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STATISTICAL ANALYSIS PLAN No LUF-44-001

Safety and Efficacy of Lipiodol® Ultra Fluid in Association with Surgical Glues during Vascular Embolization

Phase IV clinical study

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BIOSTATISTICIAN [redacted]	**Date and Visa**
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AIS	All Included Set
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
COVID	COrona VIrus Disease
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
IMP	Investigational Medicinal Product
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
LUF	Lipiodol® Ultra Fluid
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TS	Treated Set
WHO	World Health Organisation

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1. SUMMARY OF THE STUDY PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet, Protocol No. LUF-44-001: "Safety and Efficacy of Lipiodol® Ultra Fluid in Association with Surgical Glues during Vascular Embolization". This analysis plan is based on the protocol Version 3.0 dated January 20, 2017. [redacted]

1.1. Study objectives

The primary objective is to evaluate the per-procedure safety of Lipiodol® Ultra Fluid in association with surgical glues during vascular embolization.

The secondary objectives of the trial are:

- to evaluate the safety of Lipiodol® Ultra Fluid in association with surgical glues up to one month after the last vascular embolization procedure,
- to evaluate the efficacy of Lipiodol® Ultra Fluid in association with surgical glues in vascular embolization.

1.2. Study design

LUF-44-011 is a Phase IV, multicenter, open label, single arm, post-marketing study designed to investigate the safety of Lipiodol® Ultra Fluid in association with surgical glues used according to each site medical practice of vascular embolization.

The vascular embolization using Lipiodol® Ultra Fluid in association with surgical glue (e.g. the mixture) is performed as study procedure.

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

Demographic parameters are age, sex, body weight, height, and body mass index (BMI). BMI is calculated, when body weight and height are available, as follows:

$$BMI = \frac{BodyWeight\,(Kg)}{Height\,(m)^2}$$

Other baseline characteristics are:

- Subjects' medical history,
- Therapeutic/Palliative strategy at enrolment,
- Prior/concomitant medications at enrolment.

2.2. Efficacy criteria

Efficacy criteria are the following assessments:

- Target obliteration per lesion evaluated before the first procedure according to 4 level-score: 1. <50%; 2. 50-75%; 3. 75-99%; and 4. 100% corresponding to a complete nidus obliteration rate,
- Post-procedure obliteration per lesion evaluated after each procedure according to the same 4 level-obliteration-score,
- Successful lesions embolization expressed as the lesions achieving the targeted percentage of obliteration.

2.3. Safety criteria

2.3.1. Primary criterion

The primary evaluation criterion is the number and percentage of subjects experiencing adverse drugs reactions (ADRs) occurring during the course of each vascular embolization procedure after administration of Lipiodol® Ultra Fluid in association with surgical glues (e.g. the mixture) and before catheterization laboratory discharge.

All adverse events (AEs) assessed as related to the mixture of Lipiodol® Ultra Fluid and surgical glues will be qualified as ADRs.

2.3.2. Secondary Safety Criteria

Secondary criteria included to support the primary endpoint are the following:

- ADRs from the first administration of Lipiodol® Ultra Fluid in association with surgical glues up to the end of follow-up period,
- The complete set of AEs collected during the study, regardless of causal relationship assessments, from written informed consent until end of the follow-up period.

2.4. Other criteria

Not Applicable.

3. STATISTICAL METHODS

3.1. General considerations

After the database lock, the statistical analysis will be performed [redacted] under the supervision of Guerbet on the basis of the present document. A quality control of the statistical analysis will be performed by the CRO to ensure the reliability of the results prior to providing the results to Guerbet.

Tabulations of quantitative parameters will include the following summary statistics: Number of Subjects / Mean / Standard Deviation (SD) / Minimum / Median / Maximum. The mean and median will be reported to 1 decimal more than the data; SD to 2 more decimals than the data; and minimum and maximum to the same number of decimals as the data.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. Percentages will be calculated on the total of non-missing recorded categories.

