations (i.e. the elderly and patients at risk of electrolyte shifts).

Study Design

This is a non-interventional, multicentre, European, observational DUS in male and female patients who have received BLI800 (Eziclen®/Izinova®) in the postmarketing setting.

The study will be conducted in four countries where the product is already on the market (the Czech Republic, Poland, Germany and the Netherlands) and potentially may also be extended to two additional European countries, after product launch in 2015 and 2016. Based on the product launch plan across Europe and the feasibility study results, the anticipated number of participating countries for this DUS is at most six.

Study sites will include specialised gastroenterology and hepatogastroenterology departments (referral centres) and endoscopy departments (non-referral centres), and patients may be inpatients or outpatients. Patients eligible for participation in the study will require bowel cleansing prior to colonoscopy and will be prescribed BLI800 (Eziclen®/Izinova®) in accordance with the terms of the marketing authorisation. To avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. The modalities for recruitment will have to be determined prior to recruitment start.

Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure. Eligible patients will be included at the first visit (prescription). After signing an Informed Consent Form (ICF), details of patient demographics and characteristics, medical and surgical history, indication for bowel preparation, and prior (1 month) and concomitant medications will be collected. Vital signs (blood pressure, heart rate, height and body weight) and physical examination findings will be recorded. Electrocardiogram (ECG), and local laboratory test results dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake will be recorded when available, at first (prescription) and/or second (colonoscopy) visit. Any concomitant medications taken since the first visit, adverse events (AEs), and patterns and conditions of use of BLI800 (Eziclen®/Izinova®) documentation will be collected from the patient at the second visit (colonoscopy). In addition, physical examination findings will be recorded and the investigator will assess cleansing level of the colon at colonoscopy. No additional diagnostic or monitoring procedures will be performed, and descriptive methods will be used for the analysis of collected data.

For each patient, the study duration will be from signing the informed consent to discharge after the end of the procedure. The overall study duration will be approximately 2 years after first patient in.

Population

It is planned to include 1285 patients receiving BLI800 (Eziclen®/Izinova®) with the following inclusion/exclusion criteria:

- Eligibility/inclusion criteria: patients who are eligible for colon preparation with BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation and provide written informed consent.
- Exclusion criteria: patients who are not eligible for colon preparation with BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation because of a contraindication for use, or are prescribed another bowel cleansing preparation, or who have not signed the ICF.

This estimation is based on the primary endpoint and will allow to estimate the overall proportion of non-compliant patients (assumed as 50%) with a 2 sided confidence level of 95% and a precision of +/-5%.

Variables

- Patient demographics and characteristics (age and gender).
- Vital signs (blood pressure, heart rate, height and body weight).
- Physical examination.
- Medical and surgical history.
- Indication for bowel preparation.
- Patterns and conditions of use of BLI800 (Eziclen®/Izinova®)
  - Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions)
  - Date(s) and times(s) of intake
  - Patient compliance to the prescription, derived from the recorded remaining volume of BLI800 (Eziclen®/Izinova®) solution, and the time(s), remaining volume and nature of additional clear liquids to maintain hydration (see Section 9.7.4.6).
- Prior (1 month) and concomitant medications.
- Specific test results: ECG and local laboratory results from assessments performed before the anaesthesia and the colonoscopy and dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake will be collected when available. Collection of local laboratory results will be restricted to the following list: serum electrolytes, albumin, international normalised ratio (INR), creatinine, liver enzymes, bilirubin, uric acid and glucose.
- Efficacy evaluation
  - Cleansing level of the colon, assessed by the investigator at colonoscopy according to a four level scale (see Section 9.7.4.6).
- Safety evaluation
  - AEs will be collected from when the ICF is signed until discharge after the end of the colonoscopy procedure. A patient's leaflet will be distributed to the patient at the first visit, on which the patient will be instructed to record any AE experienced after product intake and prior to the procedure. The investigator (or authorised delegate) will collect the leaflet at the second visit and will record any AEs in the electronic Case Report Form (eCRF). During the second study visit, AEs will be collected by the investigator from the patient's leaflet, and the patient's interview and medical exam. The investigator will decide on the requirement for any follow up of AEs persisting beyond discharge after the procedure according to normal clinical practice.
  - The overall incidence of AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT), and by number and percentage

Primary endpoint:

The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration will be performed and will constitute the primary variable. The volume of water and clear liquids taken will be derived from the remaining volumes as recorded on the patient's leaflet and reported by the Investigator on the eCRF.

Compliance to the hydration guidelines (2 L of water or clear liquids) will be expressed in terms of a ratio (actual volume taken versus theoretical volume) and will be classed as follows:

- Excellent: 1:1
- Good: ≥3:4 and <1:1
- Low: <3:4 and ≥1:2
- Bad: <1:2

The primary endpoint is the proportion of non-compliant patients defined as having taken less than 75% of the prescribed hydration volume (2 L).

This proportion and its corresponding 95% confidence interval will be presented for the overall population as well as for each of the special populations and each of the dosing regimens.

Data Sources

The data will be collected and recorded on:

- The patient's leaflet (modalities of prescription including dosing regimen, date(s), time(s) and remaining volume of BLI800 (Eziclen®/Izinova®), time(s), remaining volume and nature of clear liquids, and AEs).
- An eCRF. The data collected on the patient's leaflet will be recorded in the eCRF by the investigator (or authorised delegate).

All the collected data will be in accordance with the daily practice of health care providers.

Start of data collection: The date from which information of the first study patient is first recorded in the study dataset.

End of data collection: The date from which the analytical dataset is completely available.

Study Size

It is planned to recruit 1285 patients. This sample size is based on the primary endpoint that is to say the proportion of non-compliant patients defined as having taken less than 75% of the prescribed hydration volume (2 L). The sample size for special population should represent 30% of the recruited patients, that is, 385 patients. Assuming a proportion of 50%, this sample size will allow estimating the proportion with a 2- sided 95% level of confidence and a precision of +/- 5%. The total included population will represent 1285 patients (nQuery advisor).

A feasibility study conducted across 11 European countries and more than 100 sites aimed to confirm the standard of care and to better estimate the sites recruitment capacity. The number of countries where the product is already on the market in 2014 is five (i.e. in the Czech Republic, Poland, Latvia, Germany and the Netherlands). Results from this feasibility study indicated that the number of participating countries could be fixed to be six at most, to include both Western and Eastern European countries, and that the number of participating sites could be limited to about 20. The study will be initiated in four countries, then potentially extended to two other European countries where the product is planned to be launched in 2015 and 2016. To avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. The modalities for recruitment will have to be determined prior to recruitment start. However, the actual numbers will depend on the drug uptake following launch.

Data Analysis

Descriptive summary statistics (number of available data, number of missing data, mean, standard deviation (SD), median, minimum and maximum for continuous data, and frequency count and percentage for categorical data) will be calculated for demographic and baseline clinical characteristics. Differences in demographic and clinical characteristics between subgroups of interest will be explored through 95% confidence intervals (CIs) of the mean for the quantitative parameters and of each category for the categorical ones.

The incidence of each targeted AE, as included in the Risk Management Plan as important risks and missing information, and AEs overall will be calculated, including the associated 95% CIs. Adjusted cumulative incidence of each related AE will be also calculated using Poisson regression, if a sufficient number of AEs is available to fit a model adjusting for potential confounders (including covariates like age, gender and relevant risk factors for the AE being examined). All statistical analyses will present the overall results as well as separately for the dosing regimens (one day and split dose) and for the special populations (including gender effect).

Milestones

Milestone	Planned date
Registration in the European Union Electronic Register of Postauthorisation studies (EU PAS register)	Q2 2015
Start of data collection	Q3 2015
Interim Progress Report	Q3 2016 or when half of the recruitment will be reached
End of data collection	Q3 2017
Final report of study results	Q1 2018

5 AMENDMENTS AND UPDATES

This protocol follows the guidelines from the European Medicines Agency (EMA) EMA/623947/2012 regarding the format and content of a noninterventional postauthorisation safety study (PASS) [1].

In the event that an amendment to this protocol is required (see Section 9.12), it will be classified into one of the following two categories:

- **Nonsubstantial amendments** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) or competent authorities for information purposes.
- **Substantial amendments** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on the safety or physical or mental integrity of the patients or that may affect the study results and their interpretation, such as changes to the objectives of the study, to the study population, to the sample size, to the definitions of the main exposure, outcome and confounding variables and to the analytical plan (as per Module VIII of the Good Pharmacovigilance Practice (GVP) guidelines for PASS) [2].

Any substantial amendments to the protocol will be submitted, before their implementation, in accordance with Article 107 of Directive 2001/83/EC [3].

6 MILESTONES

Milestone	Planned date
Registration in the EU PAS register	Q2 2015
Start of data collection	Q3 2015
Interim Progress Report	Q3 2016 or when half of the recruitment will be reached
End of data collection	Q3 2017
Final report of study results	Q1 2018

7 RATIONALE AND BACKGROUND

Colonoscopy plays an important role in the diagnosis and management of colorectal diseases. In many countries, this procedure remains the gold standard for the early detection of colorectal cancer and reduction of mortality by early detection and treatment of the cancer or precancerous lesions.

Effective bowel cleansing is necessary to ensure good visualisation of the entire colonic mucosa during colonoscopy and detection and removal of all suspicious lesions in asymptomatic individuals before progression to cancer. This requires the use of efficacious, safe, palatable and well tolerated bowel cleansing [4-10].

Patient willingness to complete the full preparation has been shown to be an important determinant of the quality of bowel preparations and is a key factor for agreeing to repeat screening within recommended intervals. Factors contributing to nonadherence to preparation instructions include ingestion of a high volume of bad tasting solution and patient discomfort.

During bowel cleansing, regardless of the formulation of the drug taken, large amounts of fluid are needed in order to fully evacuate the colon. The osmotic effect of the hypertonic/hyperosmotic preparation, when ingested with a large volume of water, produces copious watery diarrhoea, which is the expected outcome. Some potential AEs could occur during and following the preparation, some of which may be related to dehydration. Therefore, instructions to drink a sufficient amount of clear liquids prior to, during and following the hypertonic/hyperosmotic bowel cleansing preparation must be given to the patient to maintain hydration. The dietary recommendations suggest having a light breakfast the day before the procedure and all the other meals until the procedure is performed should consist of clear liquids such as water, black tea, black coffee, carbonated or noncarbonated soft drinks, strained fruit juices and clear/strained soups (see patient's leaflet in Appendix 1).

