PASS INFORMATION

Title	Cross-sectional study to assess the effectiveness of the patients' alert card to inform of the risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib)
Short title	IMPACTA
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Medicinal product	TIBSOVO®
Product reference	EU/1/23/1728/001
Procedure number	EMEA/H/C/005936
Marketing authorisation holder(s)	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex – France
Joint PASS	No
Research question and objectives	Assessment of the effectiveness of the patients' alert card to inform on the risk of differentiation syndrome in AML patients treated with TIBSOVO®, using process dimensions for patients' awareness, receipt of the material, reading, utility of the PAC, self-reported behaviour and knowledge, as part of the risk management plan.
Countries of study	Germany, France, Austria, Belgium, Greece and Poland
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1. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AML	Acute Myeloid Leukemia
aRMM	Additional Risk Minimization Measure
CA	Competent Authority
CI	Confidence Interval
DM	Data Management
DMP	Data Management Plan
DS	Differentiation Syndrome
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
IC	Induction Chemotherapy
ICF	Informed Consent Form
IDH	Isocitrate Dehydrogenase
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmaceutical Engineering
MP	Monitoring Plan
OS	Overall Survival
PAC	Patient Alert Card
PASS	Post-Authorisation Safety Study
PPI	Physician Principal Investigator
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcome
SAE	Serious Adverse Events

SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
TMF	Trial Master File
US	United States
2-HG	2-hydroxyglutarate

2. RESPONSIBLE PARTIES

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Role and affiliation	Name	Date	Signature
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Real-World Evidence Director Interim Head of Global Real-World Evidence Department	Mehdi KERTOUS	13 January 2026	Signed by: Mehdi KERTOUS 95DB53B87E464F4...

3. ABSTRACT

Title

Cross-sectional study to assess the effectiveness of the patients' alert card to inform of risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib).

Rationale and background
In May 2023, the European Medicines Agency (EMA) approved the use of TIBSOVO® (Ivosidenib) in combination with azacitidine for the treatment of adult patients newly diagnosed with Acute Myeloid Leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.
Ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha-ketoglutarate to D-2-hydroxyglutarate which impairs myeloid differentiation, increases proliferation of myeloblasts and promotes tumorigenesis.
The Risk Management Plan (RMP) for TIBSOVO® approved in Europe includes a Patient Alert Card (PAC) as an additional risk minimisation measure (aRMM) to enhance the recognition, diagnosis, and prompt treatment of the important identified risk of differentiation syndrome (DS) in the AML indication. The PAC will be distributed inside each pack of TIBSOVO® to inform patients of this risk.
Regulatory guidelines require aRMMs to be evaluated for their effectiveness. In line with this requirement, this Post-Authorisation Safety Study (PASS) will evaluate the effectiveness of the PAC to inform on the risk of DS among patients with AML treated with TIBSOVO®.

Research question and objectives
The study will evaluate the effectiveness of the PACs to inform on the risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib), using process dimensions for patients' awareness, receipt of the material, reading, utility of the PAC, self-reported behaviour, and knowledge.

Study design
This study will be a multi-national, observational cross-sectional survey among adult patients who have recently received TIBSOVO® (Ivosidenib) for treatment of AML, that will be conducted in Germany, France, Austria, Belgium, Greece and Poland

The survey will be initiated at least 12 months after TIBSOVO® launch in each EU selected country. EU countries will be selected based on the feasibility step results. The survey will be a paper survey.

Population
Participants will be identified through their Healthcare Professionals (HCPs) and will be included in the study if they are aged ≥18 years at recruitment, have taken Ivosidenib for the treatment of newly diagnosed AML in the previous 6 months, and are able to understand and complete the consent form and participant survey. Participant selection will be based on systematic sampling, i.e., all consecutive eligible participants are expected to be included in the study, with no selection other than the eligibility criteria and the study period defined.
Physicians will be identified using the lists of AML specialists provided by the Marketing Authorisation Holder. A pilot step will be conducted to determine the feasibility of recruitment and the participants/Healthcare professionals (HCPs) ratio to be used in the study.

Variables
The survey will collect data resulting from the PAC of TIBSOVO®, referring in particular to the participant's receipt, understanding of DS risk, correct identification of these symptoms onset and knowledge of the right actions to be taken. Additionally, the survey will collect information on demographic characteristics of participants including age, sex, start date of TIBSOVO® treatment, and treatment status at the time they complete the survey.

Data source
Structured, self-administered questionnaire comprising closed-ended questions or statements with multiple response choices will be used to collect the survey data. A user testing evaluation will be conducted prior to the master study.

Study size
Considering that around 200-300 patients will have been treated in Europe 12 months after launch in each country, and an expected estimate of 80% of understanding rate of the PACs, 60 evaluable surveys for primary objective are required to allow a precision of 10.2%, i.e., a confidence interval of [69.8%-90.2%], for a confidence level of 95% corresponding to a 0.05 alpha. Surveys will be considered "evaluable for primary objective" when at least 4 questions related to the primary outcome are answered.
As a 90% response rate is expected, 66 participants will have to be recruited to achieve the targeted number of evaluable surveys for primary objective.

Data analysis
Data collected from the survey will be reported as descriptive statistics. Frequency distributions will be calculated for items that address the survey objective (excluding demographic questions).

Milestones
The protocol was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) within 3 months following European Commission (EC) decision. The final study report is planned in Q3/Q4 2028.

4. AMENDMENTS AND UPDATES

Version	Date	Description
1.0	08-2023	Initial protocol
2.0	01-2024	Updated protocol following PRAC Assessment Report MEA 003.0 dated 09 November 2023
3.0	04-2024	Updated protocol following PRAC Assessment Report MEA 003.1 dated 15 March 2024
4.0	01-2026	Updated protocol following PRAC Assessment Reports MEA 003.2 dated 13 March 2025 and PRAC clarification meeting held on 22 October 2025

5. MILESTONES

Milestone	Planned date
Pilot step	08-2023 to 02-2024
Statistical Analysis Plan	01-2024
Report of Pilot step	04-2024
Registration in the EU PAS register	06-2024
Feasibility step, wave 1	06-2024 to 11-2024
Report of Feasibility step, wave 1	12-2024
Feasibility step, wave 2	03 2025 to 11 2025
Report of Feasibility step, wave 2	12-2025
Start of data collection (master study)	Q3 2026 (first participant in)*
End of data collection (master study)	Q4 2027/ Q1 2028 (last participant in)*
Final report of master study	Q3/Q4 2028*

*These timelines are subject to timely approvals from national competent authorities and ethics committees, and to the recruitment progress.

6. BACKGROUND AND RATIONALE

6.1. Background

6.1.1. Epidemiology

Acute Myeloid Leukemia (AML) is a malignant disorder which leads to the accumulation of hematopoietic precursor cells and insufficient production of red and white blood cells (other than lymphocytes) and platelets (1). It is characterized by the presence of ≥20% of blasts in the bone marrow or peripheral blood (3). The wide range of clinical manifestations of AML are attributable to the replacement of normal, functional hematopoietic cells by these immature leukemic blasts, causing anemia, neutropenia, and thrombocytopenia (4). The most common causes of death are infections and bleeding events.

AML is a rare disease, accounting for about 1% of all cancers (5). Two systematic literature reviews reported worldwide incidence rates between 1.63 and 7.9 per 100,000 individuals in the period 2001-2016 (6,7).

In Europe, during the period 2007-2016, AML incidence was estimated at 4.0 per 100,000 (8). National incidence was also reported for Germany-Austria, the Netherlands, and the Czech Republic, and ranged from 2.79 to 4.79 per 100,000 (9–11). The French network of cancer registries reported AML incidence rate of 5.7 per 100,000 in males, and 4.9 per 100,000 in females, in 2018 (12).

AML is primarily a disease of older adults, with an average age at first diagnosis of 68 years (5). As per the European cancer registries (including patients diagnosed between 1995 to 2002; index date 1st January 2003), the incidence of AML gradually increases with age at 35.3 per 100,000 for over 65 years old patients versus 5.1 per 100,000 for patients aged 15 to 24 (13). Hence, the absolute number of patients with AML is anticipated to increase substantially over the next decades due to the advancing age of the population. These registries also showed higher crude incidence rates of AML in male patients (4.0 per 100,000) than in female patients (3.4 per 100,000) (13).

