[redacted]	**Statistical Analysis Plan**
	Sponsor: Alfasigma S.p.A. **Protocol: VE-CIP2001/2021**

VE-CIP2001/2021

Velusetrag for the treatment of Chronic Intestinal Pseudo-Obstruction (CIPO). A multicenter, double-blind, placebo-controlled, cross-over, multiple (n=1) trial

Author:	[redacted]
Document status:	Final version 2.0
Release date:	10-MAY-2023

[redacted]	**Statistical Analysis Plan** **Sponsor: Alfasigma S.p.A.** **Protocol: VE-CIP2001/2021**

Document History

Status and Version	Release Date	Change Description	Reason/Comment
Draft Version 0.1	04-FEB-2022	N.A.	N.A.
Draft Version 0.2	15-FEB-2022	Internal Review	Internal Review
Draft Version 0.3	24-MAR-2022	The following section are updated: 1.1 (to explain why CMH test is not reported); 3.1, 3.3.1, 4.2, 5, 6.2 (minor changes); 6.3.1, 6.3.2 (put reference and further details are included); 6.3.4 (minor changes); 6.4.3, 6.4.4, 6.4.5, 6.4.6 (the baseline used for changes computation is updated); 6.5 (details for subgroup analysis are included) and 8 (appendix of [redacted] scoring method reported).	Sponsor's review
Draft Version 0.4	12-APR-2022	Sections 1.1, 4.4.1, 6.3.2.1 are updated. Minor changes in sections 4.2, 5, 6.3.1, 6.3.2.3, 6.3.2.7, 6.3.2.8, 6.3.2.14, 6.4.5, 6.4.6, 6.5. Description of switch added in section 6.1.	Sponsor's review Internal review
Draft Version 0.5	30-MAY-2022	Sections related to efficacy endpoint are updated.	Sponsor's review
Draft Version 0.6	15-FEB-2023	Section 1.1 Changes from The Study Protocol, Definition of baseline and first/last administration of study treatment in section 4.2 Definition, section 4.4.2. Handling of Missing Data/Imputation/Censoring Rules, section 6.1 Study subjects, section 6.3.2.6 [redacted], section 6.3.2.8 [redacted], section	Sponsor's and internal review

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Status and Version	Release Date	Change Description	Reason/Comment
		6.3.2.14. Concentration of velusetrag and THRX-830449 metabolite, section 6.4.4 laboratory parameters and section 6.4.6 other safety parameters are updated. Minor changes are applied for Sections related to efficacy endpoint.	
Draft Version 0.7	13-MAR-2023	"Patient" replaced with "Subject". Start of treatment replaced with pre-treatment. Column "Endpoints" of section 2 updated for safety and tolerability secondary objective. Section 3.3.3 updated included further details to identify prohibited medication. Definition of study phases, Figure 2 and definition of baseline/reference are updated in section 4.2. NOPD03 is included in Table 6.1-1. Details related to the sort of outputs of medical history and prior medication are included in section 6.2. The "abnormal" category of physical examination is splitted in "abnormal CS" and "abnormal NCS" in section 6.2. A listing of [redacted] and gastrointestinal symptoms is added in section 6.3.1. Descriptive tables by treatment sequence and period are deleted for primary endpoint (section 6.3.1), [redacted]	Sponsor's review

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Status and Version	Release Date	Change Description	Reason/Comment
		[redacted]	

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Status and Version	**Release Date**	**Change Description**	**Reason/Comment**
		[redacted]	
Final Version 1.0	15-MAR-2023	First Final Release	Sponsor's approval
Draft Version 1.1	20-APR-2023	Section 1.1 is updated to report the decision to not considered the variable stratum in the efficacy analyses and all efficacy sections are updated consequently (i.e., 6.3.1, 6.3.2.1, 6.3.2.2, 6.3.2.4, 6.3.2.8). Section 6.1 is updated to better clarify how subject disposition will be described and to drop tables by stratum. Time from CIPO diagnosis date to informed consent signature described in Section 6.2 is computed in years instead of months. The analysis of primary endpoint on FAS is removed in section 6.3.1. Section 6.3.2.9 related to [redacted] is updated including additional details. Section 6.3.2.11 [redacted] and section 6.3.2.13 [redacted] are updated to consider the variables as	Sponsor's review

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Status and Version	Release Date	Change Description	Reason/Comment
		categorical and to include data collected for wash-out/follow-up period and statistical model for [redacted] are removed. Formal adjustment for section 6.4.3. Further details are included for listings with abnormal values in section 6.4.4 and 6.4.6. [redacted] are updated in section 6.4.4.	
Draft Version 1.2	09-MAY-2023	Section 1.1 updated with further details on binary outcome and count data. Fisher exact test was included in the section 6.3.2.2 and 6.3.2.13. ATC codes to identify opioids treatments is section 3.3.3 were update as well as the ATC code to identify patients who took antibiotics in section 6.3.2.7. Including also start date for prior medications (including the [redacted] start date of medical history condition on which imputation rules for partial dates will be applied to compute the study day. Management of [redacted] collected with different unit of measurements where there isn't conversion faction applicable to uniform the unit are described for [redacted] Similarly, management of [redacted] collected as greater than (>) or lower than (<) will be also described. Mixed models for efficacy parameters considered as continuous variables were updated considering the reference of	Sponsor's review

[redacted]	**Statistical Analysis Plan** **Sponsor: Alfasigma S.p.A.** **Protocol: VE-CIP2001/2021**

Status and Version	Release Date	Change Description	Reason/Comment
		Model 2 described in the publication of Chen X, Chen P "A Comparison of Four Methods for the Analysis of N-of-1 Trials" PLoS One. 2014 Feb 4;9(2):e87752. doi: 10.1371/journal.pone.0087752. eCollection 2014. Due to the different approach adopted for continuous variables, the Mixed model planned for binary outcome was removed also due to possible convergence problems. The McNemar Bowker's test planned for [redacted] and [redacted] was replaced with Fisher exact test to compare treatment. Formal adjustments.	
Final Version 2.0	10-MAY-2023	Second Final Release	Sponsor's approval

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Authorization

The signatures on this page indicate review and approval of the Statistical Analysis Plan, version 2.0, dated May 10, 2023.