All bowel preparations can potentially produce undesirable effects such as headache, discomfort, abdominal distension, abdominal pain, nausea and vomiting [11]. These adverse effects are transitory and generally tolerated in the majority of the patients.

A reduced volume of solution with an acceptable taste [12] given in a split dose regimen i.e. the night prior and the morning of the procedure [13, 14] appears to be the most well supported of all preparations, without clinically significant fluid or electrolyte disorders [15, 16].

In October 2009, Ipsen Pharma SAS acquired exclusive marketing rights from Braintree Laboratories Inc. for the manufacturing, marketing and distribution of Braintree's proprietary formulation BLI800 (Eziclen®/Izinova®) which was developed in the United States of America (USA) and approved in 2010 by the Food and Drug Administration (FDA) for colonic cleansing before colonoscopy.

BLI800 (Eziclen®/Izinova®) is an oral solution composed of the sulphate salts of sodium, potassium and magnesium. Its composition per dose (bottle) includes 17.510 g of sodium sulphate anhydrous, 3.276 g of magnesium sulphate heptahydrate and 3.130 g of potassium sulphate. This new osmotic solution is absorbed via a saturable transport system. The unabsorbed sulphate in the intestine

exerts an osmotic action and produces diarrhoea, leading to effective bowel cleansing, without producing calcium salt precipitation in renal tubules [17]. Diarrhoea is the expected outcome of the bowel cleansing preparation and occurs after BLI800 (Eziclen®/Izinova®) ingestion.

Preclinical Safety Data

Long term studies in animals to evaluate the carcinogenic potential of sodium, magnesium and potassium sulphate salts have not been performed.

Studies to evaluate the possible impairment of fertility or mutagenic potential of sodium, magnesium and potassium sulphate salts have not been performed.

Administration of sodium, magnesium and potassium sulphate salts by gavage to rats and dogs for 28 consecutive days at dose levels up to 5.0 g/kg/day (6.7 times the dose level given to humans for bowel preparation) was well tolerated and resulted in the intended physiological action of a poorly absorbed osmotic load, namely soft stools, diarrhoea and emesis (in dogs only) [18]. No electrolyte imbalance was noted. Renal function tests were normal and there were no microscopic findings associated with the administration of these sulphate salts including no evidence of mineral deposition in the kidney.

Based upon these results, the no observed adverse effect level for oral administration of these sulphate salts to rats and dogs for 28 consecutive days was the highest tested dose of 5.0 g/kg/day [18].

Clinical Safety Data

BLI800 (Eziclen®/Izinova®) demonstrated a high degree of bowel cleansing in two pivotal, multicentre, investigator blinded Phase III clinical studies, with both a one day and split dose regimen achievable through the ingestion of a low volume (1 litre) of salt solution associated with adequate ingestion of 2 litres of clear liquid [19-21].

More than 750 adult patients were randomised to receive BLI800 (Eziclen®/Izinova®) or a 2 litre solution of polyethylene glycol plus vitamin C and electrolytes (MoviPrep®).

In the Phase III studies, 244 patients took BLI800 (Eziclen®/Izinova®) in a split day dose manner and 194 patients in a one day dose manner.

Results confirmed the noninferiority of BLI800 (Eziclen®/Izinova®) versus the comparator with regards to the effectiveness of bowel cleansing [22].

A total of 525 patients were exposed to BLI800 (Eziclen®/Izinova®) in Phase I, II and III studies. Clinical studies also demonstrated that BLI800 (Eziclen®/Izinova®) is safe for bowel cleansing prior to colonoscopy.

No dehydration or electrolyte shift has been observed during clinical development. The most frequent AEs occurring in the Phase III studies included gastrointestinal events (nausea, vomiting, abdominal bloating/distension, cramping/pain and discomfort) and headache, events that are typically associated with all bowel preparations.

Vomiting was reported in more patients when BLI800 (Eziclen®/Izinova®) was given as a one day preparation than when a split dose regimen was followed (12.9% compared to 8.8%, respectively; Table 2).

Table 2 Summary of Common Symptoms and Adverse Events Combined for Two Pivotal BLI800 (Eziclen®/Izinova®) Studies for the ITT Population

Study	BLI800-301 One day dose		BLI800-302 Split dose	
Patients with AEs n (%)	BLI800 N=194	MoviPrep® N=193	BLI800 N=181	MoviPrep® N=183
Abdominal bloating/distension	111 (57.2)	107 (55.4)	77 (42.5)	98 (53.6)
Abdominal cramps/pain	71 (36.6)	68 (35.2)	69 (38.1)	81 (44.3)
Nausea	89 (45.9)	75 (38.9)	69 (38.1)	62 (33.9)
Vomiting	25 (12.9)	7 (3.6)	16 (8.8)	7 (3.8)
Discomfort	123 (63.4)	116 (60.1)	102 (56.4)	126 (68.9)

AE=Adverse event, ITT=Intent to treat.

Source: References 19 and 20

Special Populations

A total of 169 patients with a history of heart disease, renal failure, hypertension or diabetes were administered BLI800 (Eziclen®/Izinova®) in the two pivotal Phase III clinical trials [19, 20]. These high risk conditions, however, did not result in differences regarding the frequencies of AEs (Table 3).

Table 3 Summary of Common Symptoms and Adverse Events Combined for Two Pivotal BLI800 (Eziclen®/Izinova®) Studies for High Risk Patients

Study	BLI800-301 One day dose		BLI800-302 Split dose	
Patients with AEs n (%)	BLI800 N=84	MoviPrep® N=101	BLI800 N=85	MoviPrep® N=86
Abdominal bloating/distension	51 (60.7)	48 (47.5)	35 (41.2)	44 (51.2)
Abdominal cramps/pain	30 (35.7)	29 (28.7)	31 (36.5)	35 (40.7)
Nausea	42 (50.0)	39 (38.6)	32 (37.6)	33 (38.4)
Vomiting	12 (14.3)	4 (4.0)	9 (10.6)	2 (2.3)
Discomfort	53 (63.1)	51 (50.5)	45 (52.9)	60 (69.8)

AE=Adverse event.

Source: References 19 and 20

No overall differences in safety were observed between the elderly populations or patients with renal, cardiac or hepatic impairment and the other patients.

Thirty patients with inflammatory bowel disease (IBD) were enrolled in the two pivotal studies [19, 20]. No overall differences in safety were observed between these patients and the other patients.

Postmarketing Experience

A total of 2918 postmarketing AEs have been reported since the launch of BLI800 (Eziclen®/Izinova®) in the USA and European Union (EU), between September 2010 and August 2014. The majority of the AEs were classified as

nonserious and expected. Gastrointestinal events were the most frequent AEs (66% of postmarketing AEs) reported during the postmarketing surveillance [18].

Rationale for Drug Utilisation Study

In January 2013, the European registration procedure was successfully concluded for BLI800 (Eziclen®/Izinova®). The postapproval commitments requested that Ipsen Pharma SAS conducts a DUS to assess drug utilisation in the real life setting in a representative sample of the European target population.

The results from this European study will complement the results from a descriptive epidemiologic study sponsored by Braintree Laboratories Inc. (Study BLI800-450) that is currently ongoing in the USA to describe the incidence of AEs associated with BLI800 (SUPREP®) and other bowel preparations within the first 3 months following administration for screening colonoscopy.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

Diarrhoea is an expected outcome of bowel cleansing preparation as a consequence of the osmotic effect and can produce undesirable effects such as headache, discomfort, abdominal distension and pain, nausea and vomiting [11].

Regardless of the formulation of the drug taken, bowel preparation can potentially lead to transitory fluid and electrolyte shifts. It is therefore important for patients to follow the instructions provided with BLI800 (Eziclen®/Izinova®) to maintain hydration.

This study primarily aims at documenting the misuse of BLI800 (Eziclen®/Izinova®), defined as non-compliance in terms of insufficient liquid intake in the real life setting and the safety profile of BLI800 (Eziclen®/Izinova®), overall and in cases of misuse, in a representative sample of the European target population.

8.2 Objectives

- Primary objective: to document the misuse of BLI800 (Eziclen®/Izinova®), defined as non-compliance in terms of insufficient liquid intake, during the postapproval period in the real life setting.
- Secondary objective: to describe the safety profile of BLI800 (Eziclen®/Izinova®) in routine clinical practice, overall and in case of misuse defined as non-compliance in terms of insufficient liquid intake, and identify any immediate/acute adverse events associated with the use of BLI800 (Eziclen®/Izinova®) in special populations (i.e. the elderly and patients at risk of electrolyte shifts).

9 RESEARCH METHODS

9.1 Study Design

In order to collect data from the real life setting, the decision was taken to conduct the study as a noninterventional study. So that the decision to prescribe BLI800 (Eziclen®/Izinova®) is taken independently from the decision to enrol the patient, and to avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. However, the actual numbers will depend on the drug uptake following launch. Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure.

9.1.1 Overview

This is a noninterventional, multicentre, European, observational DUS in male and female patients receiving BLI800 (Eziclen®/Izinova®) in a postmarketing setting. BLI800 (Eziclen®/Izinova®) will be prescribed to patients requiring bowel cleansing prior to colonoscopy in accordance with the terms of the marketing authorisation. The patient's assignment should not be influenced by the study protocol and should fall within the current practice.

Thus, consecutive patients presenting to each site for a routine colonoscopy and eligible for BLI800 (Eziclen®/Izinova®) prescription in accordance with the terms of the marketing authorisation will be offered enrolment, until 65 patients/site are enrolled.

No additional diagnostic or monitoring procedures will be performed to patients and descriptive methods will be used for the analysis of collected data. Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure. Eligible patients will be included at the first visit (prescription). AEs and patterns and conditions of use documentation will be collected from the patient at the second visit (colonoscopy).

A scientific committee composed of the principal investigator and the coordinating investigator of each of the participating countries will meet for data review (interim and final analyses). The data reviewed will include demographics (special populations), misuse and safety data.