6.1.2. Treatments

The standard treatment strategy for AML patients includes intensive induction chemotherapy (IC) or less intensive chemotherapy, followed either by post-remission Hematopoietic Stem Cell Transplantation or consolidation chemotherapy. Population-based epidemiological studies in the United States (US) indicated that approximately 60% of patients with newly diagnosed AML who were aged over 65 remained untreated and had a median survival of approximately 2 months (14). For patients who are not candidates for intensive therapies, the National Comprehensive Cancer Network guidelines recommend non-intensive therapies or best supportive care. Complete remission rates associated with these therapies are low (approximately 10%-20%), and median Overall Survival (OS) ranges from 2 to 10 months (15,16).

IDH inhibitors

AML is a genetically heterogeneous hematologic malignancy, with mutations on the gene coding for the isocitrate dehydrogenase 1 (IDH1) found in approximately 6% to 10% (17,18).

Ivosidenib (TIBSOVO®), a Servier registered product, is a potent selective inhibitor of the IDH1 mutant protein. Ivosidenib works by inhibiting the mutant IDH1 enzyme responsible for converting alpha-ketoglutarate to 2-hydroxyglutarate (2-HG) which impairs myeloid differentiation, increases proliferation of myeloblasts and promotes tumorigenesis. Ivosidenib reduces 2-HG and restores cellular differentiation (19). The molecule was authorised by the Food and Drug Administration (FDA) in the US in July 2018 for the treatment of adult patients with relapsed or refractory AML with a IDH1 mutation, as detected by an FDA-approved test. This initial approval was followed by the approval in the US of a supplemental indication for adult patients with a confirmed IDH1 mutation for newly diagnosed AML in combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (US marketing authorisation dated May 2019).

Based upon clinical data from the AGILE Phase 3 trial (20), the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) adopted a positive opinion and recommended granting a marketing authorisation for TIBSOVO® (ivosidenib) in Europe in combination with azacitidine in adult patients with newly diagnosed IDH1 R132-mutated AML who are not eligible for standard induction chemotherapy (21).
The marketing authorisation was issued throughout the European Union (EU) on 04 May 2023. Of note, there is currently no other molecularly targeted therapy approved for patients with newly diagnosed AML with an IDH1 mutation who are not candidates for IC.

Differentiation Syndrome

Differentiation syndrome (DS) was firstly reported under treatment with all-trans retinoic acid and/or arsenic trioxide in 2% to 48% of acute promyelotic leukemia treated patients (22,23). DS is a known side effect in AML patients treated with azacitidine or targeted therapies such as ivosidenib (IDH1 mutated) (24), enasidenib (IDH2 mutated) (25), and gilteritinib (FMS-like tyrosine kinase 3 [FLT3] mutated patients) (26).

In relapsed or refractory AML patients, DS occurred in 4 to 19% of patients treated with ivosidenib and 19% of patients treated with enasidenib (27,28). The AGILE Phase 3 study [ClinicalTrials.gov Identifier: NCT03173248]) on ivosidenib also reported that DS was among the most common (≥2%) serious adverse reactions. The AGILE study included patients with AML and IDH1 mutation who were ineligible for IC and were enrolled from March 2018 through May 2021 (24). Patients were randomly assigned treatment with ivosidenib and azacitidine or a matched placebo and azacitidine. The trial identified DS as an important risk in AML patients treated with ivosidenib. A total of 14% of patients treated with ivosidenib and azacitidine developed DS compared with 8% in the group treated with placebo and azacitidine. According to TIBSOVO® SmPC, the median time to onset of DS is 20 days. DS occurred as early as 3 days and up to 46 days after treatment initiation during combination therapy (21). Patients treated with ivosidenib were reported to have recovered with appropriate treatment.

The pathogenesis of DS has not been fully elucidated; it likely occurs as a result of a rapid release of cytokines and a systemic inflammatory response (25). DS symptoms could involve dyspnea, hypoxia, pleural and pericardial effusions, leukocytosis, fever, weight gain, hypotension, rash, or acute renal failure (25).

DS can be life-threatening or fatal if not treated. However, if recognized early it can usually be managed effectively in clinical practice through initiation of medicinal products such as corticosteroids, diuretics, and hydroxycarbamide in conjunction with temporary interruption of treatment as clinically indicated (25).

6.2. Rationale

Increased awareness of the early signs of DS is needed to reduce the likelihood of severe complications or fatalities among patients with AML treated with IDH-inhibitors such as ivosidenib. Therefore, the Risk Management Plan (RMP) for TIBSOVO® agreed in Europe includes a Patient Alert Card (PAC) as an additional Risk Minimization Measure (aRMM) to promote the recognition of DS by the patient and therefore facilitate prompt diagnosis, and treatment of a potential DS in AML patients treated with ivosidenib. The PAC is included inside each pack of TIBSOVO® to inform patients about this risk (see Appendix 2).

Specifically, the PAC highlights important messages that will be assessed as part of this evaluation study:

1. DS is a serious risk associated with TIBSOVO® which may lead to death
2. Description of the signs and symptoms of DS
3. The actions to be taken if such symptoms occur (i.e., the need to immediately contact his/her health care practitioner).

Regulatory guidelines require aRMMs to be evaluated for their effectiveness (29). In line with this requirement, this Post-Authorisation Safety Study (PASS) will evaluate the risk minimization effectiveness of the PAC associated with TIBSOVO®.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective is to evaluate the effectiveness of the PAC to inform on the risk of DS in AML patients treated with TIBSOVO® (ivosidenib), by assessing process dimensions for patients' awareness, receipt of the material, reading, utility of the PAC, as well as knowledge and self-reported behaviour.

Table 1 summarizes the study objectives and associated outcomes.

Table 1 Objectives and outcomes

Objectives	**Outcomes**
Primary objective • To assess the effectiveness of the PAC on DS in AML patients treated by TIBSOVO®, i.e., to assess the awareness of the PAC and the knowledge about DS.	**Primary outcome** • Number of participants having at least 80% of understanding rate from pooled questions comprising awareness and knowledge items, for primary respondents and completers.

Objectives	Outcomes
Secondary objective • To assess receipt, reading, utility and self-reported behaviour related to the PAC by AML patients treated with TIBSOVO® (ivosidenib).	**Secondary outcome** • Number of participants having at least 80% of understanding rate from pooled questions comprising receipt, reading, utility and self-behaviour dimensions, for secondary respondents and completers.
Exploratory objective • To assess the global informative value of the PAC regarding DS in AML patients treated by TIBSOVO®, i.e., to assess collectively all dimensions of the PAC: awareness, knowledge, receipt, reading, utility and self-reported behaviour.	**Exploratory outcome** • Number of participants (completers) having at least 80% understanding rate in the pooled primary and secondary scores.

8. RESEARCH METHODS

This section presents the methods that will be employed to evaluate the effectiveness of the PAC across at least three countries in the European Union (EU). Additional countries may be considered if necessary to reach the sample size needed for reliable results. The study will be conducted in 3 sequential steps: a pilot step, a feasibility step (in two waves, as appropriate), and a master study (survey collection).

8.1. Study design

A multi-national, observational cross-sectional survey among adult patients who have recently received TIBSOVO® for the treatment of AML. It will be conducted in at least three countries in the EU in which TIBSOVO® is approved.

Data for this study will be collected exclusively through a participant self-administered paper survey. No additional clinical data will be collected, and no medical record review, or interventional procedures will be performed as part of this study.

8.1.1. Inclusion and exclusion criteria

Inclusion criteria

Patients will be included if they meet all of the following criteria:

1. Adult patients (female and male) aged ≥18 years at the time of recruitment.
2. Who started TIBSOVO® for the treatment of newly diagnosed AML within the last 6 months at their physician's discretion, and have been treated with TIBSOVO® prior to enrolment in the study, whether or not still receiving TIBSOVO® at the time of recruitment.
3. Able to understand and provide written informed consent, including permission to share their responses in aggregate with the EMA or national competent authorities (CA), if requested.
4. Able to read and understand in the native language of the participating country, and willing to complete the patient survey.