	Name	Function	Signature	Date
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Alfasigma S.p.A [redacted] / [redacted]	[redacted]	[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 10-May-2023 | 19:31 CEST [redacted]	
Alfasigma S.p.A [redacted] / [redacted]	[redacted]	[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 10-May-2023 | 23:00 CEST [redacted]	

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[redacted]

6.4. [redacted]

LIST OF ABBREVIATIONS

5-HT_4	5-hydroxytryptamine receptor 4
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransaminase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BP	Blood pressure
CH_4	Methane
CIPO	Chronic intestinal pseudo-obstruction
CRF	Case report form
CSR	Clinical Study Report
CYP(3A4)	Cytochrome P450 (isozyme 3A4)
ECG	Electrocardiogram
eCRF	Electronic-case report form
EFU	End of follow up
EOT	End of treatment
ES	Effect size
ESV	Early switch visit
ETV	Early termination visit
FAS	Full analysis set

H_2	Hydrogen
[redacted]	[redacted]
ICF	Informed consent form
IWRS	Interactive web response system
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities (MEDDRA®)
mFAS	Modified full analysis set
NOPD	Non-protocol deviation
PPS	Per protocol set
PT	Preferred term
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SOC	System organ class
SOT	Start of treatment
SS	Safety set
T3	Triiodothyronine
T4	Thyroxine
[redacted]	[redacted]
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides details on the planned statistical analysis for study VE-CIP2001/2021 (CIPO) based on the study protocol final version 1.0 of May 24, 2021.

1.1. Changes from The Study Protocol

The endpoints "[redacted]" reported in section 5.2 SECONDARY STUDY OBJECTIVES AND ENDPOINTS of study protocol are analysed [redacted]

The Handling of Missing and Incomplete Data for primary endpoint has been modified in case of pre-treatment value missing. [redacted]
The reason for this is to reduce data heterogeneity between subjects [redacted]

In addition, missing imputation methodology will be applied only for the primary endpoint of the study while all other secondary endpoints will be based on observed data. For this reason, the rules explained in section 16.3.5 Handling of Missing and Incomplete Data of study protocol for the other endpoints are not reported since not applied.

[redacted]

All efficacy analyses, originally planned to be stratified by randomization stratum, will be performed only overall since all patients were randomized to Stratum 2 [redacted]), except one that was randomized to Stratum 1 [redacted]

For the binary outcome (Proportion of subjects with 1-point improvement in [redacted]), odds ratio and confidence interval using logistic model will be computed while the Cochran-Mantel-Haenszel test will not be performed due to strata distribution and it will be substituted with Fisher Exact test.

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Number of [redacted] and number of [redacted] will be analyzed as categorical variables and will be separately analyzed for treatment and wash-out/follow-up period. [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	VARIABLES	ENDPOINTS
Primary study objective: To investigate the efficacy of velusetrag in improving the symptoms severity associated with CIPO, in subjects with idiopathic CIPO and CIPO secondary to neurodegenerative or demyelinating conditions (e.g., Parkinsonian Syndromes, multiple sclerosis etc.).	Rating of each symptom (i.e., abdominal pain, bloating, nausea and vomiting) using a Likert scale from 0=Absent to 4= Extremely severe (precluding daily activities).	**Primary study endpoint:** Change in weekly global gastrointestinal symptoms average index score* from pre-treatment to the end of each treatment period. **The weekly global gastrointestinal symptoms average index score is obtained by averaging the scores for each of the 4 symptoms assessed weekly: abdominal pain, bloating, nausea and vomiting.* Rating of symptoms (i.e. abdominal pain, bloating, nausea and vomiting) is using a recall period of 7 days and a Likert scale with the following categories: 0 – Absent 1 - Mild (not influencing usual activities) 2 - Moderate (diverting from, but not urging modification of, usual activities) 3 - Severe (influencing usual activities markedly enough to urge modifications)

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OBJECTIVES	VARIABLES	ENDPOINTS
		4 - Extremely severe (precluding daily activities)
[redacted]		

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OBJECTIVES	VARIABLES	ENDPOINTS
[redacted]		

[redacted]	**Statistical Analysis Plan** **Sponsor: Alfasigma S.p.A.** **Protocol: VE-CIP2001/2021**

OBJECTIVES	VARIABLES	ENDPOINTS
[redacted]		

[redacted]	**Statistical Analysis Plan** **Sponsor: Alfasigma S.p.A.** **Protocol: VE-CIP2001/2021**

OBJECTIVES	VARIABLES	ENDPOINTS
[redacted]		

[redacted]	**Statistical Analysis Plan** **Sponsor: Alfasigma S.p.A.** **Protocol: VE-CIP2001/2021**

OBJECTIVES	VARIABLES	ENDPOINTS
[redacted]		

3. BACKGROUND AND RATIONALE

3.1. Overall Study Design and Plan Description

This is a phase II, multicenter, double-blind, placebo-controlled, two-treatment four-period cross-over, multiple (n=1) trial to evaluate the efficacy and safety of velusetrag 15 mg once a day, compared to placebo, in subjects with a diagnosis of idiopathic CIPO or CIPO secondary to primary neurodegenerative or demyelinating conditions (e.g., Parkinsonian Syndromes, multiple sclerosis, etc.).

Eligible subjects will be treated for 4 periods of 4 weeks each with either velusetrag 15 mg (2 periods) or placebo (2 periods), once daily, with a wash-out period of 2 weeks between treatment periods. The scheme of study design is provided in Figure 1 below.

Figure 1: Schematic study design

[redacted]