9.1.2 Justification of Design

9.1.2.1 Countries Involved in the Study

The study will be conducted in four countries where the product (Eziclen®/Izinova®) is already on the market (i.e. in the Czech Republic, Poland, Germany and the Netherlands). The study may potentially be extended to two additional European countries, after product launch in 2015 and 2016.

A feasibility study conducted across 11 European countries and more than 100 sites aimed to confirm the standard of care and to better estimate the sites recruitment capacity. Results from this feasibility study indicated that the number of participating countries could be fixed to be six at most, to include both Western and Eastern European countries, and that the number of participating sites could be limited to about 20.

9.1.2.2 Study Population

This study will include patients who are eligible for colon preparation with BLI800 (Eziclen®/Izinova®) and provide written informed consent (see Section 9.2.1 for the inclusion criteria).

Patients will be enrolled from specialised gastroenterology and hepatogastroenterology hospitals/clinics and endoscopy centres and may be inpatients or outpatients.

As the inclusion criteria for this study are broad, the population enrolled by these centres will be a good representation of the population who are prescribed BLI800 (Eziclen®/Izinova®) in the real life setting in accordance with the marketing authorisation.

9.2 Setting

9.2.1 Inclusion Criteria

All patients must fulfil the following criteria:

- They are eligible for a prescription of BLI800 (Eziclen®/Izinova®) as a cleansing bowel preparation in accordance with the marketing authorisation

And

- They sign the ICF.

A patient will only be included once.

A copy of the ICF can be found in Appendix 1.

9.2.2 Exclusion Criteria

Patients will not be included if:

- They are not eligible for a prescription of BLI800 (Eziclen®/Izinova®) as a cleansing bowel preparation in accordance with the marketing authorisation. Specifically, patients in whom there is a contraindication for use of this product, including patients with congestive heart failure, severe renal insufficiency of active inflammatory bowel disease, are not eligible for inclusion in this study.

Or

- They are prescribed a cleansing bowel preparation other than BLI800 (Eziclen®/Izinova®)

Or

- They do not give informed consent.

9.2.3 Study Population

The broad inclusion criteria stated in Section 9.2.1 will allow enrolment of a population representative of the population prescribed BLI800 (Eziclen®/Izinova®) in the real life setting. Patients with contraindications to BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation will not be included in the study.

Section 9.5 provides a discussion of the study population.

9.2.4 Study Duration

The overall duration of the study for each patient will be from signing the ICF until being discharged at the end of the colonoscopy procedure.

The overall study duration will be approximately 3 years from the BLI800 (Eziclen®/Izinova®) launch in each European country planned to be involved in this study.

The overall study duration will be approximately 2 years from the start of enrolment (first patient, first consent).

The study will be considered as started when the first patient's data are collected and will be considered as finished when the last patient's data are collected. Based on the feasibility study results, it is anticipated that the recruitment period will last 2 years.

9.2.5 Study Place

The study will be carried out by healthcare professionals in specialised gastroenterology and hepatogastroenterology and endoscopy departments.

9.2.6 Study Schedule

At each site, consecutive adult patients requiring bowel cleansing prior to colonoscopy and eligible for BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation will be offered participation, until 65 patients/site have signed the ICF. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. However, the actual numbers will depend on the drug uptake following launch. Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure.

9.2.6.1 First Visit (Prescription)

At the first/inclusion visit, informed consent, details of patient demographics and characteristics, medical and surgical history, indication for bowel preparation, dosing regimen (one day or split dose regimen), and prior (1 month) and concomitant medications will be collected. Vital signs (blood pressure, heart rate, height and body weight) and physical examination findings will be recorded. ECG and local laboratory test results dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake will also be recorded when available.

During this visit, the physician will also provide a patient's leaflet and explain to the patient the requirement to record preparation and clear liquid consumption (usage and compliance), and AEs on this leaflet.

9.2.6.2 Second Visit (Colonoscopy)

The second visit at the time of colonoscopy will involve the collection of available ECG and local laboratory test results (dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake), and details of any concomitant medications taken since the first visit. In addition, physical examination findings will be recorded and the investigator will assess cleansing level of the colon at colonoscopy according to the four level scale described in Section 9.7.4.6. The patient's leaflet will be collected and will be used as the source of the information on patterns and conditions of use of BLI800 (Eziclen®/Izinova®), as well as for AEs. The AEs reported by the patient on his/her leaflet will be reviewed by the investigator (or authorised delegate) and recorded in the eCRF. The investigator (or authorised delegate) will also record any AEs collected during the patient's interview and medical exam in the eCRF.

9.2.7 Study Visit(s)

After signing the ICF, data will be collected and recorded as described in Table 4:

Table 4 Data to be Collected in the eCRF

Assessment/Procedure	First visit (prescription)	Second visit (colonoscopy)
Written informed consent	X	
Patient demographics and characteristics (age and gender)	X	
Vital signs (blood pressure, heart rate, height and body weight)	X	
Physical examination	X	X
Medical and surgical history	X	
Indication for bowel preparation	X	
Prior[a] and concomitant medications	X	X
Specific test results[b]	X	X
Patterns and conditions of use of BLI800 (Eziclen®/Izinova®)[c]		X
Cleansing level assessment[d]		X
AEs[e]	X	X

AE=adverse event; ECG=electrocardiogram; eCRF=electronic case report form; IBD=inflammatory bowel disease; INR=international normalised ratio.

a prior medications will be recorded for the preceding 1 month.

b results from ECG and local laboratory assessments dated no more than 7 days prior to BLI800 (Eziclen®/Izinova®) intake will be recorded when available. Collection of laboratory results will be restricted to the following list: serum electrolytes, albumin, INR, creatinine, liver enzymes, bilirubin, uric acid and glucose.

c patients will record the following information on the patient's leaflet: the remaining volume of product preparation, as well as the date(s) and time(s) of BLI800 (Eziclen®/Izinova®) intake, and the time(s), remaining volume and nature of additional liquids.

d cleansing level of the colon will be assessed by the investigator at colonoscopy according to a four level scale, as described in Section 9.7.4.6.

e AEs are to be collected from informed consent until discharge after the end of the colonoscopy procedure. At the second visit, AEs will be collected by the investigator from the patient's leaflet, and the patient's interview and medical exam during the visit.

9.2.8 Study Discontinuation/Withdrawal

As this is a noninterventional study, no specific withdrawal criteria are specified. Patients are free to withdraw consent at any time. Data will be collected up to the time of withdrawal of consent but no additional information will be collected after this time.

9.2.9 Early Study Termination

The sponsor may terminate this study early, after consultation with the relevant regulatory authorities, if the study becomes futile i.e. if there is insufficient patient enrolment despite implementation of all reasonable measures to improve enrolment, including additional sites and European countries.

9.3 Variables

The following variables will be recorded and will allow assessment of the patterns and conditions of use of BLI800 (Eziclen®/Izinova®):

- Patient demographics and characteristics (age and gender)
- Vital signs (blood pressure, heart rate, height and body weight)
- Physical examination
- Medical and surgical history

- Indication for bowel preparation
- Patterns and conditions of use of BLI800 (Eziclen®/Izinova®)
  - Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions)
  - Date(s) and time(s) of BLI800 (Eziclen®/Izinova®) intake
  - Patient compliance to the prescription, derived from the recorded remaining volume of BLI800 (Eziclen®/Izinova®) solution, and time(s), remaining volume and nature of additional clear liquids to maintain hydration (see Section 9.7.4.6)
- Prior (1 month) and concomitant medications.
- Specific test results: ECG and local laboratory results from assessments performed before the anaesthesia and the colonoscopy and dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake will be recorded when available. Collection of local laboratory results will be restricted to the following list: serum electrolytes, albumin, INR, creatinine, liver enzymes, bilirubin, uric acid and glucose.
- Efficacy evaluation
  - Cleansing level of the colon, assessed by the investigator at colonoscopy according to a four level scale (see Section 9.7.4.6).
- Safety evaluation
  - AEs will be collected from when the ICF is signed until discharge after the end of the colonoscopy procedure. A patient's leaflet will be distributed to the patient at the first visit, on which the patient will be instructed to record any AE experienced after product intake and prior to the procedure. The investigator (or authorised delegate) will collect the leaflet at the second visit and will record any AEs in the eCRF. During the second study visit, AEs will be collected by the investigator from the patient's leaflet, and the patient's interview and medical exam. The investigator will decide on the requirement for any follow up of AEs persisting beyond discharge after the procedure according to normal clinical practice.
  - The overall incidence of AEs will be presented by MedDRA SOC and PT, and by number and percentage

9.4 Data Sources

The data will be collected and recorded on:

- The patient's leaflet
- An eCRF

All data for each patient will be collected in accordance with normal clinical practice and no additional assessments or tests considered as interventional will be required. Each patient will be identified by a unique alphanumeric code, allowing the data recorded in the patient's leaflet to be linked with the data recorded in the eCRF.

9.4.1 Data Collection

The following variables will be recorded by the patient when taking the BLI800 (Eziclen®/Izinova®) solution on a patient's leaflet provided at the first visit and transcribed to the eCRF at the second visit (colonoscopy; see Appendix 1):

- Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) (primary objective).
- Date(s) and time(s) of BLI800 (Eziclen®/Izinova®) solution intake.
- Remaining volume of BLI800 (Eziclen®/Izinova®) solution.
- Time(s), remaining volume and nature of additional clear liquids.
- AEs.

All the other variables (see Section 9.3) will be recorded by the investigator on an eCRF after the patient has signed the ICF.

During the second visit, the patient's leaflet will be collected and its content reviewed by the investigator (or authorised delegate) prior to the colonoscopy. The investigator (or authorised delegate) will interview the patient, and review and record the appropriate data from the patient's leaflet and discussion with the patient in the eCRF.

9.4.2 Data Validation and Recording

The investigator is responsible for the validity of all data collected at the site.

In compliance with Good Pharmacoepidemiology Practices (GEP/GPP), the medical records/medical notes etc. should be clearly marked and permit easy identification of a patient's participation in this study.

The sponsor is responsible for monitoring the data to verify that they are accurate and complete and that the study is conducted in compliance with the protocol, GEP/GPP and regulatory requirements.