Exclusion criteria

1. Patients who declared having participated in user testing for this study.

8.1.2. Periods and follow-up

Study period

The study will be initiated at least 12 months after product launch in each selected EU country to allow for reasonable uptake of the product.

The overall planned period for participant enrolment will last approximatively between 12 and 18 months. Indeed, as the timing of product launch and the time needed for regulatory/ethics committee approval will vary between countries, the exact length of the enrolment period is expected to differ between countries.

As this study is cross-sectional, each participant will complete his/her survey once only, on the day of enrolment (see Section 8.2).

Study Follow-up

No follow-up will be conducted after questionnaire administration. The survey will be filled in on the day of enrolment and the participant's participation will end when the Principal Physician Investigators (PPI) collects the completed survey.

Furthermore, if a participant declines to participate at a given visit, no further attempts will be made to enrol them at subsequent visits.

8.1.3. Pilot and feasibility steps

The pilot and the feasibility steps will be conducted prior to the master study (Figure 1). User testing (i.e., testing of the participant survey wording and clarity) will be performed in parallel to the pilot and feasibility steps.

Pilot steps

As recommended by the EMA, the first phase will be the conduct of a 7-month pilot step in 4 countries (Germany, France, the Netherlands and Belgium).

The specific objective of the pilot step will be to estimate the number of newly diagnosed participants with IDH1 mutated AML in each of these countries within the past 12 months.

All the sites contacted for the pilot step will be contacted for the feasibility step unless they have withdrawn their wish to participate.

Feasibility step

The second phase will be the conduct of two feasibility waves in at least 3 countries, starting 6 months after the launch of TIBSOVO® in each of these countries.

The first feasibility wave, starting in Q2 2024, will include the countries involved in the pilot step (Germany, France, and the Netherlands), except for Belgium which has a later launch date of TIBSOVO®. Additional countries such as Austria may also be involved if needed.

A second feasibility wave will be conducted, if necessary, in 3 additional countries: Belgium, Greece, and Poland.

The specific goals of the feasibility step will be as follows:

- To estimate the actual number of participants treated with TIBSOVO® in each of these countries at ≥ 6 months post-launch.
- To estimate the projected number of participants with AML who may be treated with TIBSOVO® in the next 12 months (i.e., participants meeting the eligibility criteria) in each of these countries.
- To determine the total number of sites needed for each country.
- To assess the feasibility of the master study processes and timelines.

Country-specific Go/No Go decision

A country-specific Go/No Go decision will be made according to the results of this feasibility step.

This Go/No Go decision will be made at the site and country levels according to the following criteria:

- At the site's level, the decision matrix will be:
  - Site interested (yes/no)

  and
  - Site staff availability to manage the study (yes/no).

A Go for a site is obtained when all questions have been answered 'yes'.

- At the country's level, the decision matrix will be either:
  - a minimum number of sites: 2

  or
  - a minimum number of participants enrolled in the country, whatever the number of sites: 4.

A Go for a country is obtained when either of these two above conditions is met.

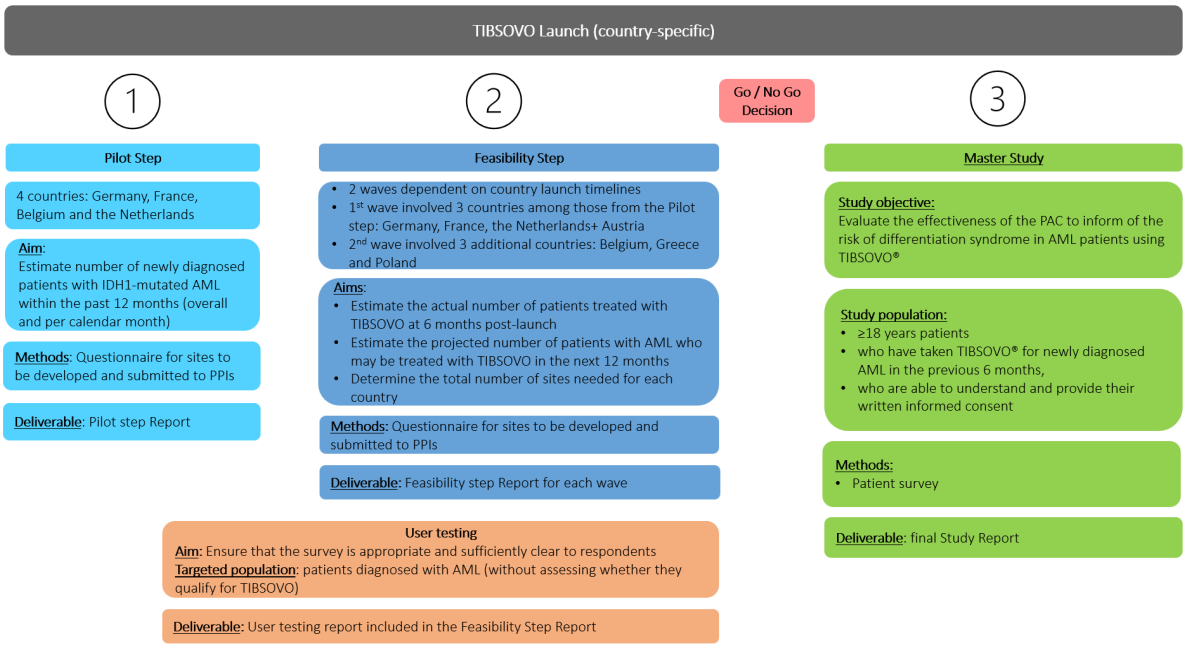

Figure 1. Study design. Additional countries to be involved in the study might be considered at the feasibility step. The feasibility step may be divided in 2 waves as described above. The first wave plans to involve France, Germany, The Netherlands, and Austria. The second wave plans to involve Belgium, Greece, and Poland. AML: Acute Myeloid Leukaemia, IDH-1: Isocitrate Dehydrogenase-1, CRF: Case Report Form, PAC: Patient Alert Card, PPI: Physician Principal Investigator.

8.1.4. Validity and readability assessment of the survey: user testing

User testing will be conducted by experienced qualitative moderators, to assess the validity and readability of the proposed survey. Moderators are experienced in healthcare research, have completed training in user testing debriefing and will be individually briefed on the study.

The aim of the user testing will be to ensure that the survey is appropriate and sufficiently clear to respondents.

The user testing will be designed to ensure that:

Survey questions are comprehensive to ensure that the variables and issues that will impact the study objective are being considered as appropriate;

- The survey is concise and manageable by respondents to minimize respondent burden and missing data, and to ensure high-quality data collection.
- Interpretations are consistent across all respondents;
- Explanation of key terms are added where necessary;

The user testing will be conducted by telephone with screen-sharing, to allow both research moderators and respondents to read at the same time the survey questions. The respondents will not be requested to fill in the survey, moderators will simply collect verbal information. User testing is a well-established qualitative research methodology used to identify problems with survey questions and response options (30).

User testing will be designed to help identify problems with survey questions, wording, response choices, etc., and ensure that respondents understand the questions.

The user testing data will be used to optimise the language used in the questionnaire prior to implementing the participant surveys. Findings from the testing will be used to improve clarity and comprehension of the survey questions.

8.1.4.1. Participants eligibility for the user testing

To be eligible to participate in the user testing, participants must be diagnosed with AML, but not treated with TIBSOVO®. Participants will be recruited via physicians' referral in the relevant countries, in collaboration with the CRO's research partner, experienced in recruiting investigators and study participants.

8.1.4.2. Sample size for the user testing

This user testing will be conducted in 9 participants (3 from each of the 3 countries identified for the pilot step) prior to the master study. The user testing will be conducted independently and in parallel to the pilot and feasibility steps since user testing does not require approval by an independent ethics committee (IEC).

This sample size is based on both qualitative research standards and feasibility considerations.

After the first four interviews, recruitment will be paused, and a preliminary analysis will be performed by the research team. Results of the preliminary analysis will help to determine if any changes are needed prior to conducting the remaining user testing.

8.1.4.3. User testing format and analysis

User testing will be conducted via telephone using a desktop sharing platform.