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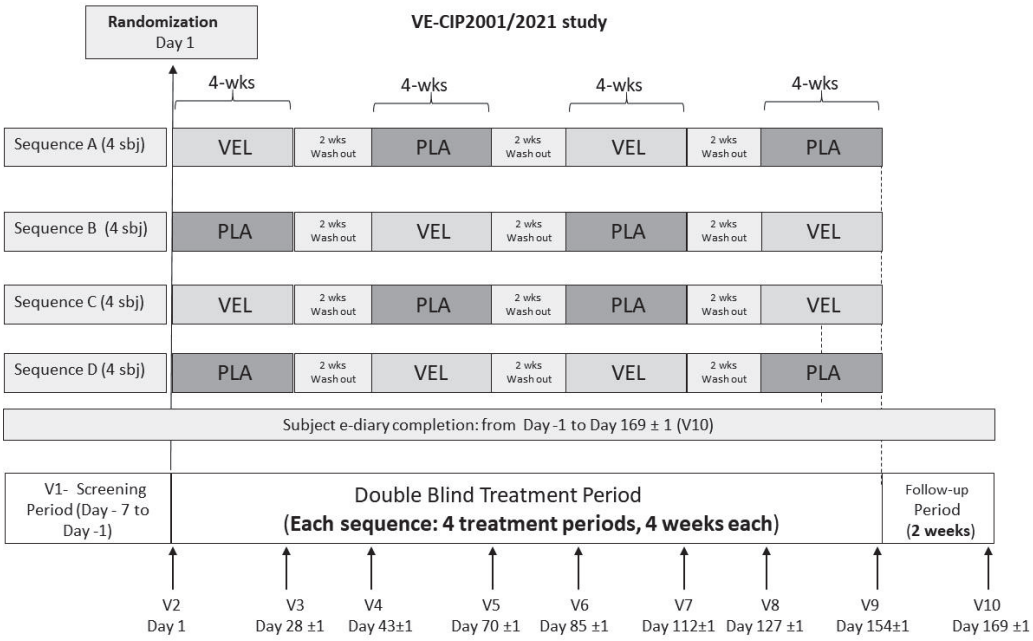

After an up to 7-day screening period (from Day -7 to Day -1, V1), at randomization visit (V2), eligible subjects will be randomly allocated to one of the following four sequences:

A. VEL-PLA-VEL-PLA
B. PLA-VEL-PLA-VEL
C. VEL-PLA-PLA-VEL
D. PLA-VEL-VEL-PLA

Where:
VEL= velusetrag 15 mg once daily for 4 weeks.
PLA= matching placebo once daily for 4 weeks.

There will be a 2-week wash-out period between each treatment period and a final 2-week follow-up period at the end of the last treatment period.

Subjects will be assessed during a total of 10 visits during the study, as detailed in the Study Schedule of Assessments, including the screening visit, a start of treatment visit (SOT) and an end of treatment visit (EOT) for each of the 4 treatment periods, for a total of 8 visits, and a final End of Follow up Visit (EFU), 2 weeks after the end of the last treatment period.

If the subject cannot go back to the clinical center for one or more of the following visits: EOT- 2 (Visit 5), EOT- 3 (Visit 7), EOT- 4 (Visit 9), End Of Follow Up (EFU, Visit 10) or in case of an early termination visit (ETV), the visit will be scheduled at the subject's home and will be performed by a home nursing service. The clinical study staff at the clinical center may also attend the visit remotely.

Overall, each subject will be involved in the study for a screening period of up to 7 days before randomization and approximately a 24-week period after randomization.

Subjects under treatment with a [redacted] must have a 5-day wash-out period before randomization (note: symptomatic treatments other than [redacted] will be permitted throughout the study, see section 10.8 Prior and Concomitant Therapy in the study protocol).

If, during a treatment period or during a wash-out period, a subject should experience an exacerbation of CIPO related gastrointestinal symptoms that is not controlled by permitted medications and is not judged as an adverse event, he/she will attend an early switch visit (ESV) at the clinical site. After being reassessed, he/she will be offered to directly switch to the next scheduled treatment period (SOT-2 or SOT-3 or SOT-4) without completing the ongoing treatment or wash-out period. Only one early switch is possible during the study. ESV will be Day 1 of the relevant period (SOT-2 or SOT-3 or SOT-4) based on the timing of early switch.

In case of ESV/SOT-2 or ESV/SOT-3 or ESV/SOT-4, the subsequent visits will follow the relevant sequential number (see Study Schedule of Assessments in section 3.4).

3.2. Selection of Study Population

Sixteen male and female subjects with a diagnosis of idiopathic CIPO or CIPO secondary to primary neurodegenerative or demyelinating conditions (e.g., Parkinsonian Syndromes, multiple sclerosis, etc.) who meet all the inclusion and none of the exclusion criteria will be enrolled in this study.

[redacted]

Subjects will be enrolled in up to 5 centres.

A complete list of all inclusion criteria and exclusion criteria are provided in Section 9.2 and 9.3 of the study protocol, respectively.

3.3. Treatment

3.3.1. Treatment Administered

The investigational products that will be administered in the study were:

- Velusetrag [redacted]
- Placebo [redacted]

3.3.2. Method of Assigning Subjects to Treatment Group

Eligible subjects will be randomly allocated in a 1:1:1:1 manner (4 subjects per treatment sequence), in a blinded fashion, to one of the following four treatment sequences:

A. VEL-PLA-VEL-PLA
B. PLA-VEL-PLA-VEL
C. VEL-PLA-PLA-VEL
D. PLA-VEL-VEL-PLA

Where:

VEL= velusetrag 15 mg ([redacted] mg [redacted]) once a day for 4 weeks.
PLA= matching placebo ([redacted]) once a day for 4 weeks.

Since the study is a cross-over study, each subject will take both investigational products during the study according to treatment sequence assigned by randomization.

Randomization will be stratified into 3 strata by CIPO diagnosis (idiopathic or secondary to neurodegenerative or demyelinating disease) and by [redacted] responder status (responder/naive or non-responder) as follows:

- [redacted] non-responder
- responder/naïve and idiopathic CIPO

- [redacted] responder/naïve and CIPO secondary to neurodegenerative or demyelinating disease.

Non responders are defined as all subjects that, based on investigator's judgement, have an history of a lack of benefit [redacted]

3.3.3. Prior and Concomitant Therapy

Use of the following <u>medications is not allowed</u> within 2 weeks prior to Screening and/or planned throughout the duration of the study:

- Scopolamine [redacted]
- Erythromycin [redacted]
- Strong CYP3A4 inhibitors or strong CYP3A4 inducers.

[redacted]

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	(not exhaustive list*)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

- Strong P-gp transporter inhibitors.

Strong P-gp Inhibitors	
[redacted]	[redacted] **(not exhaustive list*)**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]

- Strong BCRP transporter inhibitors.

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

In addition, use of:

- Opioids is not allowed within 8 weeks from screening and/or planned throughout the duration of the study. [redacted]
- [redacted] are not allowed starting from 5 days before randomization and throughout the duration of the study

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

*As the list of prohibited agents is not exhaustive, the selection of prohibited medications done by using ATC and PT will be confirmed through a medical review of all concomitant medications (including medications for CIPO)

Orally poorly absorbed opioids [redacted] that could be used to treat potential adverse events, such as diarrhea, may be used if medically indicated.