9.5 Study Size

It is planned to recruit 1285 patients. This sample size is based on the primary endpoint, that is to say the proportion of non-compliant patients defined as having taken less than 75% of the prescribed hydration volume (2 L). The sample size for special population should represent 30% of the recruited patients, that is, 385 patients. Assuming a proportion of 50%, this sample size will allow estimating the proportion with a 2- sided 95% level of confidence and a precision of +/- 5%. The total included population will represent 1285 patients (nQuery advisor).

A feasibility study conducted across 11 European countries and more than 100 sites aimed to confirm the standard of care and to better estimate the sites recruitment capacity. Results from this study indicated that the number of participating countries could be fixed to be six at most, to include both Western and Eastern European countries, and that the number of participating sites could be limited to about 20.

In order to meet the primary protocol objective, sites will be identified from a mass mailing issued to all potential sites based on their capabilities to conduct a noninterventional study in the indication. Equi-repartition between practice types ("specialised gastroenterology, hepatogastroenterology departments or referral

centres", "endoscopy departments/non referral centres") will be attempted prior to study initiation to ensure that at risk patients are enrolled, as specialised and referral centres are more likely to recruit patients with infrequent disease, or in-patients with diseases where the preparation may require more precautions.

To avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. However, the actual number of enrolled patients per site will depend on the drug uptake following launch.

Special populations will be included. Details of the expected representation of each case are provided below, based on the current knowledge and epidemiology:

- elderly patients (age ≥65): represent 30% of the general patient population for the indication.
- patients with hepatic insufficiency: represent up to 10% of the general population, likely to be included in hepatogastroenterology centres.
- patients with hyperuricaemia or history of gout: represent 10% of the general population, often associated with cardiovascular risk factors and age.

9.6 Data Management

Data management will be conducted by a Contract Research Organisation (CRO) contracted by the sponsor. All data management procedures will be completed in accordance with the sponsor and the contracted CRO Standard Operating Procedures.

Data will be collected in the eCRF in compliance with FDA 21 Code of Federal Regulations (CFR) Part 11. The data collected by patients in the patient's leaflet will be recorded by the investigator (or authorised delegate) at site in the eCRF. Electronic data capture will be utilised for collecting patient data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries on the eCRF will be made under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be legally binding equivalent of the handwritten signature. Only sponsor authorised users will be given access to the eCRF as appropriate to their study responsibilities. All users must have successfully undergone software application training prior to entering data into the eCRF.

The sponsor and the CRO will ensure that appropriate data entry methods are used. Each enrolled patient will be attributed a patient identification code that will be used in the storage and data management.

The sponsor and the CRO will ensure that an appropriate eCRF is developed to capture the data accurately and suitable queries are raised to resolve any missing or

inconsistent data. Any queries generated during the data management process will be tracked by the contracted data management CRO.

As required by Good Clinical Practice (GCP), the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF (see Section 8).

9.6.1 Data Collection

The coding of AE, medical history, concomitant medication, concomitant non-drug therapies and concomitant surgery terms will be performed by the contracted CRO, directed, reviewed and approved by the sponsor. Concomitant medications will be coded using the World Health Organisation Drug Dictionary (WHODRUG) and AEs/medical and surgical history and nondrug therapy terms will be coded using MedDRA.

9.6.2 Data Archiving and Retention

Data archiving and retention will be in accordance with Article 12.2 of the implementation regulations (EU/520/2012) from the EU.

Pharmacovigilance data and documents relating to individual authorised medicinal products will be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents will be retained for a longer period where EU or national laws so requires.

9.7 Data Analysis

9.7.1 Site and Patient Classification and Definitions

Screened site	Site which has been contacted for participation in the registry and confirmed that they are currently following patients who may be eligible for the registry (this includes both participating and nonparticipating sites).
Participating site	Site which has agreed to participate to the registry.
Registry patient	Patient who has at least partially taken the drug and has signed an ICF
Registry completed patient	Patient who has signed an informed consent, taken the drug and successfully completed the colonoscopy examination.

9.7.2 Analyses Population Definitions

Registry population	All registry patients
Complete population	All registry completed patients

The primary analysis will be performed on the **registry population**.

9.7.3 Sample Size Determination

It is planned to recruit 1285 patients. This sample size is based on the primary endpoint that is to say the proportion of non-compliant patients defined as having taken less than 75% of the prescribed hydration volume (2 L). The sample size for special population should represent 30% of the recruited patients, that is, 385 patients. Assuming a proportion of 50%, this sample size will allow estimating the

proportion with a 2- sided 95% level of confidence and a precision of +/- 5%. The total included population will represent 1285 patients (nQuery advisor).

Each site will be required to offer enrolment to consecutive patients requiring bowel cleansing prior to colonoscopy and eligible for BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation. All eligible patients at each study centre will be offered enrolment, until 65 patients are enrolled per site. However, the actual numbers will depend on the drug uptake following launch.

9.7.4 Statistical and Analytical Methods

As this is a descriptive study, no formal statistical testing will be carried out. However, two sided 95% CI will be calculated for each proportion or mean. Also, some inferential analyses will be performed on an exploratory basis.

Statistical analyses will be performed by a sponsor assigned CRO.

A reporting and analysis plan describing the planned statistical analyses in detail with tables, figures and listings templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS®) (Version 8 or higher).

9.7.4.1 Statistical Analyses

All statistical analyses will be presented overall as well as per BLI800 (Eziclen®/Izinova®) dosing regimen (one day or split dose) and for special populations (Section 9.5).

9.7.4.2 Site Recruitment and Patient Inclusion

Descriptive summary statistics (n, mean, SD, median, minimum and maximum) or frequency counts of the data collected during the site recruitment process (characteristics of all participating sites collected: geographical location (region/country), type of site (gastroenterology/hepatogastroenterology departments, or referral centres versus endoscopy departments, or non-referral centres), with the aim to document the characteristics of the selected sites (and the reasons for nonparticipation) will be performed. A log file with the characteristics of all study sites screened but nonparticipating versus those participating in the study, including country and healthcare provider specialty (gastroenterology versus endoscopy) will be maintained.

Sites participating in the study will be randomly selected from a list including all sites performing colonoscopies. Sites will be separated in lists per site type (referral vs non referral) and a randomization process will be applied on each list. A mass mailing (questionnaire) will then be performed on the centers retained by randomization in each list.

This process will be further refined based on the chronological order of site acceptance by a phone contact in order:

1) to confirm the site capacity to conduct the study.
2) to reach final qualification of the randomly selected recruiting sites
    - Equally balanced between referral and non-referral sites, including small and large sites,

- Proportionally dispatched across countries according to their respective whole population size.

A screening log with the characteristics of all patients screened versus those participating in the study by site will be maintained.

9.7.4.3 Demographic and Other Baseline Characteristics

Descriptive summary statistics (number of available data, number of missing data, mean, standard deviation (SD), median, minimum and maximum for continuous data, and frequency count and percentage for categorical data) will be calculated for demographic and baseline clinical characteristics. Differences in demographic and clinical characteristics between subgroups of interest will be explored through 95% confidence intervals (CIs) of the mean for the quantitative parameters and of each category for the categorical ones.

Missing data will not be replaced but they will be displayed in all relevant tables.

9.7.4.4 Patient Disposition and Withdrawals

The numbers and percentages of patients included in the registry population will be tabulated by region/country and site.

9.7.4.5 Safety Evaluation

Descriptive summary statistics of serious AEs (SAEs) and other nonserious AEs, related or unrelated to BLI800 (Eziclen®/Izinova®), will be presented.

AEs will be coded using MedDRA. Analyses and summary tables will be based upon the registry population.

Listings of AEs will be presented by patient, primary SOC and PT. The incidence of each targeted AE, as included in the Risk Management Plan as important risks and missing information, and AEs overall will be calculated, including the associated 95% CIs. Adjusted cumulative incidence of each related AE will also be calculated using Poisson regression, if a sufficient number of AEs are available to fit a model adjusting for potential confounders (including covariates like age, gender and relevant risk factors for the AE being examined).

All statistical analyses will present the overall results as well as separately for the dosing regimens (one day and split dose) and for the special populations (including gender effect).

9.7.4.6 Endpoints and Evaluations

The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration will be performed and will constitute the primary variable. The volume of water and clear liquids taken will be derived from the remaining volumes as recorded on the patient's leaflet and reported by the Investigator on the eCRF. Compliance to the hydration guidelines (2 L of water or

clear liquids) will be expressed in terms of a ratio (actual volume taken versus theoretical volume) and will be classed as follows:

- Excellent: 1:1
- Good: ≥3:4 and <1:1
- Low: <3:4 and ≥1:2
- Bad: <1:2

The primary endpoint is the proportion of non-compliant patients defined as having taken less than 75% of the prescribed hydration volume (2 L).

This proportion and its corresponding 95% confidence interval will be presented for the overall population as well as for the special populations and each of the dosing regimens (see also Section 9.7.5 for other subgroup analyses). The proportion of patients non-compliant to the volume of BLI800 (Eziclen®/Izinova®) will be analysed and presented in the same manner.

The preparation/hydration ratio between the two volume components of the preparation will also be assessed as follows:

- Adequate ratio: corresponding to 3:4 compliance for both volume of BLI800 and water/clear liquids
- Inadequate ratio: corresponding to any other compliance scenario than the "Adequate ratio" defined above

Cleansing level of the colon will be assessed by the investigator at colonoscopy using the following four level scale:

Score	Grade	Description
1	Poor	Large amounts of faecal residue, additional cleansing required
2	Fair	Enough faeces or fluid to prevent a completely reliable exam
3	Good	Small amounts of faeces of fluid not interfering with exam
4	Excellent	No more than small bits of adherent faeces/fluid

9.7.5 Subgroup Analyses

Descriptive statistics for baseline data and for the safety endpoints will be provided for each region/country. Analyses will also be stratified on the dosing regimen of BLI800 (Eziclen®/Izinova®) i.e. one day or split dose and for special populations (see Section 9.5).

Differences in demographic and clinical characteristics between subgroups of interest will be explored through 95% CIs of the mean/median for the quantitative parameters and of each category for the categorical ones.

The incidence of AEs will be analysed according to the indication for bowel preparation and special populations (see Section 9.5). The relationship of frequently occurring AEs to patient characteristics such as age, gender, dosing regimen, will be explored using forest plot representation.