Duration will be computed as follows:

(End Date – Start Date) + 1 day(s)

Of note, duration of AEs with same "Start Date" and "End Date" will be listed as "< 1 day".

Time interval between two events (for example, visits, assessments, …) will be computed as follows:

Date of Event 2 – Date of Event 1 day(s)

The baseline value will be defined as the last available value prior to the first administration of the investigational product.

All outputs will be produced using SAS® version 9.4 or a later version.

3.2. Null and alternative hypothesis

No specific hypothesis can be set up and no statistical test are planned (see 3.3 for justification).

3.3. Determination of sample size

According to Guerbet best knowledge of the use of Lipiodol® Ultra Fluid along with glues in embolization procedure, no particular safety signal with a related incidence could lead to design a safety study with a specific sample size. Therefore, the number of subjects for the study is based on the requirement of 125 subjects as specified by SEC radio-diagnostic on January 19th, 2017.

3.4. Adjustment for covariates

Not applicable.

3.5. Handling of dropouts or missing data

No imputation will be performed in this trial.

3.6. Interim analyses and data monitoring

No formal interim analysis was planned. Nevertheless, a Data Safety Monitoring Board (DSMB) will be set up within Guerbet including a safety physician, Guerbet medical expert and the clinical project manager. This DSMB will review the following monitored data on a quarterly basis as a minimum:

- AEs and SAEs,
- Fatal SAE as soon as it is reported,
- Any reason (adverse event or completion of the treatment/palliative strategy) of any new therapeutic / palliative procedure administration within the follow-up period.

[redacted]

3.7. Multicenter studies

The number of patients included in each center will be displayed in a disposition table.

3.8. Multiple comparisons/Multiplicity

Not applicable as no statistical tests are planned.

3.9. Use of an "efficacy subset" of subjects

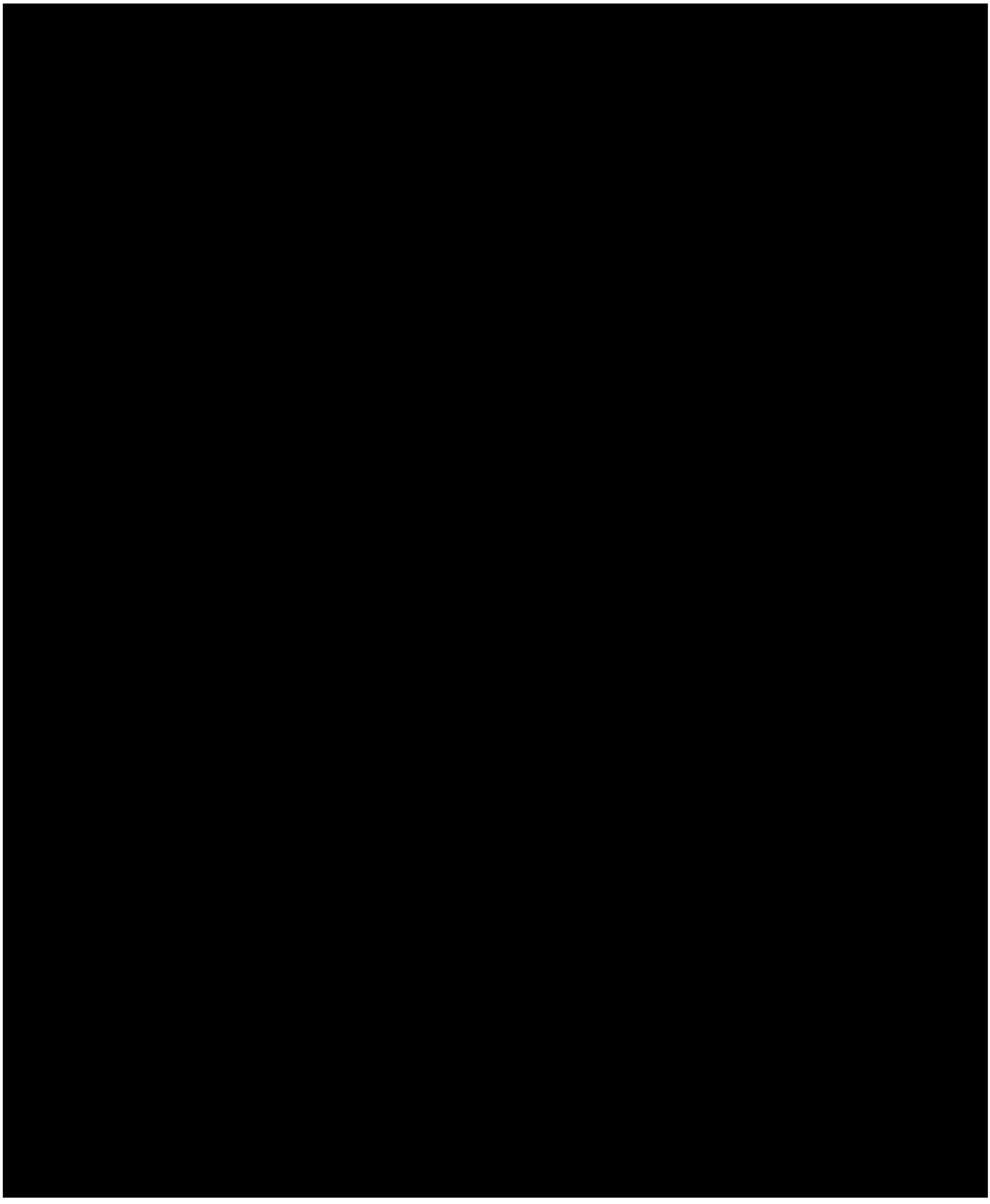
Not applicable.