If a [redacted] or scopolamine, or erythromycin and an opioid for analgesic use is taken during the study, the subject will be considered a treatment failure and will be withdrawn from the study.

Additional prescription and over-the-counter medications are permitted, provided that such agents are not known to be strong inducers or inhibitors of CYP3A4, P-gp and BCRP activity.

The selection of prohibited medications will be done by using ATC and PT and it will be reviewed and confirmed through a medical review of all concomitant medications (including medications for CIPO).
Any addition or change in regimen of concomitant medications that affect CYP3A4, P-gp and BCRP activity should be in accordance with inclusion or exclusion criteria and recorded in the source documents and the electronic-case report form (eCRF).

Medication(s) used to relieve main symptoms of CIPO are allowed and the use of the following concomitant medications will be registered in the e-diary daily:

- Treatments for nausea and vomiting and/or non-serotoninergic prokinetics.
- Treatments for constipation.
- Treatments for diarrhea.
- Treatments for abdominal pain.
- Others (e.g., octreotide, somatostatin, pancreatic enzymes, probiotics, rifaximin, metronidazole, fluconazole, etc.).

Further details on prohibited and permitted medications are reported in Section 10.8 PRIOR AND CONCOMITANT THERAPY of the study protocol.

3.4. Schedule of Time and Events

The schedule of assessments is shown in Table 3.4.1.

Table 3.4.1: STUDY SCHEDULE OF ASSESSMENTS

	Screening Period	1st Treatment Period [a]		2nd Treatment Period [a]		3rd Treatment Period [a]		4th Treatment Period [a]		EFU [n]	ETV	ESV [o]
		Randomiz. SOT-1	EOT-1	SOT-2	EOT-2	SOT-3	EOT-3	SOT-4	EOT-4	End of Follow-up	Early Termination Visit	Early switch Visit
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ETV**	**ESV**
Day	*-7 to -1*	*1*	*28(±1)*	*43(±1)*	*70(±1)*	*85 (±1)*	*112(±1)*	*127(±1)*	*154(±1)*	*169(±1)*		*Any time between Day 1 and 126*
Informed Consent	X											
On Site Visit	X	X	X	X		X		X				X
On Site Visit or home visit [b]					X		X		X	X	X	
Medical, surgical history and previous medications	X											

[redacted]

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	Screening Period	1st Treatment Period [a]		2nd Treatment Period [a]		3rd Treatment Period [a]		4th Treatment Period [a]		EFU [n]	ETV	ESV [o]
		Randomiz. SOT-1	EOT-1	SOT-2	EOT-2	SOT-3	EOT-3	SOT-4	EOT-4	End of Follow-up	Early Termination Visit	Early switch Visit
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ETV**	**ESV**
Assessment of responder status [redacted]	X											
Demographics	X											
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]											
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]									
[redacted]	[redacted]		[redacted]									
[redacted]	[redacted]											
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Inclusion/ Exclusion Criteria Evaluation	X	X										
Randomization		X										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Screening Period	1st Treatment Period [a]		2nd Treatment Period [a]		3rd Treatment Period [a]		4th Treatment Period [a]		EFU [n]	ETV	ESV [o]
		Randomiz. SOT-1	EOT-1	SOT-2	EOT-2	SOT-3	EOT-3	SOT-4	EOT-4	End of Follow-up	Early Termination Visit	Early switch Visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ETV	ESV
[redacted]												
Drug dispensing		X		X		X		X				X
Drug administration time recording [k]		X	X	X	X	X	X	X	X			X
Drug accountability [l]			X		X		X		X		X	X
[redacted]												

SOT: Start of Treatment; EOT: End of Treatment; EFU: End of Follow up; ETV: Early Termination Visit; [redacted]; ESV: Early Switch Visit.

a. Subjects will undergo a 2-week wash-out period between treatment periods.
b. If the subject cannot go back to the clinical site for one or more of the following visits: Visit 5, 7, 9 and 10 or ETV, they can be performed at the subject's home.
c. Assessment of responder status to [redacted]

[redacted]

k. Dose to be taken under observation at each scheduled visit at the clinical center. The exact time of dose administration should be recorded at all visits.
l. If the subject cannot go back to the clinical center for Visit 5, 7, 9 or ETV, the empty packs and the unused investigational product of the relevant period will be collected by the study nurse during the home visit.
m. In all subjects on V2 and V3, blood samples will be collected [redacted]. Actual time of collection must be recorded for each sample.
n. The final 2 week follow up period are considered also as final 2 week wash out period for the 4th treatment period.
o. In case, during a treatment period or during a washout period, a subject should experience an exacerbation of the CIPO related gastrointestinal symptoms that is not controlled by permitted medications and is not judged as an adverse event, he/she will attend an early switch visit (ESV) at the site. After being reassessed, he/she will start the next scheduled treatment period (SOT-2 or SOT-3 or SOT-4), without completing the ongoing treatment or washout period. ESV will be Day 1 of the relevant period (SOT-2 or SOT-3 or SOT-4) based on the timing of early switch. Only one early switch is allowed during the study.

3.5. Sample Size and Power Estimation

The sample size is based on the main analysis (t-test) of the primary endpoint, which consists in the differences between velusetrag and placebo within each paired treatment cycle (2 per subject).

A total of 16 subjects [redacted] will be randomized leading to 32 pairs. Accounting for 25% dropouts/missing pairs, 18 pairs should be available for the primary analysis on the subgroup of subjects with history of benefit [redacted] or naïve [redacted] and 24 pairs should be available for the analysis on the overall population.

With a two-sided significance level of 5%, the planned sample size will lead to power levels above 80% to detect effect size (ES) above 0.7 (see table 3.5.1 below).

Table 3.5.1 Power for different values of effect size and number of pairs

Power for different values of Effect Size* and number of pairs			
Number of pairs	ES: 0.6	ES: 0.7	ES: 0.8
18	67%	80%	89%
24	80%	91%	96%
28	86%	94%	98%
32	91%	97%	99%

** More than medium to moderate effect size (Cohen, 1988)*

Estimates obtained using SAS PROC POWER

If based on a blinded review of the data the rate of missing pairs is found to be higher, the sample size might be increased by the Sponsor.

4. DEFINITIONS AND GENERAL METHODOLOGY

4.1. General Methodology

Statistical tables, figures, listings and analyses will be produced using SAS® for Windows release 9.4 or later (SAS Institute Inc., Cary, NC, USA).