9.7.6 Interim Analyses

One interim population description, compliance and safety analyses is planned to be performed once half of the population target will be included (642 patients) or at the latest 1 year after the start of data collection.

9.7.7 Final Analysis

A final population description, compliance and safety analyses will be performed after the end of data collection.

9.8 Quality Control

The investigator is responsible for the validity of all data collected at his/her site. In addition, a scientific committee composed of the Principal Investigator and the Coordinating Investigator of each participating countries, will meet for each data review (interim and final).

9.8.1 Routine Monitoring and Monitoring Procedures

A risk based approach to monitoring will be applied to this noninterventional study to ensure that the rights and welfare of the patients are respected and that the data are of an appropriate quality. Sponsor assigned monitors will conduct a combination of remote data reviews and periodic site visits to address specific site requirements and data quality.

Unscheduled on-site monitoring will be triggered according to predefined criteria stipulated in the study specific monitoring plan e.g. sustained inability to contact the investigator or research team, suspected fraud, incomplete ICFs and missing eCRFs.

9.8.2 Inspections and Auditing Procedures

Authorised personnel from external competent authorities and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 9.8.3 and to any other locations used for the purpose of the study in question.

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor representative as soon as possible, to assist with preparations for the inspection.

9.8.3 Source Data Verification

Within the framework of a noninterventional study, the source data verification will be performed by the sponsor.

The source documents must, as a minimum, contain the following:

- A statement that the patient is included in a PASS/DUS.
- The identity of the study.
- The date(s)/time(s) of intake of BLI800 (Eziclen®/Izinova®).
- The date that the written informed consent was provided by the patient.
- The date/time the patient had the colonoscopy procedure.

- The date/time of discharge after the procedure i.e. end of the study.
- Patient demographics and characteristics.
- Medical and surgical history.
- Prior and concomitant medications.
- Indication for bowel preparation.
- ECG and local laboratory results from tests performed before the anaesthesia and the colonoscopy and dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake, when available.
- Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions), remaining volume of BLI800 (Eziclen®/Izinova®), and time(s), remaining volume and nature of additional clear liquid.
- All AE related information with start and end dates.

Definitions for source data and source documents are given below:

- Source Data: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- Source Documents: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The patient must have consented to their medical records being viewed by sponsor authorised personnel and by local and possibly foreign competent authorities. This information is included in the ICF.

9.8.4 Data Quality

Monitored eCRF transferred from the investigational site to the assigned data management group will be reviewed for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the data management group/monitor for clarification/correction.

The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

9.9 Limitations of the Research Methods

This study primarily aims at documenting the misuse of BLI800 (Eziclen®/Izinova®) in the real life setting and therefore does not include a control group receiving a different bowel cleansing preparation other than BLI800 (Eziclen®/Izinova®).

Following a new product launch, the physician could reserve the use of the new drug to a well-known and simple population of patients. In order to limit this potential selection bias, enrolment will be performed in a naturalistic fashion on consecutive patients.

9.10 Other Aspects

In accordance with Article 107M of Directive 2001/83/EC outlining payments to healthcare professionals for participating in non-interventional post-authorisation safety studies, compensation to Investigators shall be restricted to time and expenses incurred. Patients will not be compensated for their participation in this study.

9.11 Regulatory Approval

As required by applicable local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where approval is required.

This study complies with the EU Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

9.12 Compliance with Good Pharmacoepidemiology Practice and Ethical Considerations

This study is a noninterventional study initiated by the marketing authorisation holder (MAH) under obligation imposed by the Reference Member State (RMS) in accordance with Articles 21a and 22a of Directive 2001/83/EC [3] and Articles 10 and 10a of Regulation (EC) N°726/2004 [23]. Therefore this study does not fall under the scope of the EU Directive 2001/20/EC of the European Parliament and of the Council of 04 April 2001.

This study is conducted in compliance with IECs/IRBs, informed consent regulations, the declaration of Helsinki [24], the GEP/GPP guidelines [25] and the protocol was designed in compliance with guidance for the format and content of the protocol of noninterventional postauthorisation safety studies [26]. In addition, this study will adhere to all local requirements.

Before initiating this study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written ICF, any consent form updates, any written information to be provided to patients and a statement from the IEC/IRB that they comply with GEP/GPP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect patient safety or data integrity are classified as

administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

9.13 Informed Consent

This is a noninterventional study, so by definition any risk to the patient associated with participation in the study relates to the use of their sensitive health information. Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature and purpose of the study to each patient, the patient's legally acceptable representative or impartial witness. In compliance with the applicable national regulations, written informed consent for the collection and use of the patient's sensitive data must be obtained prior to the patient entering the study. Sufficient time will be allowed to discuss any questions raised by the patient.

The sponsor will provide a sample ICF (Appendix 1). The final version controlled form must be agreed to by the sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient or by the patient's legally acceptable representative, and by the person (the investigator or a person designated by the investigator) who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the study as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. Patients who have completed the study should be informed of any new information that may impact on the use of their sensitive health information.

The investigator should (where applicable), with the consent of the patient, inform the patient's primary physician about their participation in the study.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

10.1 Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG).

This definition includes events occurring from the time of the patient giving informed consent until the end of the study.

10.2 Categorisation of Adverse Events

10.2.1 Intensity Classification

AEs will be classified as mild, moderate or severe according to the following criteria:

Mild: symptoms do not alter the patient's normal functioning

Moderate: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient

Severe: symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.

10.2.2 Causality Classification

The relationship of an AE with the medicinal product will be classified according to the following:

Related: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with the medicinal product in the sense that it is plausible, conceivable or likely

Not related: reports including good reasons and sufficient information (e.g. plausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the medicinal product.

10.2.3 Assessment of Expectedness

The expectedness of an AE will be assessed against the approved Summary of Product Characteristics for BLI800 (Eziclen®/Izinova®).

10.3 Recording and Reporting of Adverse Events

Investigators will be provided with adverse event reporting form(s).

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative.

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. to the medicinal product or other illness). The investigator is required to assess causality and record that assessment.

The investigator will decide on the requirement for any follow up of AEs persisting beyond discharge after the procedure according to normal clinical practice.

10.3.1 Reporting Requirements

All serious adverse events, whether they are, related/unrelated and all related non-serious events must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the Pharmacovigilance contact specified in Section 10.4.4.

Non-serious unrelated adverse events will not be subject to expedited reporting as such events are considered unlikely to contribute significant relevant new information regarding the safety of the medicinal product but will be reviewed on a quarterly basis by the Sponsor as part of routine signal detection for BLI-800.

However, the following adverse events do not need to be collected and/or reported:

- colonoscopy findings such as polyps and/or colorectal cancer as their diagnosis is the goal of the endoscopic examination ;

- misuse (specifically defined as non-compliance to the hydration guidelines), since this is the primary endpoint of the study and will be reported as such.

10.3.2 Mandatory Information for Reporting Adverse Events

The following information is the minimum that must be provided to the sponsor's Pharmacovigilance contact within 24 hours for each related AE:

- Study number.
- Centre number.
- Patient identification code.
- Description of the AE.
- Investigator's name and contact details.

The additional information included in the AE form must be provided to the sponsor or representative as soon as it is available.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary related AE considered as the foremost untoward medical occurrence from secondary related AEs which occurred as complications. The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

10.4 Serious Adverse Events

10.4.1 Definitions

A serious adverse event is any adverse event occurring at any dose that:

(1) Results in death;

(2) Is life threatening, that is an event that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death;

(3) Results in inpatient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons;

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;

(5) Results in congenital anomaly/birth defect in the offspring of a patient who received the medicinal product;

(6) Is an important medical event that may not result in death, be life threatening or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Regardless of the above criteria, any additional adverse reaction that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate safety database system.

- **Hospitalisation** is defined as any inpatient admission (even if less than 24 hours) (unless it occurs to ensure treatment compliance). For chronic or long term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit.
- **Prolongation of hospitalisation** is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. Prolongation in the absence of a participating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
- Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

10.4.2 Special Situations

This is any incidence of drug exposure during pregnancy or breast-feeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse (other than non-compliance to the hydration guidelines) or lack of therapeutic efficacy whilst using the medicinal product. A 'special situation' should be collected by the Investigator and reported to Ipsen whether or not these 'special situations' are associated with an adverse event.

10.4.2.1 Pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the medicinal product has interfered with a contraceptive method.

If the medicinal product is used during pregnancy, the outcome of the pregnancy will then need to be collected. Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor using a SAE form. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

10.4.2.2 Overdose

An overdose is any dose of the medicinal product given to a study participant that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be reported to Ipsen within 24 hours. An overdose should be reported even if it does not result in an AE.

10.4.3 Deaths

All adverse events resulting in death whilst using the medicinal product must be reported within 24 hours of the investigator knowledge of the event.

The convention for recording death is as follows:

- Adverse event term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction).
- Outcome: fatal.
- The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the adverse event term may be 'Death' or 'Sudden death'.

  All fatal outcomes should be considered as adverse events, even if this fatal outcome is not considered to be related to the medicinal product.

10.4.4 Reporting of Serious Adverse Events

All SAEs (as defined in Section 10.4.1) regardless of suspected relationship to the medicinal product must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the Pharmacovigilance contact.

SAEs should be reported using the SAE reporting form and these should be sent to Pharmacovigilance PPD or faxed (Fax: PPD

Any SAE with a suspected causal relationship to the medicinal product occurring at any other time after completion of the study must be promptly reported.

If related AEs (adverse reactions) occur with "non Ipsen products", the Investigator should inform the competent authority in the Member State where the reactions occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

10.5 Reporting to Competent Authorities

Reporting of serious and nonserious suspected adverse reactions will be done in accordance with the applicable regulatory requirements including Module VI of the EMA GVP guidelines [27].

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical study agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical study agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical study agreements, governing the relationship between the sponsor and authors (or author's institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

11.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the applicable requirements for reporting noninterventional postauthorisation safety studies, including Module VIII of the EMA GVP guidelines [28]. A final CSR will be prepared where any patient has signed informed consent, regardless of whether the study is completed or prematurely terminated. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

12 REFERENCES

1 Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies. European Medicines Agency EMA/623947/2012 from 26th September 2012.