Before starting the interview, the moderator must obtain informed consent from participants for their participation in user testing. Due to an anticipated time commitment of 45 minutes to participate in the user testing, participants who complete the user testing will receive an appropriate compensation as per British Healthcare Business Intelligence Association fair market value guidelines.

During the conduct of the user testing, the survey will be presented item by item, and feedback will be obtained for each question. The interviewer will also record information regarding any questions received from participants or other feedback indicating difficulty with any question or wording.

Since the study is being conducted firstly (pilot phase) in Germany, France, the Netherlands and Belgium, translations will be obtained first, and user testing will be conducted using the French, Dutch, and German survey translations. As part of the translations, each survey will be further reviewed to align with the local language of the TIBSOVO® PAC approved for each participating country, and for consistency in use of local participant terminology.

All interviews will be recorded and verbatim transcribed from local language to English. Content analysis of the user testing will be organised by question to identify issues with respect to relevance, clarity, interpretation, appropriateness of the survey content, and overall burden. Specifically, if a question or element in the survey is misunderstood from what was intended, the moderator will identify the statements/descriptions/terms that caused the misunderstanding. The CRO will deliver to Servier a tracker which will comprise a listing of each question of the survey, the participants' feedback on the question, the potential issues flagged, and the suggested modifications and recommendations. Based on the findings, recommendations will

be made, as needed, to revise the language and content of master study materials. The final survey will then be reviewed and approved by Servier.
A user testing report including proposed changes to the participant survey will be provided to the PRAC as a stand-alone document.

8.2. Settings

Based on the results of the pilot and the feasibility steps, the countries involved in the master study will be Germany, France, Belgium, Austria, Greece and Poland.

As patients with AML are mainly treated by specialist physicians in hospitals or specialized cancer centres, PPIs will be identified in all possible sites in targeted countries and contacted. The final selection of sites will be informed following the pilot and feasibility steps (see decision matrix detailed in the Section 8.1.3).

In the countries where AML treatment could be prescribed and/or administered in outpatient settings and private clinics, such as in Germany, haematologists will be identified, and efforts will be made to approach as many as possible for willingness to be the point of contact with eligible participants (see Section 8.1.1).

PPIs or staff delegated by the PPI will assess participants eligibility, present the study to the participant, collect the consent, and provide the survey questionnaire to the participant.

Participant selection will be based on systematic sampling, i.e., all consecutive eligible participants are expected to be included in the study, with no selection other than the eligibility criteria and study period defined (see Section 8.1.1).

The participant will fill in the survey in the absence of PPIs or delegated staff, ideally in a waiting room, so there will be no influence from the PPIs or delegated staff (or participant perception thereof). The help of the participant caregiver is however possible if needed. Upon completion, the participant will enclose the completed survey in the pre-paid envelope provided with the questionnaire, seal it, and return it to the PPIs or delegated staff.

PPIs or delegated staff are not requested to open the envelop, check the completeness of the survey or review or correct participant answers.

8.3. Variables

8.3.1. Exposure assessment

TIBSOVO® will be administered, and as decided by the participant's physician, regardless of the participant's participation in the master study. No tests or reference treatments are utilized in this cross-sectional, non-interventional survey of participants.

8.3.2. Participant survey

The proposed survey includes the following (Appendix 1):

- Survey introduction that describes the survey objective;
- Questions regarding the awareness, receipt, reading, utility of the TIBSOVO® PAC, participants' knowledge, and self-reported behaviour;

- Questions regarding participant demographics (age and sex), the start date of TIBSOVO® treatment, and the treatment status (currently ongoing or not);

The initial participant survey will be refined based on insights from user testing (see Section 8.1.4).

8.3.3. Outcome assessment

Measure of understanding

The understanding rate – also called primary endpoint – will be assessed by calculating the primary score (based on 6 scored questions related to primary outcome) and will be interpreted considering an acceptable level/threshold of awareness and knowledge, as defined in Section 8.7.3.

The secondary endpoints will be assessed by calculating the secondary score (based on 5 scored questions related to secondary outcomes) and will be interpreted considering an acceptable level/threshold of receipt, reading, utility, and self-reported behaviour, as defined in Section 8.7.3.

Table 2 lists the study outcomes and the 15 out of 19 related-survey questions (Appendix 1), with 4 questions descriptive only (questions 5, 7, 10, and 11) and the other 11 questions contributing to the score (see Section 8.7.3.1). The 4 survey questions related to participant demographics and TIBSOVO® treatment (questions 16, 17, 18, and 19) are not listed in Table 2 as they are not directly related to the study outcomes. These 4 questions are descriptive only.

Table 2. Study outcomes and definitions

Study outcomes	Definitions	Questions numbers
Primary outcome		
Awareness	Proportion of participants who were aware of the PAC	1, 4, 5
	Proportion of participants informed via their HCPs about DS related to TIBSOVO®.	11
Knowledge	Proportion of participants with correct responses to 4 DS-risk related questions	12, 13, 14, 15
Secondary outcome		
Receipt	Proportion of participants who found the PAC in the TIBSOVO® box	2
Reading	Reason for not reading the PAC, when applicable	7

Utility	Proportion of participants by level of reported usefulness Proportion of participants by source of information about side effects of TIBSOVO®	8, 9, 10
Self-reported behaviour	Proportion of participants with correct responses to 2 self-reported behaviour questions	3, 6

Total number of questions related to study outcomes = 15 out of 19; PAC: Patient Alert Card; HCPs: Health Care Practitioners; DS: Differentiation Syndrome.

8.3.4. Participant demographics and treatment information

The following demographics and TIBSOVO® treatment information will be collected from the participant survey:

- Sex: male / female
- Age (years);
- Start date of TIBSOVO® treatment;
- TIBSOVO® treatment status (ongoing/stopped).

8.4. Data source

The participant survey will be the only data source for this master study.

This will be a self-administered paper questionnaire.

To facilitate participant recruitment, PPIs will be provided with survey information packs that include study information sheet and informed consent form, and pre-addressed/postage paid envelope for returning the completed paper survey to the CRO.

8.5. Sample size

This approximative sample size is based on both practical and statistical considerations, including the low number of targeted participants.

Considering a 90% response rate, 66 participants will have to be recruited to achieve the targeted number of evaluable surveys for primary objective (**Table 3**). Surveys will be considered "evaluable for primary objective" when at least 4 questions related to the primary outcome are completed.

Considering an expected estimate of 60 evaluable surveys for primary objective and an expected 80% understanding rate (score) overall, i.e., at least 80% of the participants with an individual understanding rate of 80% obtained score or higher, the precision will be equal to 10.2%, i.e., a 95% confidence interval (CI) of [69.8%-90.2%] (see Section 8.3.3 for definition of understanding rate).

If the targeted number of 60 evaluable surveys for primary objective is too difficult to reach, a target of 50 evaluable surveys for primary objective would allow acceptable precision of 11.1% with CI of [68.9%-91.1%]. Fifty-six (56) participants would thus have to be recruited. Indeed, due to the rarity of the disease and of the IDH1 mutation, we anticipate a low recruitment rate.

Table 3. Sample sizes according to understanding rates and precision

Understanding rates	80%				
Precision	7.0%	8.8%	9.4%	10.2%	11.1%
95% CI	73.0-87.0	71.2-88.8	70.6-89.4	69.8-90.2	68.9-91.1
Evaluable Surveys for primary objective	126	80	70	**60**	**50**
Sample size considering a 90% response rate	140	88	77	**66**	**56**

CI: Confidence Interval

8.6. Data Management

Data management (DM) will be in accordance with the standard operating procedures (SOPs) of the CRO. All DM processes, managements and SOPs used for this study will be described in the Data Management Plan (DMP).

8.6.1. Survey Collection

Survey collection and accurate documentation are the responsibility of the PPI. Before starting the master study, PPIs will be trained on the background and objectives of the study, on ethical considerations and regulatory obligations. Training on the handling of paper surveys will be provided to PPI and delegated staff, if any.

The participant will self-complete the paper survey and place it in the pre-paid envelope provided. The PPI or delegated staff will then send the sealed envelope to the CRO via postal service. The returned completed survey will be recorded by the CRO trained data entry staff in the EDC system. Single manual data entry will be performed. The quality reviewer will compare the information written or ticked in paper survey against the computerized information.