Data from all sites will be pooled and summarized. Continuous data will be summarized by the number of observations, mean, standard deviation (SD), median, first and third quartiles (i.e., 25th and 75th percentiles), minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %).

All efficacy analyses have the objective to show the superiority of velusetrag over placebo. All statistical analysis will be two-sided at a nominal level of 5%. Confidence intervals will be set at the 95% level.

4.2. Definitions

Study Phases

Screening phase (i.e., Visit 1): the screening phase is defined as starting from the screening visit up to randomization.
The screening visit can be performed within Day -7 and Day -1 before randomization.

First treatment period running from Visit 2 to Visit 3 and corresponding to the first period in which subjects took the first treatment assigned at randomization according to treatment sequence.

Wash-out after first treatment period corresponds to the 2-weeks after Visit 3 (EOT-1) in which subjects will not take any investigational product.

Similarly, there will be a **second, third and fourth treatment period** running from each respective start of treatment visit (SOT-2, SOT-3 and SOT-4) to each end of treatment visit (EOT-2, EOT-3 and EOT-4) after 28 days.

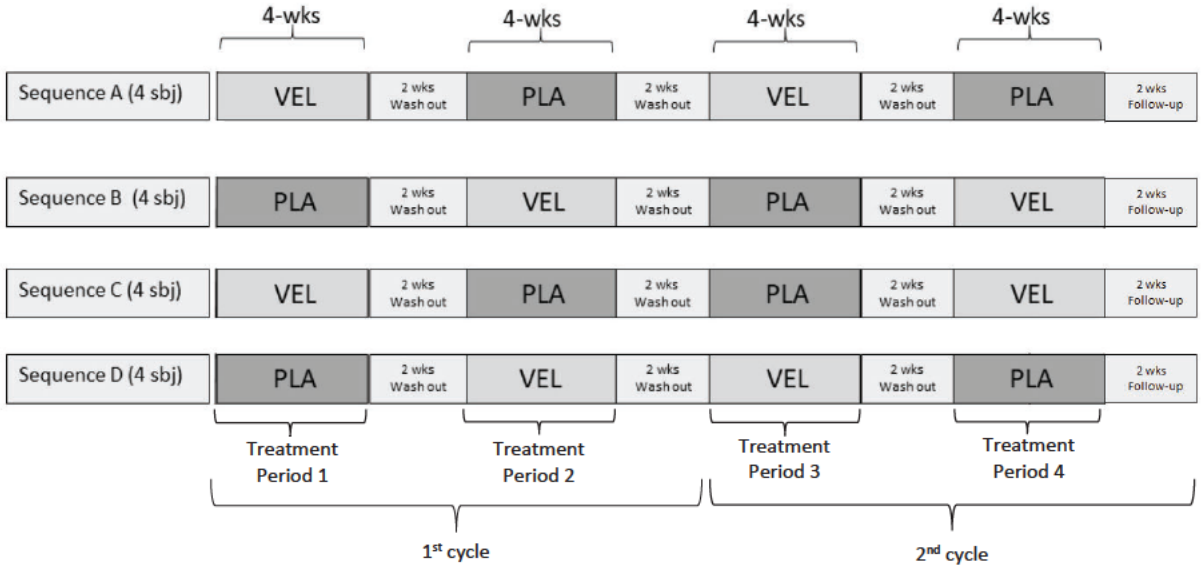
Wash-out periods after second and third treatment period corresponds to the 2 weeks after EOT-2 and EOT-3 respectively. Finally, the **follow-up of 2-weeks** corresponds to the 2 weeks after the EOT-4. During these phases the subject will not take any investigational product.

Definition of cycles

Each subject will be followed for two cycles of both treatments (i.e., VEL-PLA or PLA-VEL). The 1st cycle is made up of Period 1 and Period 2. The 2nd cycle is made up of Period 3 and

Period 4. In the Figure 2 below there are represented period and cycle based on study design.

Figure 2: Schematic design of period and cycle



Definition of Screening Failures

A screening failure is defined as a subject who signs the informed consent and has not been randomized to treatment.

Definition of Baseline/Reference

Due to the cross-over study design structure, for efficacy evaluation Baseline (for Period 1)/Reference (for Period 2, 3, 4) values are the last values collected prior to each treatment period initiation. For eDiary data the Baseline/Reference values are those recorded at the day before the start of treatment visit (Day -1 for Period 1, end of wash-out for the Period 2, 3, 4), while for other variables recorded in eCRF the Baseline/Reference are the last values collected before each treatment period first intake.

The Baseline for changes computation for the safety assessments is at the Visit 2 (SOT-1) except for laboratory data that is Visit 1.

For efficacy evaluation after the discontinuation of each treatment, the reference for changes computation is defined as the end of treatment visit for each period: Visit 3 (EOT-1) for period 1, Visit 5 (EOT-2) for period 2, Visit 7 (EOT-3) for period 3 and Visit 9 (EOT-4) for period 4.

In case of early switch visit or premature interruption of treatment, the reference for changes computation within each period should be adjusted accordingly based on ESV visits.

First/Last Administration of Study Treatment

Considering the overall study, the date of first administration of treatment (i.e., velusetrag or placebo) is the earliest start date of the 4 periods reported in the "Study treatment dispensed" CRF page while the date of last administration of treatment (i.e., velusetrag or placebo) is the date reported in the "End of treatment disposition" CRF page (i.e., maximum of the last administration of the 4 periods).

According to the study design, subjects will not receive the treatment during the wash out periods. For each study period, the date of first administration of treatment is the start date reported in the "Study treatment dispensed" CRF page on the corresponding SOT visit (i.e., Visit 2 (SOT-1) for period 1, Visit 4 (SOT-2) for period 2, Visit 6 (SOT-3) for period 3 and Visit 8 (SOT-4) for period 4)) while the date of last administration of treatment is the last treatment intake date reported in the "Study treatment returned" CRF page on the corresponding EOT visit (i.e., Visit 3 (EOT-1) for period 1, Visit 5 (EOT-2) for period 2, Visit 7 (EOT-3) for period 3 and Visit 9 (EOT-4) for period 4). In case of early switch visit or premature interruption of treatment, the first and last intake within each period should be adjusted accordingly.

Study day

The study day describes the day of the event or assessment date relative to the reference start date, which is defined as the date of Randomization.

The study day will be calculated as the difference between the date of each considered efficacy/safety assessment and the reference start date plus 1 day.