2 Guideline on Good Pharmacovigilance Practices: Module VIII – Post-Authorisation Safety Studies. European Medicines Agency EMA/330405/2012 from 9th July 2012.

3 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Official Journal of the European Union L-311 from 28th November 2004:67-128.

4 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF: Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329:1977-81.

5 Gurudu SR, Ramirez FC, Harrison ME, Leighton J, Crowell M. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. Gastrointest Endosc 2012; 76:603-8.

6 Harewood GC, Sharma VK, Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc 2003; 58:76-9.

7 Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European Multicenter Study. Gastrointest Endosc 2005; 61:378-84.

8 Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. Quality indicators for colonoscopy. ASGE/ACG Task Force on Quality in Endoscopy. Gastrointest Endosc 2006; 63:S16-S28.

9 Rabeneck L, Paszat L. Circumstances in which colonoscopy misses cancer. Frontline Gastroenterol 2010; 1:52-8.

10 Romero RV, Mahadeva S. Factors influencing quality of bowel preparation for colonoscopy. World J Gastrointest Endosc 2013; 5:39-46.

11 Belsey J, Epstein O, Heresbach D. Systematic review: adverse event reports for oral sodium phosphate and polyethylene glycol. Aliment Pharmacol Ther 2009; 29:15-28.

12 Harewood GC, Wiersema MJ, Melton LJ 3rd. A prospective, controlled assessment of factors influencing acceptance of screening colonoscopy. Am J Gastroenterol 2002; 97:3186-94.

13 Kilgore TW, Abdinoor AA, Szary NM, Schowengerdt SW, Yust JB, Choudhary A, Matteson ML, Puli SR, Marshall JB, Bechtold ML. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a

meta-analysis of randomized controlled trials. Gastrointest Endosc 2011; 73:1240-45.

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15 Lichtenstein GR, Cohen LB, Uribarri J. Review article: Bowel preparation for colonoscopy--the importance of adequate hydration. Aliment Pharmacol Ther 2007; 26:633-41.

16 Marmo R, Rotondano G, Riccio G, Marone A, Bianco MA, Stroppa I, Caruso A, Pandolfo N, Sansone S, Gregorio E, D'Alvano G, Procaccio N, Capo P, Marmo C, Cipolletta L. Effective bowel cleansing before colonoscopy: a randomized study of split-dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions. Gastrointest Endosc 2010; 72:313-20.

17 Patel V, Nicar M, Emmett M, Asplin J, Maguire JA, Santa Ana CA, Fordtran JS. Intestinal and renal effects of low-volume phosphate and sulfate cathartic solutions designed for cleansing the colon: pathophysiological studies in five normal subjects. Am J Gastroenterol 2009; 104:953-65.

18 BLI800 Periodic Safety Update Report (PSUR). Data lock point, 05 August 2014. To be submitted on 14 October 2014.

19 Clinical study report for Braintree study BLI800-301: A safety and efficacy evaluation of BLI800 oral sulfate solution vs MoviPrep® as bowel cleansing preparations in adult patients. Dated from 28th April 2008.

20 Clinical study report for Braintree study BLI800-302: A safety and efficacy evaluation of BLI800 oral sulfate solution vs MoviPrep® as spilt-dose bowel cleansing preparations in adult patients. Dated from 28th April 2008.

21 Di Palma J, Rex D. Advances in bowel preparations: new formulation and clinical results. Gastroenterol Nurs 2011; 34:S2-8.

22 Di Palma JA, Rodriguez R, McGowan J, Cleveland Mv. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. Am J Gastroenterol 2009; 104:2275-84.

23 Regulation (EC) N°726/2004 of the European Parliament and of the Council of 31 March 2004. Official Journal of the European Union L-136/1 from 30th April 2004.

24 Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Bulletin of the World Health Organization, 2001;79:373-4.

25 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued in 1996, revised in April 2007.

26 Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies EMA/623947/2012 from 26th September 2012.

27 Guidelines on Good Pharmacovigilance Practices: Module VI - Management and Reporting of Adverse Reactions to Medicinal Products. European Medicines Agency EMA/873138/2011 from 22nd June 2012.

28 Guideline on Good Pharmacovigilance Practices: Module VIII - Post-Authorisation Safety Studies. European Medicines Agency EMA/813938/2011 from 19th April 2013.

LIST OF APPENDICES

Appendix 1 LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1			List of all the investigators and their contact details
2			ICF
3			Patient's leaflet
4			eCRF

eCRF=electronic case report form; ICF=informed consent form.

Appendix 2 EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE (ENCEPP) CHECKLIST FOR STUDY PROTOCOLS

This checklist is provided as Appendix 2.

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A multicentre, European, observational, Drug Utilisation Study (DUS) of BLI800 (Eziclen®/Izinova®) as a bowel cleansing preparation

Study reference number:
Ipsen study number 8-79-58800-001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	13 & 15
1.1.2 End of data collection[2]	☒	☐	☐	13 & 15
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	13 & 15
1.1.5 Registration in the EU PAS register	☒	☐	☐	13 & 15
1.1.6 Final report of study results.	☒	☐	☐	13 & 15

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	10 & 20
2.1.2 The objective(s) of the study?	☒	☐	☐	10 & 20
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	11 & 22
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10-11 & 21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12 & 25
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	11 & 22
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	22
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	11 & 21
4.2.4 Disease/indication?	☒	☐	☐	22
4.2.5 Co-morbidity?	☒	☐	☐	26-27
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	11 & 22

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	24-25
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	24-25
8.1.3 Covariates?	☒	☐	☐	24-25
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24-25
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	25
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24-25
8.3 Is a coding system described for:				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	27
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	27 & 29
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	27
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	25

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	28

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	28-30
10.3 Are descriptive analyses included?	☒	☐	☐	28-30
10.4 Are stratified analyses included?	☒	☐	☐	30
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	29
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25-26
11.3 Are methods of quality assurance described?	☒	☐	☐	30-32
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☒	☐ ☐	☐ ☐	21 & 32
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	32

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33-34
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	33

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	39
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	39

Comments:

When two different page numbers are given, one refers to the abstract and the other to the main body of the protocol. When the field related to the page number(s) is empty, this is because the corresponding pieces of information can be found in several sections of the document.

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Appendix 3 ADDITIONAL INFORMATION

No additional information is required for this study.

Appendix 4 AMENDMENT FORM No. 1

PROTOCOL TITLE:	A multicentre, European, observational, Drug Utilisation Study (DUS) of BLI800 (Eziclen®/Izinova®) as a bowel cleansing preparation
PROTOCOL NUMBER	8-79-58800-001
AMENDED PROTOCOL VERSION NUMBER & DATE	Final: 13August 2015 (including amendment N°1)

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**[19 FEBRUARY 2015]**	**[13 AUGUST 2015]**
Page	**Section**	**WAS**	**IS**
1	PASS Information (Country(ies) of study)	The study will be conducted in the Czech Republic, Poland, Germany and the Netherlands, where BLI800 (Eziclen®/Izinova®) is already on the market, and potentially in two other European countries, where the product will be launched during the study period (i.e. in ~~2014 and 2015~~).	The study will be conducted in the Czech Republic, Poland, Germany and the Netherlands, where BLI800 (Eziclen®/Izinova®) is already on the market, and potentially in two other European countries, where the product will be launched during the study period (i.e. in **2015 and 2016**).
11	3	**Coordinating Investigator**: <<Name, title, responsibility>> <<Contact details>>	**Coordinating Investigator: Prof. Dr. Wolfgang Fischbach** **Medizinische Klinik II** **Klinikum Aschaffenburg-Alzenau** **63739 Aschaffenburg** **Germany** **Coordinating Investigator:** **Dr. Manon Spaander** **Department of Gastroenterology** **Erasmus MC Cancer** **PO box 2040** **3000 CA Rotterdam** **The Netherlands** **Coordinating Investigator: Prof. Stepan Suchanek** **Military University Hospital** **Department of Gastrointestinal Endoscopy** **U Vojenské nemocnice 1/1200** **169 02 Praha 6** **Czech Republic**
12	4 (Study Design)	The study will be conducted in four countries where the product is already on the market (the Czech Republic,	The study will be conducted in four countries where the product is already on the market (the Czech Republic,

		Poland, Germany and the Netherlands) and potentially may also be extended to two additional European countries, after product launch in ~~2014 and 2015.~~	Poland, Germany and the Netherlands) and potentially may also be extended to two additional European countries, after product launch in **2015** and **2016.**
13	4 (Study Design)	~~Patients will be enrolled by a naturalistic strategy (consecutively), whereby all eligible patients/site will be offered enrolment until 65 patients/site are enrolled. However, the actual numbers will depend on the drug uptake following launch.~~	**To avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. The modalities for recruitment will have to be determined prior to recruitment start.**
14	4 (Variables)	**Variables** • Patient demographics and characteristics (age and gender). • Vital signs (blood pressure, heart rate, height and body weight). • Physical examination. • Medical and surgical history. • Indication for bowel preparation. • Patterns and conditions of use of BLI800 (Eziclen®/Izinova®) o Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) o Date(s) and times(s) of intake o Patient compliance to the prescription, derived from the recorded volume of BLI800 (Eziclen®/Izinova®) solution ~~taken~~, and the time(s), volume and nature of additional clear liquids ~~taken~~ to maintain hydration (see Section 9.7.4.6).	**Variables** • Patient demographics and characteristics (age and gender). • Vital signs (blood pressure, heart rate, height and body weight). • Physical examination. • Medical and surgical history. • Indication for bowel preparation. • Patterns and conditions of use of BLI800 (Eziclen®/Izinova®) o Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) o Date(s) and times(s) of intake o Patient compliance to the prescription, derived from the recorded **remaining** volume of BLI800 (Eziclen®/Izinova®) solution, and the time(s), **remaining** volume and nature of additional clear liquids to maintain hydration (see Section 9.7.4.6).

