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Title page

A randomized, double-blind, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of two different doses of vilaprisan (BAY 1002670) versus placebo in women with symptomatic endometriosis

Assess safety and efficacy of vilaprisan in subjects with endometriosis

Bayer study drug	BAY 1002670 / Vilaprisan		
[Study purpose:]	Dose finding, safety		
Clinical study phase:	IIb	**Date:**	15 Jan 2020
Study No.:	BAY 1002670 / 15792	**Version:**	1.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Abbreviations

CRF	Case Report Form
CSR	Clinical Study Report
EIS	Endometriosis Impact Scale
ESD	Endometriosis Symptom Diary
PAEC	Progesterone receptor modulator-associated endometrial changes
PRO	Patient-Reported Outcomes
SAP	Statistical Analysis Plan

1. Introduction

The Statistical Analysis Plan (SAP) is based on the following clinical study protocol (CSP) version:

- Amendment 07 and 08 global amendments forming integrated protocol Version 6.0, dated 28 NOV 2019

2. Study Objectives

Originally, the study includes the following objectives:

Primary objective:

- assess efficacy of two doses of vilaprisan compared to placebo in women with symptomatic endometriosis

Secondary objective:

- evaluate the safety and tolerability of two different doses of vilaprisan in women with symptomatic endometriosis

Exploratory objective:

- explore efficacy and safety in sub-populations (e.g. subjects with endometriosis diagnosed by imaging vs subjects with surgically confirmed endometriosis)

Other objectives:

- evaluate the variability in exposure in relation to the efficacy and safety for vilaprisan in subjects with symptomatic endometriosis
- confirm psychometric properties of the newly developed Patient-Reported Outcomes (PRO) instruments: Endometriosis Symptom Diary (ESD) and Endometriosis Impact Scale (EIS) (will be analyzed and reported separately)
- evaluate biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease including assessments of exploratory biomarkers to investigate disease activity

With the implementation of the protocol amendments 07 and 08 no further recruitment is possible. With the data available from subjects recruited before the temporary pause the original study objectives cannot be reached. Safety evaluations including the added safety evaluations of the endometrium, adrenal glands, bone, and skin may add to the understanding of the safety of vilaprisan.

3. Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

The study originally includes the following phases: a screening phase, a placebo-controlled dose-finding phase, followed by a drug-free interval encompassing 2 menstrual bleeding episodes, a placebo-controlled extension phase, and a follow-up phase.

Endometriosis symptoms and their impact on subjects' daily life was to be documented throughout the study, i.e. from start of the screening until the follow-up phase.

With the implementation of the protocol amendments 07 and 08, this study design is no longer valid. No subjects will receive further study drug treatment.

Study design valid with the implementation of amendments 07 and 08:

The study was temporarily paused since December 2018. With the implementation of amendments 07 and 08 no further subjects will be recruited and none of the enrolled subjects will receive further study drug treatment. All subjects who were randomized and started vilaprisan before the temporary pause will be asked to have a comprehensive safety evaluation (with particular focus on endometrial, adrenal, and skin safety) performed, which is implemented with this amendment. This also applies to subjects who have discontinued the study before or during the temporary pause, provided they have taken at least one dose of vilaprisan.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

All data will be presented in the subject data listing as they are recorded. Generation of listings will be conducted by or under the supervision of the sponsor's study statistician.

Listings will be generated after all safety data has been cleaned, locked and released for analysis.

Apart from listing generation no further statistical analysis or summary table generation will be conducted.

4.2 Blind Review

For all data collected prior to the protocol amendments 07 and 08, the results of the final data assessment for the assignment to analysis sets will be documented in the final list of important deviations, validity findings and assignment to analysis set(s) which will be finalized before the initial database lock. No important deviations and validity findings will be documented and evaluated at the final database lock.

5. Analysis Sets

5.1 Assignment of analysis sets

Safety analysis set (SAF)

The safety analysis set population consists of all randomized subjects who received at least 1 dose of study medication after randomization.

6. Statistical Methodology

6.1 Population characteristics

- Demographics and baseline characteristics
- Medical history
- Endometriosis relevant history

- Endometriosis treatment eligibility questionnaire
- Reproductive and menstrual history
- Drug accountability, treatment exposure and study drug expose
- Prior/concomitant medication

Population characteristics will be be listed as recorded.

6.2 Efficacy

Efficacy data will be listed as they are recorded on the Case Report Form (CRF) and electronic diary (eDiary). Efficacy variables will be not derived.

6.2.1 Biomarker

The listings will be provided, if applicable.

6.3 Pharmacokinetics/pharmacodynamics

The listings will be provided, if applicable

6.4 Safety

Safety variables include the following variables:

- Adverse events
- Vital signs
- Endometrial histology (classical histology, diagnosis of PAEC, individual features of PAEC)
- Endometrial thickness and endometrial/ myometrial/ ovarian changes based on ultrasound
- Laboratory parameters
- Findings resulting from liver monitoring
- Findings resulting from adrenal monitoring
- Findings resulting from skin monitoring
- Cervical cytology
- Bone mineral density
- Vaginal bleeding pattern

Safety data will be listed as recorded.

7. Document history and changes in the planned statistical analysis

All derivations of efficacy variables, all statistical analyses and summary statistics were deleted from the protocol with the implementation of the protocol amendment 07 and 08 to reflect that only a few subjects were randomized and/or received study medication.