If the considered event starts before the Randomization date, the study day will be calculated as the difference between the date of the assessment and the reference start date. Therefore, the study day will be negative.

4.3. Coding of Therapies and Medical Terms

The World Health Organization Drug Dictionary (WHO-DD) Version_B3_Q1_2021 will be used to code medications reported in the prior medication, [redacted], concomitant medication and medications for CIPO (gastrointestinal symptoms) eCRF pages.

The Medical Dictionary for Regulatory Activities (MedDRA) English version 24.0 will be used to code medical terms reported in the Medical History, non-drug therapies or surgical and medical procedures and Adverse Events eCRF pages.

At the end of the study, if an updated version of the dictionaries is available, dictionaries will be updated after Sponsor's approval, if needed.

4.4. Handling of Drop-Outs or Missing Data

4.4.1. Missing or Partial Dates

For incomplete dates, the imputation will be performed according to the following rule:

- If the date is completely missing, no imputation will be performed
- In case of day missing, the day will be replaced with 15
- In case of day and month missing, the day will be replaced with 1, the month with July

The imputation rules will be applied to the date of CIPO diagnosis, start date for prior medications (including the [redacted]), start date of medical history condition, start date for concomitant medications (including the medications for CIPO) and adverse events.

In case that these rules led to CIPO diagnosis later than the informed consent date, CIPO diagnosis will be imputed as the informed consent date. Similarly, in case that imputations led to start date later than the end date for concomitant medications and adverse events, the 1st day of the month will be imputed instead of the 15th.

4.4.2. Handling of Missing Data/Imputation/Censoring Rules

The following rules to impute missing data will be applied for the efficacy primary endpoint and further details are provided in section 6.3.1.

Missing pairs (treatment difference velusetrag minus placebo) can occur when at least one of the following is missing:

- Pre-treatment velusetrag value missing
- End of treatment velusetrag value missing
- Pre-treatment placebo value missing
- End of treatment placebo value missing

[redacted]

[redacted]

These rules of imputation will be applied only if a subject starts the period of interest (i.e., if he/she performs the corresponding start of treatment visit).

The above approach will be used for the FAS and as sensitivity analysis for mFAS1, [redacted], PPS.

No missing imputation will be applied for secondary efficacy endpoints.

4.4.3. Handling of Drop-Out Subjects

Subjects who discontinue the study for any reason will be analyzed for efficacy and safety purposes.

4.5. Multiple Comparison/Multiplicity

Not applicable.

4.6. Multicentre Studies/Center Pooling

The data from all sites will be pooled and analyzed. Given the small sample size, no analysis will be performed by site or country.

5. ANALYSIS POPULATIONS

The following analysis populations are defined based on the study protocol:

- **Screened population:** all subjects who provided informed consent. A screening failure is defined as a screened subject who has not been randomized to treatment.
- **Randomized population:** all screened subject who has been randomized to treatment.
- **Safety Set (SS)**: all treated subjects (i.e., subject who received at least one [redacted] of the investigational product or placebo).
- **Full Analysis Set (FAS):** all randomized and treated subjects.
- **Modified Full Analysis Set 1 (mFAS1):** all subjects responder/naïve to [redacted] randomized and treated who reported data on the primary endpoint at least once during a velusetrag treatment period and at least once during a placebo treatment period in the same cycle.
- [redacted]

- **Per Protocol Set (PPS):** all subjects in the mFAS1 who fulfil the study protocol requirements in terms of compliance to treatment and collection of primary efficacy data, and with no major deviations that may affect study results.

For the PPS analysis, if within a period, the compliance is below 80%, the primary endpoint data of this period will be excluded from the analysis. E.g., if compliance data are 100%, 100%, 60%, 60%, the subject is included in the PPS (overall compliance at 80%) but the observations of the third and fourth period are excluded.

The complete list of deviations will be defined in a specific protocol deviation handling plan and a blind data review meeting will occur prior to unblinding. The decisions for exclusion of subjects from the PPS will be taken in a blinded manner and documented.

Analysis on the SS will be performed according to the actual treatment received.

Analysis on the FAS, mFAS1, [redacted] will be performed according to the treatment and stratum assigned at randomization following the intent-to-treat principle.

Analysis on the PPS will be performed according to the actual stratum, while no cases of study treatment different from the randomized one can belong to the PPS (i.e., subjects receiving a study treatment different from the randomized one will be excluded from the PPS).

6. STATISTICAL METHODOLOGY

6.1. Study Subjects

The number of subjects who complete the screening phase [redacted] and the number of subjects who discontinue the screening phase [redacted] together with the primary reason for discontinuation will be summarized overall on the screened population. The number of randomized subjects included will also be displayed.

[redacted]

Subject disposition will be provided on the randomized population by treatment sequence and overall summarizing the number of subjects randomized and the number of treated subjects. The number of subjects who complete the treatment [redacted] and the number of subjects who discontinue the treatment [redacted] together with the reason for study discontinuation will be provided. Similarly, the number of subjects who complete the study [redacted] and the number of subjects who

discontinue the study [redacted] together with the reason for study discontinuation will be provided.

In addition, the number of subjects who enter in each period including wash-out/follow-up (i.e., performed the corresponding SOT visit) and the number of subjects who complete the treatment, who perform switch in treatment period, who discontinue the treatment together with the reason for treatment discontinuation, who complete wash-out/follow-up, who perform switch in the wash-out period or who discontinue the wash-out/follow-up will be also provided considering each period. [redacted]

[redacted]

The numerousness of the analysis populations (SS, FAS, mFAS1, [redacted] and PPS) will be described and the reasons for excluding a subject from an analysis population will be provided on the randomized population by treatment sequence.

The number of subjects reporting at least one major protocol deviation and the number of subjects reporting each considered major PD will be summarized on the randomized

population by treatment sequence and overall. Similarly, the number of subjects reporting at least one minor protocol deviation and the number of subjects reporting each considered minor PD will be summarized on the randomized population by treatment sequence. The list of confirmed protocol deviations and their classification as major/minor was defined in the specific protocol deviation handling plan.

[redacted]

Table 6.1-1: [redacted]

[redacted]

6.2. Background and Demographic Characteristics

Background and demographic characteristics will be summarized descriptively by treatment sequence and overall on the FAS, mFAS1.