15	4 (Primary endpoint)	The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration will be performed and will constitute the primary variable. Compliance to the hydration guidelines (2 L of water or clear liquids) will be expressed in terms of a ratio (actual volume taken versus theoretical volume) and will be classed as follows: • Excellent: ≥~~90%~~ • Good: ≥~~75%~~ and <~~90%~~ • Low: <~~75%~~ and ≥~~50%~~ • Bad: <~~50%.~~	The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration will be performed and will constitute the primary variable. **The volume of water and clear liquids taken will be derived from the remaining volumes as recorded on the patient's leaflet and reported by the Investigator on the eCRF.** Compliance to the hydration guidelines (2 L of water or clear liquids) will be expressed in terms of a ratio (actual volume taken versus theoretical volume) and will be classed as follows: • Excellent: **1:1** • Good: **≥3:4 and <1:1** • Low: **<3:4 and ≥1:2** • Bad: **<1:2**
15	4 (Data Sources)	The data will be collected and recorded on: • The patient's leaflet (modalities of prescription including dosing regimen, date(s), time(s) and remaining volume of BLI800 (Eziclen®/Izinova®) ~~intake~~, time(s), remaining volume and nature of clear liquids ~~taken~~, and AEs). • An eCRF. The data collected on the patient's leaflet will be recorded in the eCRF by the investigator (or authorised delegate).	The data will be collected and recorded on: • The patient's leaflet (modalities of prescription including dosing regimen, date(s), time(s) and **remaining** volume of BLI800 (Eziclen®/Izinova®), time(s), **remaining** volume and nature of clear liquids, and AEs). • An eCRF. The data collected on the patient's leaflet will be recorded in the eCRF by the investigator (or authorised delegate).
16	4 (Study Size)	A feasibility study conducted across 11 European countries and more than 100 sites aimed to confirm the standard of care and to better estimate the sites recruitment capacity. The number of countries where the product is already on the market in 2014 is five (i.e. in the Czech Republic, Poland, Latvia, Germany and the Netherlands). Results from this feasibility study indicated that the number of participating countries could be fixed to be six at most, to include both Western and Eastern European countries, and that the number of participating sites could be limited to	A feasibility study conducted across 11 European countries and more than 100 sites aimed to confirm the standard of care and to better estimate the sites recruitment capacity. The number of countries where the product is already on the market in 2014 is five (i.e. in the Czech Republic, Poland, Latvia, Germany and the Netherlands). Results from this feasibility study indicated that the number of participating countries could be fixed to be six at most, to include both Western and Eastern European countries, and that the number of participating sites could be limited to

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<td>about 20. The study will be initiated in four countries, then potentially extended to two other European countries where the product is planned to be launched in ~~2014~~ and ~~2015~~. ~~Patients will be enrolled by a naturalistic strategy (consecutively), whereby all eligible patients at each study centre will be offered enrolment, until 65 patients are enrolled per site.~~ However, the actual numbers will depend on the drug uptake following launch.</td>
<td>about 20. The study will be initiated in four countries, then potentially extended to two other European countries where the product is planned to be launched in 2015 and 2016. To avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. The modalities for recruitment will have to be determined prior to recruitment start. However, the actual numbers will depend on the drug uptake following launch.</td>
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<td>16</td>
<td>4 (Milestones)</td>
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<table>
<tr><th>Milestone</th><th>Planned date</th></tr>
<tr><td>Registration in the European Union Electronic Register of Postauthorisation studies (EU PAS register)</td><td>Q2 2015</td></tr>
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<td>17</td>
<td>5</td>
<td>~~There are no protocol amendments or updates.~~
This protocol follows the guidelines</td>
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<tr><td></td><td></td><td>from the European Medicines Agency (EMA) EMA/623947/2012 regarding the format and content of a noninterventional postauthorisation safety study (PASS) [1].</td><td>the format and content of a noninterventional postauthorisation safety study (PASS) [1].</td></tr>
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<tr><td>24</td><td>9.1</td><td>In order to collect data from the real life setting, the decision was taken to conduct the study as a noninterventional study. So that the decision to prescribe BLI800 (Eziclen®/Izinova®) is taken independently from the decision to enrol the patient, ~~consecutive patients presenting to each site for a routine colonoscopy and eligible for BLI800 (Eziclen®/Izinova®) prescription in accordance with the terms of the marketing authorisation will be offered enrolment, until 65 patients/site are enrolled~~. However, the actual numbers will depend on the drug uptake following launch. Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure.</td><td>In order to collect data from the real life setting, the decision was taken to conduct the study as a noninterventional study. So that the decision to prescribe BLI800 (Eziclen®/Izinova®) is taken independently from the decision to enrol the patient, and to avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator’s unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. However, the actual numbers will depend on the drug</td></tr>
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<tr><td>26</td><td>9.2.6</td><td>At each site, consecutive adult patients requiring bowel cleansing prior to colonoscopy and eligible for BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation will be offered participation, until 65 patients/site have signed the ICF. However, the actual numbers will depend on the drug uptake following launch. Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure.</td><td>At each site, consecutive adult patients requiring bowel cleansing prior to colonoscopy and eligible for BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation will be offered participation, until 65 patients/site have signed the ICF. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator’s unit, Investigators will be authorised to space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. However, the actual numbers will depend on the drug uptake following launch. Patients will be followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure.</td></tr>
<tr><td>27</td><td>9.2.6.1</td><td>During this visit, the physician will also provide a patient's leaflet and explain to the patient the requirement to record preparation and clear liquid consumption (usage and compliance), and AEs.</td><td>During this visit, the physician will also provide a patient's leaflet and explain to the patient the requirement to record preparation and clear liquid consumption (usage and compliance), and AEs on this leaflet.</td></tr>
<tr><td>28</td><td>9.2.7</td><td>Table 3 Data to be Collected in the eCRF
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		Patient demographics and characteristics (age and gender)	X		Patient demographics and characteristics (age and gender)	X	
		Vital signs (blood pressure, heart rate, height and body weight)	X		Vital signs (blood pressure, heart rate, height and body weight)	X	
		Physical examination	X	X	Physical examination	X	X
		Medical and surgical history	X		Medical and surgical history	X	
		Indication for bowel preparation	X		Indication for bowel preparation	X	
		Prior[a] and concomitant medications	X	X	Prior[a] and concomitant medications	X	X
		Specific test results[b]	X	X	Specific test results[b]	X	X
		Patterns and conditions of use of BLI800 (Eziclen®/Izinova®)[c]		X	Patterns and conditions of use of BLI800 (Eziclen®/Izinova®)[c]		X
		Cleansing level assessment[d]		X	Cleansing level assessment[d]		X
		AEs[e]	X	X	AEs[e]	X	X
		AE=adverse event; ECG=electrocardiogram; eCRF=electronic case report form; IBD=inflammatory bowel disease; INR=international normalised ratio. a prior medications will be recorded for the preceding 1 month. b results from ECG and local laboratory assessments dated no more than 7 days prior to BLI800 (Eziclen®/Izinova®) intake will be recorded when available. Collection of laboratory results will be restricted to the following list: serum electrolytes, albumin, INR, creatinine, liver enzymes, bilirubin, uric acid and glucose. c patients will record the following information on the patient's leaflet: the volume of product preparation ~~taken~~, as well as the date(s) and time(s) of BLI800 (Eziclen®/Izinova®) intake, and the time(s), volume and nature of additional liquids ~~taken~~. d cleansing level of the colon will be assessed by the investigator at colonoscopy according to a four level scale, as described in Section 9.7.4.6. e AEs are to be collected from informed consent until discharge after the end of the colonoscopy procedure. At the second visit, AEs will be collected by the investigator from the patient's leaflet, and the patient's			AE=adverse event; ECG=electrocardiogram; eCRF=electronic case report form; IBD=inflammatory bowel disease; INR=international normalised ratio. a prior medications will be recorded for the preceding 1 month. b results from ECG and local laboratory assessments dated no more than 7 days prior to BLI800 (Eziclen®/Izinova®) intake will be recorded when available. Collection of laboratory results will be restricted to the following list: serum electrolytes, albumin, INR, creatinine, liver enzymes, bilirubin, uric acid and glucose. c patients will record the following information on the patient's leaflet: the **remaining** volume of product preparation, as well as the date(s) and time(s) of BLI800 (Eziclen®/Izinova®) intake, and the time(s), **remaining** volume and nature of additional liquids. d cleansing level of the colon will be assessed by the investigator at colonoscopy according to a four level scale, as described in Section 9.7.4.6. e AEs are to be collected from informed consent until discharge after the end of the colonoscopy procedure. At the second visit, AEs will be collected by the investigator from the patient's leaflet, and the patient's		

		interview and medical exam during the visit.	interview and medical exam during the visit.
29	9.3	• Patterns and conditions of use of BLI800 (Eziclen®/Izinova®) o Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) o Date(s) and times(s) of intake o Patient compliance to the prescription, derived from the recorded volume of BLI800 (Eziclen®/Izinova®) solution ~~taken~~, and the time(s), volume and nature of additional clear liquids ~~taken~~ to maintain hydration (see Section 9.7.4.6).	• Patterns and conditions of use of BLI800 (Eziclen®/Izinova®) o Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) o Date(s) and times(s) of intake o Patient compliance to the prescription, derived from the recorded **remaining** volume of BLI800 (Eziclen®/Izinova®) solution, and the time(s), **remaining** volume and nature of additional clear liquids to maintain hydration (see Section 9.7.4.6).
30	9.4.1	The following variables will be recorded by the patient when taking the BLI800 (Eziclen®/Izinova®) solution on a patient's leaflet provided at the first visit and transcribed to the eCRF at the second visit (colonoscopy; see Annex 1): • Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) (primary objective). • Date(s) and time(s) of BLI800 (Eziclen®/Izinova®) solution intake. • Volume of BLI800 (Eziclen®/Izinova®) solution taken. • Time(s), volume and nature of additional clear liquids taken. • AEs.	The following variables will be recorded by the patient when taking the BLI800 (Eziclen®/Izinova®) solution on a patient's leaflet provided at the first visit and transcribed to the eCRF at the second visit (colonoscopy; see Annex 1): • Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions) (primary objective). • Date(s) and time(s) of BLI800 (Eziclen®/Izinova®) solution intake. • Remaining volume of BLI800 (Eziclen®/Izinova®) solution. • Time(s), remaining volume and nature of additional clear liquids. • AEs.
31	9.5	~~Patients will be enrolled by a naturalistic strategy (consecutively), whereby all eligible patients/site will be offered enrolment, until 65 patients/site are enrolled.~~ However, the actual ~~numbers~~ will depend on the drug uptake following launch. Special populations will be included. Details of the expected representation of each case are provided below, based on the current knowledge and epidemiology:	**To avoid bias in the recruitment of patients, Investigators will be asked to include all consecutive patients consulting for a colonoscopy to achieve the recruitment target of 65 patients per site during a restricted and defined period. If consecutive inclusions are not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators will be authorised to**