When computerized systems are used for the original recording of data, the following criteria should be met:

- Documented evidence that the EDC has been validated;
- The system provides adequate security to ensure that only authorised persons can enter/change data and allows audit trail of entries/changes;
- Existence of procedure for manual data entry in the event of a system failure;
- When possible, compliance with the Code of Federal Regulation title 21 part 11 (21CFR11) and the EMA guideline on computerized systems (EMA/INS/GCP/112288/2023);

Audits may be conducted at any time, during or after the study, to ensure the integrity of the study data.

Details of the data capture will be specified in the DMP.

8.6.2. Monitoring

Servier and the CRO will have access to a pseudonymized, complete, real-time overview of completed participant surveys.
Monitoring on-site visits or phone calls covering check of informed consent signature process and participant eligibility may be conducted. The monitoring process will be defined in the Monitoring Plan (MP). The MP will specify the frequency of monitoring, monitoring procedures, and the distribution of monitoring reports.
The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. The documents must be available for review in the event the study site is selected for monitoring, audits, or inspections.

8.6.3. Storage of Records and Archiving

The EDC will be employed for the data entry of participant survey. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

Servier is responsible for the archiving of the data together with any study-related documentation in secure servers, according to applicable laws and regulations.

The PPIs must archive documents at their study sites according to local requirements, considering possible audits and inspections from Servier and/or local authorities. The documents must be available for review in the event the study site is selected for monitoring, audits, or inspections and must be safely archived.

8.6.3.1. Investigator Site File

Each site will receive an Investigator Site File at master study initiation, which contains records and documents pertaining to the conduct of the study, including the correspondence sheet related to the participating participants, all original signed informed consent forms (ICFs) (if applicable), and adequate documentation of relevant correspondence.

Source data consist of the original surveys. No copies will be kept on site.

The PPI should retain the Investigator Site File 15 years after study discontinuation or completion in case of audit/inspection. In the event that local regulations are more stringent than that specified above, the local regulations will be adhered to.

8.6.3.2. Trial Master File (TMF)

Servier and the CRO will archive the TMF/eTMF in accordance with applicable regulatory requirements and will inform the PPIs when the archiving of the study documentation is no longer required.

8.7. Data analysis

8.7.1. General considerations

This is a descriptive study; therefore, no formal hypothesis will be tested.

A formal statistical analysis plan (SAP) provides details of all analyses, and presentation of the study data will be approved prior to database lock, in accordance with the CRO SOPs.

All continuous variables will be summarized with descriptive statistics including number of observations, mean, standard deviation, median, quartiles, minimum and maximum values. Number of missing observations will also be displayed.

Categorical variables will be summarized in frequency tables including number of observed responses in each category as well as percentages. Number of missing observations will also be displayed. Missing data will not be considered in the denominator while calculating the percentages.

All analyses will be presented overall, by country, if assessable.

All analyses will be performed using SAS® statistical software Version 9.4 or later (Cary, NC: SAS Institute Inc.).

8.7.2. Analysis of the study population and characteristics

8.7.2.1. Disposition of participants

The participant groups are defined as follow:

"**Screened**" will be defined as the total number of participants who were enrolled and not enrolled.

"**Enrolled**", will be defined as eligible participants who signed the ICF.

"**Non-Enrolled**", will be defined as participants who did not meet all the eligibility criteria.

"**Non-respondents**" will be defined as participants from the enrolled set who did not answer any survey outcomes question.

The **full analysis set (FAS)** will include participants from the enrolled set who answered at least one survey outcomes question.

"**Primary respondents**" will be defined as participants who answered at least 4 survey questions related to the primary outcome.

"**Secondary respondents**" will be defined as participants who answered at least 3 survey questions related to the secondary outcome.

"**Total respondents**" will be defined as the participants who answered at least 4 survey questions related to the primary outcome and at least 3 survey questions related to the secondary outcome.

"**Primary completers**" will be defined as participants who answered all questions related to the primary outcome.

"**Secondary completers**" will be defined as participants who answered all questions related to the secondary outcome.

"**Total completers**" will be defined as participants who answered all questions related to the primary and secondary outcome.

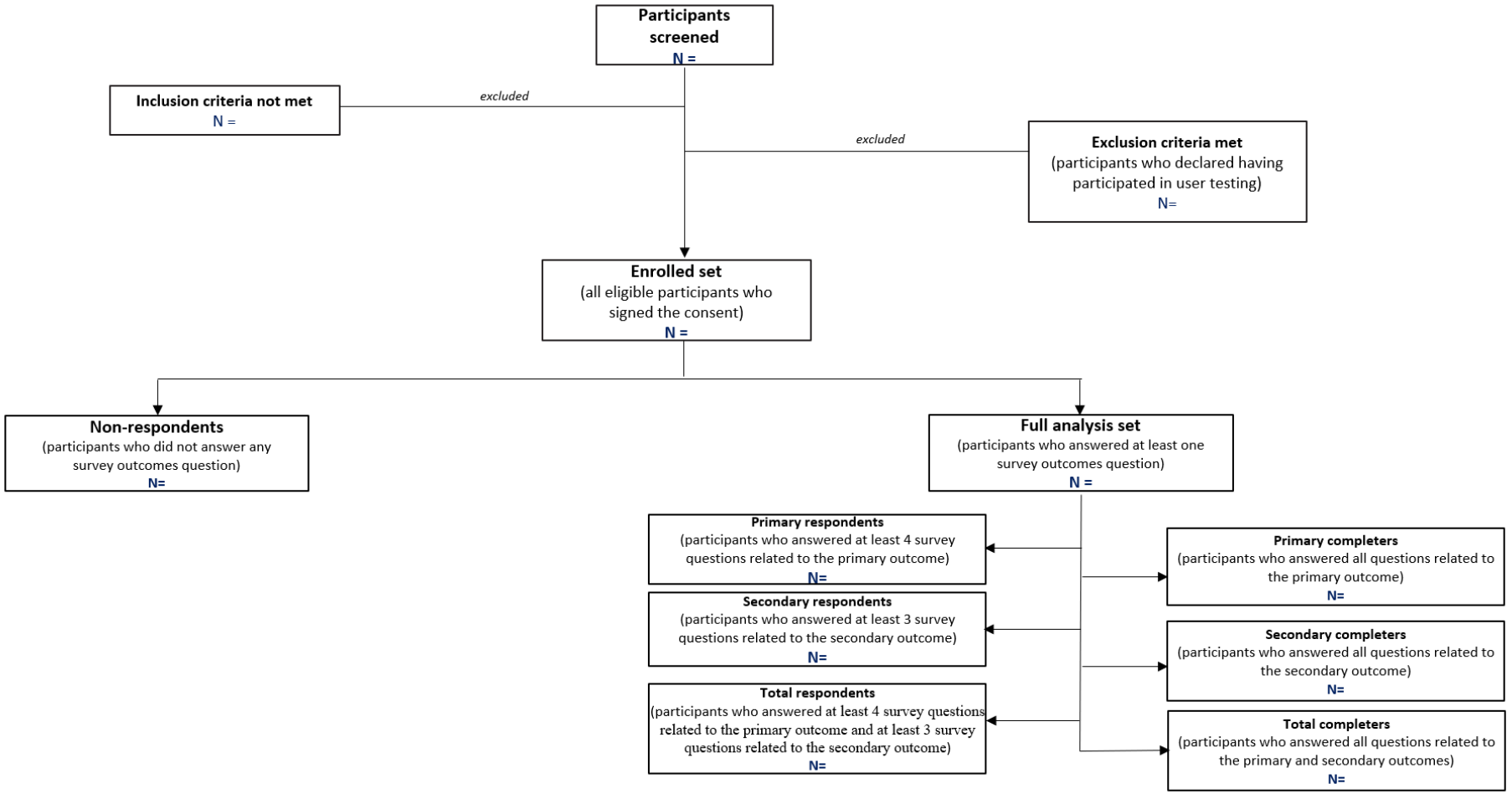

Figure 2. Flow chart of the study population

N: number of participants in each category.