[redacted]

- [redacted]

Medical and surgical history findings will be summarized by System Organ Class and Preferred Term according to the MedDRA dictionary, [redacted] Subjects will only be counted once per MedDRA level, and the medical history will be sorted by descending incidence of SOCs and then PTs in the overall group. Medical and surgical history findings will be summarized separately:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Prior medication (except [redacted]) administered during the last 30 days before screening visit will be summarized [redacted]

Prior [redacted] administered before screening visit will be summarized [redacted]

In addition, the following variables will be summarized at Visit 1 on the FAS population according to treatment sequence:

- [redacted]
- [redacted]

- [redacted]

6.3. Efficacy Evaluation

6.3.1. Primary efficacy analysis

Definition of primary endpoint

The primary endpoint is the change in weekly global gastrointestinal symptoms average index score from pre-treatment (Baseline/Reference, depending on the period) to the end of each treatment period.

The weekly global gastrointestinal symptoms average index score is obtained by averaging the scores for each of the 4 symptoms assessed weekly: abdominal pain, bloating, nausea and vomiting.

Each symptom (i.e., abdominal pain, bloating, nausea, vomiting) was rated using a recall period of 7 days and a Likert scale with the following categories:

0 – Absent

1 - Mild (not influencing usual activities)

2 - Moderate (diverting from, but not urging modification of, usual activities)

3 - Severe (influencing usual activities markedly enough to urge modifications)

4 - Extremely severe (precluding daily activities)

[redacted]

Analysis methodology

[redacted]

[redacted]

Considering the evaluable pairs [redacted] the [redacted] will be summarized [redacted]

Of note, each subject should be evaluated twice: once for each cycle. Consequently, each subject can contribute to 0, 1 or 2 pairs and only data that constitute pair evaluable for primary endpoint will be considered in this and in the following analysis.

Differences between velusetrag and placebo will be computed within each cycle [redacted]

[redacted]

These analyses will be provided on the mFAS1 without any missing data imputation as primary analysis.

Finally, a listing will be provided on Randomized population considering the intake of each [redacted] collected in the eDiary together with the individual gastrointestinal symptoms and the weekly global gastrointestinal symptoms average index score.

Data handling rules

Missing data will be handled as described in Section 4.4.2.

Sensitivity analysis

[redacted]

[redacted]

6.3.2. Secondary efficacy analysis

[redacted]

[redacted]

These analyses will be performed only on mFAS1 and [redacted] without missing imputation.

[redacted]

Definition

The [redacted] will be computed as described in section 6.3.1.

The proportion of subjects with change between the end of treatment and pre-treatment value ≤ - 1 point will be computed and considered as “Success” while the proportion of subjects with change between the end of treatment and pre-treatment value>-1 will be considered as “Failure”.

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

Each symptom (i.e., [redacted]) was rated using a recall period of 7 days and a Likert scale with the following categories:

0 – Absent

1 - Mild (not influencing usual activities)

2 - Moderate (diverting from, but not urging modification of usual activities)

3 - Severe (influencing usual activities markedly enough to urge modifications)

4 - Extremely severe (precluding daily activities)

The endpoint is the [redacted] score from pre-treatment to the end of each treatment period. A [redacted] represents improvement.

[redacted]

[redacted]

[redacted]

Definition

The number of [redacted] and [redacted] will be provided in the eDiary every 7 days together with the evaluation of the [redacted] of [redacted] on average according to [redacted] scale.

Changes in the number of [redacted] and number of [redacted] will be computed between the end of each treatment period and the pre-treatment (Baseline/Reference).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

The [redacted] on average was recorded according to [redacted] by means of eDiary. The [redacted] scale ranges from 1, which corresponds to Type 1 (i.e., separate hard lumps, like nuts that indicates [redacted]) to 7, which corresponds to Type 7 (i.e., watery, no solid piece that indicates [redacted]).

The [redacted] scale will be categorized according to the following categories that indicates the subjects' status:

- [redacted]
- [redacted]
- [redacted]

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

The [redacted] will be provided in the eDiary every 7 days according to a scale from 0=very unhappy to 10=very happy.

Changes in [redacted] will be computed between the end of treatment number and the pre-treatment number (Baseline/Reference). A positive change represents an improvement.

[redacted]

[redacted]

[redacted]

Definition

The [redacted] will be computed based on the [redacted] to assess [redacted] consists in timed and standardized measurement of [redacted] after the ingestion of a solution of water and [redacted]

This evaluation will be performed only during the first treatment period of the study.

Changes in [redacted] will be computed between the post-treatment [redacted] (i.e., end of first treatment period at Visit 3 (EOT-1)) and the pre-treatment [redacted] (i.e., Screening value at Visit 1).

[redacted]

[redacted]

[redacted]

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

[redacted]

[redacted]

Definition

[redacted] levels are [redacted], [redacted], [redacted] and [redacted]. Their levels will be collected at pre-treatment (Baseline/Reference) and at the end of follow-up after the fourth period and at ETV and ESV.

Changes in [redacted] will be computed between the end of each 2-week wash-out period (or follow up period) and the relevant pre-treatment values (Baseline/Reference)(i.e., for period 1: levels at V4 – levels at V1; for period 2: levels at V6 – levels at V4; for period 3: levels at V8 – levels at V6 and for period 4: levels at V10 – levels at V8).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

For each [redacted], the subject provides daily the status of the intakes:

- Not taken
- Taken at the prescribed dose
- Taken at reduced dose
- Taken at increased dose

For each [redacted] collected in the eDiary, excluding antacids [redacted] the following flag are calculated:

- Increase flag: for each day, a drug will be considered as taken at increase dose [redacted]

Baseline/Reference is defined as the last information collected in the eDiary in the previous phase. It will be Day -1 for Treatment Period 1, the last day in Treatment Period 1 for Wash-out Period 1 and so on.

These flags will be reviewed and updated by means of Medical Review to evaluate if the computed flags are clinically consistent.

[redacted]

- [redacted]

The numerator will be considered as follows:

- Proportion of days with dose increased (at least 1 medication): [redacted]
- Proportion of days with dose increased (1-2 medications): [redacted]
- Proportion of days with dose increased (>=3 medications): [redacted]
- Proportion of days with dose decreased (at least 1 medication): [redacted]
- Proportion of days with dose decreased (1-2 medications): [redacted]
- Proportion of days with dose decreased (>=3 medications): [redacted]
- Proportion of days with drug added (at least 1 medication): [redacted]
- Proportion of days with drug removed (at least 1 medication): [redacted]

Analysis methodology

[redacted]

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

The [redacted] is a [redacted] used to assess generic [redacted] outcomes from the subject's perspective. It is often used as a [redacted] measure. Generic subject-reported outcome (PRO) measures like the [redacted] including the impact of any and all illnesses on a broad range of functional domains. The [redacted] consists of a subset of [redacted] from the [redacted] covering the same [redacted] domains of [redacted], including [redacted]

[redacted] (norm based score) that represents [redacted] and [redacted] components of [redacted] and [redacted] will be derived by means of the [redacted]

Analysis methodology

[redacted]

Data handling rules

No missing imputation will be performed.