			space the inclusions (e.g. inclusion of one subject after every two, or three, etc.), and will follow the same recruitment frequency until achievement of the recruitment target. However, the actual **number of enrolled patients per site** will depend on the drug uptake following launch. Special populations will be included. Details of the expected representation of each case are provided below, based on the current knowledge and epidemiology:
		• elderly patients: represent 30% of the general patient population for the indication.	• elderly patients (**age ≥65**): represent 30% of the general patient population for the indication.
32	9.6.1	The coding of AE, medical history ~~and~~ concomitant medication terms will be performed by the contracted CRO, directed, reviewed and approved by the sponsor. Concomitant medications will be coded using the World Health Organisation Drug Dictionary (WHODRUG) and AEs/medical and surgical history and nondrug therapy terms will be coded using MedDRA.	The coding of AE, medical history, concomitant medication, **concomitant non-drug therapies and concomitant surgery** terms will be performed by the contracted CRO, directed, reviewed and approved by the sponsor. Concomitant medications will be coded using the World Health Organisation Drug Dictionary (WHODRUG) and AEs/medical and surgical history and nondrug therapy terms will be coded using MedDRA.
34	9.7.4.6	The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration will be performed and will constitute the primary variable. Compliance to the hydration guidelines (2 L of water or clear liquids) will be expressed in terms of a ratio (actual volume taken versus theoretical volume) and will be classed as follows: • Excellent: ≥~~90%~~ • Good: ≥~~75%~~ and <~~90%~~ • Low: <~~75%~~ and ≥~~50%~~ • Bad: <~~50%.~~	The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration will be performed and will constitute the primary variable. **The volume of water and clear liquids taken will be derived from the remaining volumes as recorded on the patient's leaflet and reported by the Investigator on the eCRF.** Compliance to the hydration guidelines (2 L of water or clear liquids) will be expressed in terms of a ratio (actual volume taken versus theoretical volume) and will be classed as follows: • Excellent: **1:1** • Good: **≥3:4** and **<1:1** • Low: **<3:4** and **≥1:2** • Bad: **<1:2**
35	9.7.4.6	The preparation/hydration ratio between	The preparation/hydration ratio between

		the two volume components of the preparation will also be ~~studied~~: • ~~Excellent: >45% and ≤55% (considering that the ideal ratio is 1 L/2 L i.e. 50%)~~ • ~~Good: >40% and ≤45%, and >55% and ≤60%~~ • ~~Low: ≤40% or >60%.~~	the two volume components of the preparation will also **be assessed as follows:** • **Adequate ratio: corresponding to ≥3:4 compliance for both volume of BLI800 and water/clear liquids** • **Inadequate ratio: corresponding to any other compliance scenario than the "Adequate ratio" defined above**
36	9.7.6	One interim population description, compliance and safety analyses is planned to be performed ~~approximately~~ 1 year after the start of data collection.	One interim population description, compliance and safety analyses is planned to be performed **once half of the population target will be included (642 patients) or at the latest** 1 year after the start of data collection.
36	9.8.1	~~Nonscheduled on site~~ monitoring will be triggered according to predefined criteria stipulated in the study specific monitoring plan e.g. sustained inability to contact the investigator or research team, suspected fraud, incomplete ICFs and missing eCRFs.	**Unscheduled on-site** monitoring will be triggered according to predefined criteria stipulated in the study specific monitoring plan e.g. sustained inability to contact the investigator or research team, suspected fraud, incomplete ICFs and missing eCRFs.
37	9.8.3	• Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions), volume of BLI800 (Eziclen®/Izinova®) ~~taken~~, and time(s), volume and nature of additional clear liquid ~~taken~~.	• Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions), **remaining** volume of BLI800 (Eziclen®/Izinova®), and time(s), **remaining** volume and nature of additional clear liquid.
38	9.9	Following a new product launch, the physician could reserve the use of the new drug to a ~~well known~~ and simple population of patients. In order to limit this potential selection bias, enrolment will be performed in a naturalistic fashion on consecutive patients.	Following a new product launch, the physician could reserve the use of the new drug to a **well-known** and simple population of patients. In order to limit this potential selection bias, enrolment will be performed in a naturalistic fashion on consecutive patients.
40	10	**Management and Reporting of Adverse Events/~~Adverse Reactions~~**	**Management and Reporting of Adverse Events**
40	10.3	**10.3 Recording and Reporting of Adverse Events/ ~~Reactions~~** Investigators will be provided with ~~AE and SAE report forms~~.	**10.3 Recording and Reporting of Adverse Events** Investigators will be provided with **adverse event reporting form(s).**
41	10.3.1	~~Any related AE, nonserious or serious, independent of the circumstances or suspected cause,~~ must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the Pharmacovigilance contact	**All serious adverse events, whether they are, related/unrelated and all related non-serious events** must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the Pharmacovigilance contact

		specified in Section 10.4.4.	specified in Section 10.4.4. **Non-serious unrelated adverse events will not be subject to expedited reporting as such events are considered unlikely to contribute significant relevant new information regarding the safety of the medicinal product but will be reviewed on a quarterly basis by the Sponsor as part of routine signal detection for BLI-800.** **However, the following adverse events do not need to be collected and/or reported:** **- colonoscopy findings such as polyps and/or colorectal cancer as their diagnosis is the goal of the endoscopic examination ;** **- misuse (specifically defined as non-compliance to the hydration guidelines), since this is the primary endpoint of the study and will be reported as such.**
41	10.3.2	**10.3.2 Mandatory Information for Reporting ~~Related~~ Adverse Event~~/Reaction~~** The following information is the minimum that must be provided to the sponsor's Pharmacovigilance contact within 24 hours for each related AE: • Study number. • Centre number. • Patient identification code. • Description of the ~~related~~ AE. • Investigator's name and contact details. The additional information included in the AE form must be provided to the sponsor or representative as soon as it is available. The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary related AE considered as the foremost untoward medical occurrence	**10.3.2 Mandatory Information for Reporting Adverse Events** The following information is the minimum that must be provided to the sponsor's Pharmacovigilance contact within 24 hours for each related AE: • Study number. • Centre number. • Patient identification code. • Description of the AE. • Investigator's name and contact details. The additional information included in the AE form must be provided to the sponsor or representative as soon as it is available. The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary related AE considered as the foremost untoward medical occurrence

		from secondary related AEs which occurred as complications.	from secondary related AEs which occurred as complications. **The investigator should also provide the batch number and expiry date of the concerned product wherever possible.**
41	10.4.1	A serious adverse ~~reaction~~ is any adverse ~~reaction~~ occurring at any dose that: • …	A serious adverse **event** is any adverse **event** occurring at any dose that: • …
42	10.4.2		**10.4.2 Special Situations** **This is any incidence of drug exposure during pregnancy or breast-feeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic efficacy whilst using the medicinal product. A 'special situation' should be collected by the Investigator and reported to Ipsen whether or not these 'special situations' are associated with an adverse event.**
43	10.4.2.1	**10.4.2 Pregnancy** Pregnancy itself is not regarded as an adverse ~~reaction~~ unless there is a suspicion that the medicinal product has interfered with a contraceptive method. If the medicinal product is used during pregnancy, the outcome of the pregnancy will then need to be collected. Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor using a SAE form. The sponsor will request further information from the investigator as to the ~~curse~~ and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.	***10.4.2.1 Pregnancy*** Pregnancy itself is not regarded as an adverse **event** unless there is a suspicion that the medicinal product has interfered with a contraceptive method. If the medicinal product is used during pregnancy, the outcome of the pregnancy will then need to be collected. Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor using a SAE form. The sponsor will request further information from the investigator as to the **course** and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.
43	10.4.2.2		***10.4.2.2 Overdose*** **An overdose is any dose of the medicinal product given to a study participant that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be reported to Ipsen within 24 hours. An overdose should be reported even if it does not result**

			in an AE.
43	10.4.3	All adverse ~~reactions~~ resulting in death whilst using the medicinal product must be reported within 24 hours of the investigator knowledge of the event. The convention for recording death is as follows: • Adverse ~~reaction~~ term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction). • Outcome: fatal.The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the adverse ~~reaction~~ term may be 'Death' or 'Sudden death'.	All adverse **events** resulting in death whilst using the medicinal product must be reported within 24 hours of the investigator knowledge of the event. The convention for recording death is as follows: • Adverse **event** term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction). • Outcome: fatal. • The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the adverse **event** term may be 'Death' or 'Sudden death'. **All fatal outcomes should be considered as adverse events, even if this fatal outcome is not considered to be related to the medicinal product.**
43	10.4.4	All SAEs (as defined in Section 10.4.1) regardless of suspected relationship to the medicinal product must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the Pharmacovigilance contact. SAEs should be reported using the SAE reporting form and these should be sent to Pharmacovigilance PPD or faxed PPD Any SAE with a suspected causal relationship to the medicinal product occurring at any other time after completion of the study must be promptly reported.	All SAEs (as defined in Section 10.4.1) regardless of suspected relationship to the medicinal product must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the Pharmacovigilance contact. SAEs should be reported using the SAE reporting form and these should be sent to Pharmacovigilance PPD or faxed PPD Any SAE with a suspected causal relationship to the medicinal product occurring at any other time after completion of the study must be promptly reported. **If related AEs (adverse reactions) occur with "non Ipsen products", the Investigator should inform the competent authority in the Member State where the reactions occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	**8-79-58800-001**

AMENDED PROTOCOL VERSION NUMBER & DATE	Final: 13 August 2015 (including amendment N°1)	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
REASON(S) FOR CHANGES	• Revision to the adverse event collection and reporting section to ensure the protocol is in compliance with GVP Module VI obligations. • MHRA inspection deliverable.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*