The following variables will be described overall and by country:

- Total number of screened participants, and total number of eligible participants,
- Number and percentage of participants who do not meet each specific eligibility criteria and reasons for exclusion,
- Number and percentage of participants from the enrolled set,
- Number and percentage of non-respondents,
- Number and percentage of participants from the FAS,
- Number and percentage of primary respondents,
- Number and percentage of secondary respondents,
- Number and percentage of total respondents,
- Number and percentage of primary completers,
- Number and percentage of secondary completers,
- Number and percentage of total completers.

8.7.2.2. Description of participant demographics

Frequencies and percentages will be used to summarize the distribution of participant demographics described in Section 8.3.4, including missing responses, for the FAS, and for the primary completers, overall and by country.

8.7.3. Survey analysis

For each individual question, frequency and percentages of respondents will be described with mean score and percentage of correct answers, overall and by country.

Denominators used to calculate response and understanding rates for individual survey questions will reflect the number of respondents who will complete each individual survey question, including responses of 'I do not remember/ I am not sure/ I do not know'.

In the event of multiple-choice questions, the number and percentage of respondents reporting all correct responses will be provided, as well as the number and percentage of respondents reporting at least one correct response.

8.7.3.1. Main analysis

Analyses will be conducted for primary and secondary objectives, and overall (by pooling the two objectives' questions), based on outcome-related survey questions, i.e. questions 1 to 15. This main analysis is based on a respondent-level approach, as missing data is tolerated.
Scoring definitions and corresponding questions are shown in **Table 4**.

Table 4 Scoring definitions for the primary, secondary and exploratory outcomes

Study outcomes	Scoring Definitions
Primary outcome	
Awareness	4 questions, 2 of which contribute to the score (questions 1 and 4), and the other 2 (questions 5 and 11) are descriptive
Knowledge	4 questions contributing to the score (questions 12,13,14 and 15)
Primary score	Score that summarizes the overall awareness and knowledge, with 6 questions contributing to the score (questions 1,4,12,13,14 and 15)
Secondary outcome	
Receipt	1 question contributing to the score (question 2)
Reading	1 question descriptive (question 7)
Utility	2 questions contributing to the score (questions 8 and 9) 1 question descriptive (question 10)
Self-reported behaviour	2 questions contributing to the score (questions 3 and 6)
Secondary score	Score that summarizes the overall utility, self-behaviour, and receipt, with 5 questions contributing to the score (questions 2,3,6,8, and 9)
Exploratory outcome	
Overall score	Score calculated with all 11 questions contributing to the score.

Primary objective

The primary outcome is the measure of understanding, also called primary score. It is assessed using pooled questions from awareness and knowledge dimensions.

The number and percentage of participants will be described according to the estimated modalities of understanding rate. An acceptable level/threshold as recommended by EMA would be 80% of understanding rate.

Primary score will be calculated based on 6 questions. It will only be calculated for primary respondents, i.e., participants who answered at least 4 questions related to the primary outcome.

In order to normalize the maximum score to 100, the primary score will be calculated by multiplying by 50 the sum of points and dividing by the number of answered questions.

- <60%, the understanding rate is considered as insufficient.
- Between 60 and 79%, the understanding rate is deemed acceptable.

- >= 80%, the understanding rate is deemed good

Secondary objective

The secondary outcome is assessed using pooled questions from receipt, reading, utility and self-behaviour dimensions.

The number and percentage of participants will be described according to the estimated modalities of secondary score. An acceptable level/threshold as recommended by EMA would be 80 %.

Secondary score will be calculated based on 5 questions. It will only be calculated for secondary respondents, i.e., participants who answered at least 3 questions related to the secondary outcome.

In order to normalize the maximum score to 100, the secondary score is calculated by multiplying by 50 the sum of points and dividing by the number of answered questions.

- <60%, the understanding rate is considered as insufficient.
- Between 60 and 79%, the understanding rate is deemed acceptable.
- >= 80%, the understanding rate is deemed good.

Exploratory objective

An overall score will be calculated by pooling all 11 scored questions as detailed in Table 4.

This overall score will be calculated on primary and secondary respondent populations, i.e., at least 4 questions related to the primary outcome AND at least 3 questions related to the secondary outcome have to be answered.

In order to normalize the maximum score to 100, the overall score is calculated by multiplying by 50 the sum of points and dividing by the number of questions.

8.7.3.2. Completers analysis

All the main analyses will be repeated for primary and secondary completers.

This approach means that for:

- Primary outcome: no missing answer is allowed among the 6 questions related to primary outcome, whether or not there is any missing answer to question related to the secondary outcome.
- Secondary outcome: no missing answer is allowed among the 5 questions related to secondary outcome, whether or not there is any missing answer to question related to the primary outcome.
- Exploratory outcome (overall score): no missing answer is allowed among the 11 questions related to both primary and secondary outcomes. If either primary or secondary outcome has one missing answer, then the overall analysis will not be conducted.

A dimension score will be calculated for each of the dimensions, only if all questions related to the dimension are answered.

8.7.4. Missing or Incomplete Data

Missing data will be reviewed solely for the purposes of deriving the outcomes. No replacement or imputation will be performed. Descriptive statistics for continuous variables will include the available number of answers, and descriptive statistics for categorical variables will include a category for "I do not know/I do not remember/I am not sure" and "missing", when applicable.

8.8. Quality control

SOPs will be followed where appropriate to ensure data quality and integrity, including archival of statistical programs and validation of derived variables and analyses, as per ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) and ENCePP Code of Conduct for PAS studies (31,32).

All key study documents (including this protocol, participant survey, SAP, and study report) will undergo quality control review and senior scientific review. For the analysis, programming conducted by the study analyst will be reviewed by a senior statistician.

8.9. Limitations of the research methods

This study will endeavour to collect an estimate of 60 participants evaluable surveys for primary objective. From a statistical perspective, this sample size is small, and therefore subgroup analyses may lack precision.

To promote generalizability, PPIs will be requested to invite all eligible participants from their practices to participate in the survey. Nonetheless, the characteristics of the participants who accept to participate in the survey may differ from those who do not participate. To reduce selection bias, a consecutive enrolment of eligible participants is planned whenever possible.

Furthermore, there will be no formal statistical comparison with the non-respondent subgroup since a very small number of non-respondents is expected, i.e., a very small number of participants who will not answer at all. Indeed, if they accept to participate, and as they will respond to the survey on the same day as their enrollment, they will probably answer at least one question.

The selection of a threshold for success is subjective, therefore, the results will be contextualized with other available information in line with the EMA Guidelines of Pharmacovigilance, Module XVI (29).

The measures to minimize information bias for this study are:

- User testing will be conducted to assess and improve the clarity and precision of the survey;
- Participants are instructed to complete the survey in one sitting (to minimize the likelihood of looking up the correct answers);
- Questions must be answered in sequence or as instructed;
- Participants who complete the survey will not be contacted to clarify or revise their responses.

8.10. Other aspects

8.10.1. Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. They should be agreed by Servier before submission to relevant competent authorities.
Major (i.e., substantial, significant) amendments will be approved by the relevant competent authorities and will usually require submission or notification to the relevant IEC for approval, if applicable. In such cases, the amendment will be implemented at the study site only after favourable opinion has been obtained. The CRO must send a copy of the approval letter from the IEC to Servier.
Minor (non-substantial) protocol amendments, including administrative changes, will be filed by each participating PPI, and will be notified to the relevant IECs or competent authorities where required by local laws and/or pertinent regulations.
Any amendment that could have an impact on the participant's agreement to participate in the study requires an updated participant informed consent.

8.10.2. Protocol deviation

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The PPI is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of participants.

When a deviation from the protocol is identified, the PPI must ensure the CRO is notified. The CRO will follow up with the PPI, as applicable, to assess the deviation and the possible impact on the reliability of the study results.

8.10.3. Study Management

This study will be performed by the contract research organization the CRO, with guidance, input, review, and approval of Servier, including development of materials, recruitment, training and management of study sites, data management and analysis.
Servier reserves the right to discontinue the study prior to inclusion of the intended number of participants but intends only to exercise this right for valid scientific or administrative reasons. However, the discontinuation of the study requires approval of the EMA. In a such event, an interim report will be provided. Both Servier and the CRO reserve the right to terminate the PPI participation according to contractual agreement. The CRO is to notify the IEC in writing of the study completion or early termination and send a copy of the notification to Servier.

PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Conduct of the Study

In this study, the treatment decision falls within current established practice. No additional diagnostic, therapeutic, or monitoring processes are required for participation in the study, and the prescription of TIBSOVO® is clearly separated from the decision to include the participant in the study.

The study will be conducted in compliance with this protocol, the principles laid down by the current revision of the Declaration of Helsinki, the ISPE guidelines for Good Pharmacoepidemiology Practices and local legal and regulatory requirements (32,33). This PASS will also follow the EU Good Pharmacovigilance Practices (GVP) Modules VIII and XVI guidelines (29,34).

9.2. Institutional Review Board(s) (IRBs)/Independent Ethics Committee(s)

Prior to the start of the master study, documented approval or favourable opinion from adequate IRBs/IECs, and CAs where applicable, will be obtained for the participating sites in all countries where reference to an IRBs/IEC/CA is required. When necessary, an extension, amendment, or renewal of the IRBs/IEC/CA approval must be obtained and forwarded to Servier.

9.3. Participant Information and Consent

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki (33), IRBs/IECs requirements and local regulations, PPIs, or their delegate, must get written consent, in all countries where it is required, from each participant after giving the appropriate information regarding the aims, methods, anticipated benefits, risks, their rights and any other relevant aspect of the study relevant to the decision (or not) to participate. Informed consent forms and all verbal and written study related information must be provided in a language fully comprehensible to the participants. The participants must be informed that they are free not to participate in the study and they have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study. The investigator is to discuss with the participant about appropriate steps for withdrawal of their consent from the study.

The initial and any subsequently revised participant information letter and ICF must receive the IECs/IRBs approval/favourable opinion prior to being given to participants.

Informed consent will be sought using the approved ICF and signed and dated by the PPIs or the delegated staff and the participant before completing the master study. By signing the informed consent form, the participant consents to participate in the study.

An original copy of each signed ICF must be given to the participant. A second original copy must be filed in the Investigator Site File at the study site.

9.4. Participant Confidentiality

Servier, the CRO as well as all PPIs, and delegated staff participating in this study ensure adherence to all applicable data privacy protection regulation. All personal data related to study participants, PPIs, and delegated staff will be treated in compliance with all applicable national and international data protection and privacy laws and regulations, including the GDPR legislation (Regulation (EU) 2016/679)(35).

To ensure confidentiality, data will only be transferred in an encoded form. Participant individual data will be pseudonymized. A unique survey code will be assigned to each participant. This unique survey code will be entered into the study-specific database and only the PPIs will have access to the link between the participant survey unique code and participant identity. All records identifying the participant will be kept confidential at the study sites and will not be made publicly available.

The entire documentation made available to Servier and the CRO will not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify participants. Participants' names will not be supplied to Servier or the CRO. If a participant's name appears on any document, it must be obliterated before a copy of the document is supplied to Servier or the CRO. Servier PV officer may ask for additional clarification to the PPI but will not be allowed to directly contact any participant.

9.5. Participant Insurance

In this study, no risks beyond regular therapy exist for the participant, so that there is no additional hazard arising from study participation. Therefore, there is no need for additional protection of the participant by a specific participant insurance. The general regulations of medical law and the professional indemnity insurance of the PPIs involved, provide sufficient protection for both participant and PPI.
Furthermore, no study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

This study is collecting information from participants using a survey at a single time point. It is not designed to collect information on any specific Servier product. Collecting adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), other safety findings or product complaints is not part of the study objectives. AEs, ADRs, other safety findings or product complaints are therefore not foreseen to be reported.

Nonetheless, it is expected that PPIs could spontaneously report any safety events (AEs/ADRs, other safety findings or product complaints), using Adverse event / Adverse drug reaction / Special situation form, in accordance with routine practice. Such reports should be submitted to the marketing authorisation holder via relevant Local Pharmacovigilance office mail box for the country in accordance with local procedures. In the case of any handwritten note related to an AE / SAE/ ADR / Special situation reported by the participant on the survey, the CRO data entry staff will report it to the Sponsor.
Any AE information received will be documented and reported following the Servier procedures, EU Guideline on Good Pharmacovigilance Practices and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004).

The process for safety reporting will be further described in a safety management plan.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the survey objectives, detailed methods, results, discussion, and conclusions will be developed for submission to EMA within 12 months of the end of data collection or study discontinuation.

In addition, the protocol and an abstract summarizing the study results will be posted on the EU PAS register, as per ENCePP Code of Conduct for PAS studies (31).

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (36). The rights of the PPIs and of Servier with regard to the publication of this study results are described in the PPI contract. As a general rule, no study results should be published prior to finalization of the study report.

Should the data from this study be considered for reporting at a scientific meeting or for publication in a scientific journal, Servier will be responsible for these activities and will work with the CRO and the PPIs to determine how the publication is written, the number and order of the authors, the journal or scientific meetings to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Servier, such consent and approval not to be unreasonably withheld. Furthermore, Servier should communicate to the EMA and the competent authorities of the Member States participating in the master study , the final manuscript of the article within two weeks after first acceptance for publication, in order to allow the EMA to review the results and interpretations to be published in advance.

12. REFERENCES

1. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. Lancet Lond Engl. 2018 Aug 18;392(10147):593–606. [PE0166456]

2. Cancer.net [Internet]. 2023 [cited 2023 Jun 1]. Leukemia - Acute Myeloid - AML: Statistics. Available from: https://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics#:~:text=The%20disease%20is%20the%20second,of%20diagnosis%20is%20age%2068.

3. Percival ME, Lai C, Estey E, Hourigan CS. Bone marrow evaluation for diagnosis and monitoring of acute myeloid leukemia. Blood Rev. 2017 Jul;31(4):185–92. [PE0163498]

4. Hamid GA. Chapter 3: Acute Leukemia Clinical Presentation. In: Leukemia [Internet]. Guenova, M. InTech Open; 2013. Available from: http://dx.doi.org/10.5772/45914

5. American Cancer Society. cancer.org. 2023 [cited 2023 Jun 1]. Key Statistics for Acute Myeloid Leukemia (AML). Available from: https://www.cancer.org/cancer/types/acute-myeloid-leukemia/about/key-statistics.html [PE0173211]

6. Lubeck DP, Danese M, Jennifer D, Miller K, Richhariya A, Garfin PM. Systematic Literature Review of the Global Incidence and Prevalence of Myelodysplastic Syndrome and Acute Myeloid Leukemia. Blood. 2016 Dec 2;128(22):5930–5930. [PE0166412]

7. Panjabi S, Bychenkova A, McCloskey C, Nair S, Price K, Yucel E. PCN331 humanistic burden of newly diagnosed versus relapsed/refractory acute myeloid leukemia. Value Health. 2019 Nov 1;22:S500. [PE0166413]

8. Hughes M. The Global Incidence And Prevalence Of Acute Myeloid Leukemia Over The Next Ten Years (2017-2027). J Cancer Res Ther. 2017 Supp;13:pS50-S50. [PE0166414]

9. Nagel G, Weber D, Fromm E, Erhardt S, Lübbert M, Fiedler W, et al. Epidemiological, genetic, and clinical characterization by age of newly diagnosed acute myeloid leukemia based on an academic population-based registry study (AMLSG BiO). Ann Hematol. 2017 Dec;96(12):1993–2003. [PE0163431]

10. Zatloukalová S, Azeem K, Čerňan M, Holý O. Epidemiology, risk factors and possibilities for the prevention of acute leukaemia. Epidemiol Mikrobiol Imunol Cas Spolecnosti Epidemiol Mikrobiol Ceske Lek Spolecnosti JE Purkyne. 2021;70(3):208–20. [PE0166424]

11. Dinmohamed AG, Visser O, van Norden Y, Blijlevens NMA, Cornelissen JJ, Huls GA, et al. Treatment, trial participation and survival in adult acute myeloid leukemia: a population-based study in the Netherlands, 1989-2012. Leukemia. 2016 Jan;30(1):24–31. [PE0166411]

12. Santé Publique France. National estimates of cancer incidence and mortality in metropolitan France between 1990 and 2018 - Study based on the French network of cancer registries, Francim - Overview. Santé Publique France; 2018.