6.3.2.11. [redacted]

Definition

The number of [redacted] during each treatment period will be collected and analyzed as well as the number of [redacted] during each wash-out/follow-up period.

Analysis methodology

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

The [redacted] is used to provide an evaluation of the type of diet followed by the subject. [redacted]:

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

Analysis methodology

[redacted]

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

The number of [redacted] during each treatment period will be collected and analyzed as well as the number of [redacted] during each wash-out/follow-up period.

Analysis methodology

[redacted]

Data handling rules

No missing imputation will be performed.

[redacted]

Definition

The effect of [redacted] will be evaluated considering the following set of variables previously described:

- [redacted]

- [redacted]

Analysis methodology

[redacted].

6.3.2.15. Concentration of velusetrag and THRX-830449 metabolite

Definition

Serial blood samples for assessment of [redacted] will be collected [redacted]

For each sample, the possible results will be a number indicating the concentration in pg/mL or one of the following other cases: NQ = < Assay LLQ, IS = Insufficient Sample, NR = Not Reportable, or NA =Not Analysed. If results is equal to IS = Insufficient Sample, NR = Not Reportable, NA =Not Analysed or NQ =< Assay LLQ the concentration is not available and will be missing for the summary table and graph.

Analysis methodology

[redacted]

Data handling rules

No missing imputation will be performed.

6.3.3. Exploratory efficacy analysis

Not applicable.

[redacted]

[redacted]

6.4. Safety Evaluation

The safety analyses will be performed on subjects included in the SS.

6.4.1. Extent of Exposure

Exposure time will be computed in weeks within each period of treatment as follows:

(Last intake date in the study period - First intake date in the study period +1)/7

[redacted]

6.4.2. Concomitant medications

[redacted] are defined as therapies ending or ongoing after the start of study treatment (i.e., first intake of treatment in the period 1). [redacted] will be presented by ATC Code [redacted] and Preferred Term by actual treatment on the SS, presenting the number and percentage of subjects with at least one concomitant medication. [redacted]

[redacted]

Similarly, medications for CIPO will be presented by ATC Code [redacted] and Preferred Term by actual treatment on the Safety Population, presenting the number and percentage of subjects with at least one medication for CIPO. Subjects will be counted once in each category, outputs will be sorted in the overall group by descending frequencies of ATC [redacted] and Preferred Term.

Non-drug therapies or surgical and medical procedures

Similarly, non-drug therapies or surgical and medical procedures will be summarized by SOC and Preferred Term by actual treatment on the Safety Population, [redacted]

6.4.3. Adverse Events

Treatment-emergent adverse events (TEAEs) will be reported by actual treatment. Adverse events starting on or after the first intake of treatment (i.e., first intake in the period 1) are considered TEAEs. [redacted]

[redacted]

In addition, TEAEs will be summarized by actual treatment, MedDRA System Organ Class and Preferred Terms considering:

[redacted]

Adverse events will be classified as velusetrag emergent if the last treatment taken before the start of the adverse event was velusetrag, or placebo emergent if the last treatment taken before the start of the adverse event was placebo.

In addition, a summary of TEAEs will be provided by treatment sequence. [redacted]

6.4.4. Laboratory parameters

The safety laboratory tests include [redacted]. The following variables are measured during the study:

- [redacted]

- [redacted]
- [redacted]

Of note, [redacted] will be collected with different unit of measurements (i.e., sec or ratio). Since there is no conversion factor applicable to uniform the units, these parameters will be summarized separately according to unit of measurements.

[redacted]

[redacted]

6.4.5. Vital signs/Physical examination

Vital signs [redacted] and Biometrics measurements [redacted] will be descriptively analyzed [redacted]

6.4.6. Other safety parameters

[redacted] (e.g., without artifacts) will be performed and the average of the three readings will be used to determine [redacted] will be reviewed at the clinical center and final interpretation of all [redacted] will be completed by a central reviewer and sent to the site for Investigators' subject evaluation and filing. This final investigation will be considered for the following analyses:

- [redacted]
- [redacted]

Pregnancy test and COVID-19 rapid swab will be only listed.

6.5. Subgroup Analyses

Not applicable.

6.6. Interim Analysis and Data Monitoring

Not applicable.

7. REFERENCES

Not applicable.

8. APPENDIX

Not applicable.

DocuSign

Certificate Of Completion

Envelope Id: 16D69DD0BF734456ADF0523603E96616
Status: Completed
Subject: Complete with DocuSign: VE-CIP2001_2021_Statistical_Analysis_Plan_final2.0_20230510.pdf
Source Envelope:
Document Pages: 59
Signatures: 4
Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna
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Record Tracking

Status: Original
10-May-2023 | 18:38
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Signer Events	Signature	Timestamp
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[redacted] Security Level: Email, Account Authentication (Required)	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 10-May-2023 | 18:46 CEST [redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 10-May-2023 | 18:41 Viewed: 10-May-2023 | 18:46 Signed: 10-May-2023 | 18:47
Electronic Record and Signature Disclosure: Accepted: 10-May-2023 | 18:46 ID: [redacted]		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10-May-2023 | 18:47 Viewed: 10-May-2023 | 19:30 Signed: 10-May-2023 | 19:31
Electronic Record and Signature Disclosure: Accepted: 10-May-2023 | 19:30 ID: [redacted]		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10-May-2023 | 19:31 Viewed: 10-May-2023 | 22:59 Signed: 10-May-2023 | 23:00
Electronic Record and Signature Disclosure: Accepted: 10-May-2023 | 22:59 ID: [redacted]		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	10-May-2023 | 18:40
Certified Delivered	Security Checked	10-May-2023 | 22:59
Signing Complete	Security Checked	10-May-2023 | 23:00
Completed	Security Checked	10-May-2023 | 23:00

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 11-Mar-2022 | 12:12
Parties agreed to: [redacted]

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