13. Visser O, Trama A, Maynadié M, Stiller C, Marcos-Gragera R, De Angelis R, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer Oxf Engl 1990. 2012 Nov;48(17):3257–66. [PE0143078]

14. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica. 2012 Dec;97(12):1916–24. [PE0163449]

15. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015 Jul 16;126(3):291–9. [PE0163039]

16. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol Off J Am Soc Clin Oncol. 2012 Jul 20;30(21):2670–7. [PE0162718]

17. Bullinger L, Döhner K, Döhner H. Genomics of Acute Myeloid Leukemia Diagnosis and Pathways. J Clin Oncol Off J Am Soc Clin Oncol. 2017 Mar 20;35(9):934–46. [PE0162867]

18. Issa GC, DiNardo CD. Acute myeloid leukemia with IDH1 and IDH2 mutations: 2021 treatment algorithm. Blood Cancer J. 2021 Jun 3;11(6):107. [PE0162842]

19. Popovici-Muller J, Lemieux RM, Artin E, Saunders JO, Salituro FG, Travins J, et al. Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1 Mutant Cancers. ACS Med Chem Lett. 2018 Apr 12;9(4):300–5. [PE0165240]

20. Fernandez PM, Recher C, Doronin V, Calado RT, Jang JH, Miyazaki Y, et al. AGILE: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Ivosidenib in Combination with Azacitidine in Adult Patients with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation. Blood. 2019 Nov 13;134(Supplement_1):2593–2593. [PE0163974]

21. European Medicines Agency. Tibsovo (ivosidenib) An overview of Tibsovo and why it is authorised in the EU [Internet]. 2023 [cited 2023 Jun 1]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tibsovo-0#:~:text=The%20study%20showed%20that%20Tibsovo,74)%20of%20patients%20on%20placebo.

22. Frankel SR, Eardley A, Heller G, Berman E, Miller WH, Dmitrovsky E, et al. All-trans retinoic acid for acute promyelocytic leukemia. Results of the New York Study. Ann Intern Med. 1994 Feb 15;120(4):278–86. [PE0163115]

23. Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. Br J Haematol. 2019 Oct;187(2):157–62. [PE0173651]

24. Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. N Engl J Med. 2022 Apr 21;386(16):1519–31. [PE0167327]

25. Fathi AT, Stein EM, DiNardo CD, Levis MJ, Montesinos P, de Botton S. Differentiation syndrome with lower-intensity treatments for acute myeloid leukemia. Am J Hematol. 2021 Jun 1;96(6):735–46. [PE0165058]

26. Tzogani K, Røshol H, Olsen HH, Aas IB, Dalhus ML, Håkonsen GD, et al. The European Medicines Agency Review of Gilteritinib (Xospata) for the Treatment of Adult Patients with Relapsed or Refractory Acute Myeloid Leukemia with an FLT3 Mutation. The Oncologist. 2020 Jul;25(7):e1070–6. [PE0173650]

27. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med. 2018 Jun 21;378(25):2386–98. [PE0163035]

28. Norsworthy KJ, Mulkey F, Scott EC, Ward AF, Przepiorka D, Charlab R, et al. Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis. Clin Cancer Res Off J Am Assoc Cancer Res. 2020 Aug 15;26(16):4280–8. [PE0161659]

29. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Module XVI : Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3). 2021 Feb. Report No.: EMA/204715/2012 Rev 3. [PE0161068]

30. Evaluating survey questions. In: Groves RM, Fowler Jr FJ, Couper MP, Lepkowski JM, Singer E, Tourangeau R. Survey Methodology. 2nd ed. Wiley; 496 p. 263-266 (Wiley Series in Survey Methodology). [PE0175503], [PE0175504]

31. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The ENCePP Code of Conduct. 2018 Mar. Report No.: EMA/929209/2011. [PE0111078]

32. Public Policy Committee. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2–10. [PE0131813]

33. World Medical Association. WMA Declaration of Helsinki – Ethical involving human subjects [Internet]. 2022 [cited 2023 Jan 27]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

34. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3). 2017 Oct. Report No.: EMA/813938/2011 Rev 3*. [PE0143907]

35. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) [Internet]. [cited 2023 Jan 30]. Available from: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32016R0679

36. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals [Internet]. 2023 May. Available from: www.icmje.org

13. APPENDICES

Appendix 1: List of stand-alone documents

Appendix 2: TIBSOVO® Patient Alert Card

Appendix 3: ENCePP checklist for Study Protocols

Appendix 1: LIST OF STAND-ALONE DOCUMENTS

Document reference	**Date**	**Title**
Servier_IMPACTA_Survey_v5.0	11-2025	MEA - Cross-sectional study to assess the effectiveness of aRMM – Questionnaire
Servier_IMPACTA_ Survey Correct Answers_v5.0	11-2025	MEA - Cross-sectional study to assess the effectiveness of aRMM – Answers to Questionnaire
Servier_IMPACTA_Statistical Analysis Plan_v3.0	01-2026	MEA - Cross-sectional study to assess the effectiveness of aRMM – SAP

Appendix 2: TIBSOVO® Patient Alert Card

CONTENT OF THE PATIENT ALERT CARD

PATIENT ALERT CARD – ACUTE MYELOID LEUKAEMIA

Tibsovo 250 mg film-coated tablets
ivosidenib

Information for the patient treated for acute myeloid leukaemia

This Patient Alert Card contains important information for you and healthcare professionals about Tibsovo.

- Keep this card with you at all times.
- Tell any doctor, pharmacist or nurse that you are taking Tibsovo.
- Contact immediately a healthcare professional and show him the Patient Alert Card if you get any of the symptoms listed below.
- Make sure you use the latest version of this card. This will be the one found in your latest box of tablets.

About your treatment

- Tibsovo is used to treat adults with acute myeloid leukaemia (AML) and is given in combination with another anti-cancer medicine called 'azacitidine'. Tibsovo is only used in patients whose AML is related to a change (mutation) in the IDH1 protein.
- Tibsovo can cause **serious side effects** including a serious condition known as **differentiation syndrome**.
- Differentiation syndrome may be life-threatening if not treated.
- Differentiation syndrome in patients with AML happened up to 46 days after starting treatment.

Seek urgent medical attention if you get any of the following **symptoms** of differentiation syndrome:

- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or light-headedness
- rapid weight gain
- swelling of your arms or legs

See the Tibsovo Package Leaflet for more information.

Information for healthcare professionals

- Patients treated with Tibsovo have experienced differentiation syndrome which may be life-threatening or fatal if not treated.
- Differentiation syndrome in patients with AML happened up to 46 days after starting treatment.
- Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells.
  Symptoms include:

  Non-infectious leukocytosis, peripheral oedema, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumour lysis syndrome and creatinine increased.

Appendix 3: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 section number 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). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Cross-sectional study to assess the effectiveness of the patients' alert card to inform on risk of differentiation syndrome in AML patients treated with for TIBSOVO® (Ivosidenib)

EU PAS Register® number:
Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

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.

The study will be registered following European Medicines Agency endorsement and prior to start of data collection.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section 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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
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**	**Section Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number(s)**
4.1 Is the source population described?	☒	☐	☐	8.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.1.2
4.2.2 Age and sex?	☒	☐	☐	8.1.1
4.2.3 Country of origin?	☒	☐	☐	8.2
4.2.4 Disease/indication?	☒	☐	☐	8.1.1
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.1.1

Comments:

Section 8.1.2 specified there is no follow-up.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 8.3.1 specified there is no exposure, since this is an observational study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number(s)**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.3 and 8.7.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.3 and 8.7.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	8.3.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number(s)**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number(s)**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.3.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 8.3.1 specified there is no exposure, since this is an observational study. The start date of treatment and treatment status (i.e. ongoing or stopped) will be abstracted from participant survey, as part of the participants' characteristics (section 8.3.4).

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number(s)**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.2
10.4 Are stratified analyses included?	☒	☐	☐	8.7.3
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.3.2

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number(s)**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6.3
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.1.3 and 8.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.4

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number(s)**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	8.10.1 and 8.10.2

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number(s)**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: __HAUVILLE Cécile_____

Date: 13 January 2026

Signature: _____

Signé par :
Cecile HAUVILLE
AC12943868BA498...