3.10. Active control studies intended to show equivalence

Not applicable.

3.11. Examinations of subgroups

Not applicable.



[redacted]

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of subjects

Subject disposition will be based on all subjects included who have sign their informed consent form (ICF) and tabulated for the following categories:

- Total number of subjects enrolled,
- Total number of subjects exposed (at least one injection of the mixture regardless of the quantity),
- Number (percentage) of subjects by study visit,
- Number (percentage) of subjects completing the study,
- Number (percentage) of subjects prematurely discontinuing from study,
- Primary reason for premature discontinuation.

Of note, If a patient withdrew for Adverse Event and at least one adverse event is coded with PT=« COVID-19 » then the reason of premature withdrawal will be put at COVID-19 but if no AE is coded with PT=« COVID-19 » then the reason of premature withdrawal will be put at Adverse Event other than COVID-19.

Moreover, if a patient withdrew for other reason, then the reason of premature withdrawal will be derived from the specify field as the following:

Specify field of "Other Reason"	Reason of premature withdrawal
"COVID-19 crisis preventing patient to follow protocol schedule"	COVID-19 pandemic preventing patient to follow protocol schedule
"Withdrawal of patient's consent due to Covid-19 pandemic"	Withdrawal of patient's consent due to COVID-19 pandemic
Other	Other reason

Listings of the disposition of subjects will be provided in CSR appendix 16.2.1.

5.2. Data Sets Analysed and protocol deviations

Data sets analysed

There will be two subject sets defined for this study: All Included Set (AIS) and Treated Set (TS).

All Included Set (AIS): this is the target set consisting of all subjects enrolled in the study and having signed the informed consent. This set will be used for describing disposition, demographic data, medical history and concomitant medication, unless otherwise noted.

Treated Set (TS): will include all AIS subjects receiving at least one injection of the mixture of Lipiodol® Ultra Fluid and surgical glues regardless of the quantity. This set will be used for describing demographic and baseline data, extent of exposure and all safety and efficacy parameters.

Analyses Sets	AIS	TS
Disposition	✓	
Demographics and Baseline characteristics	✓*	✓
Exposure		✓
Safety assessment: Main criterion		✓
Safety assessment: Secondary criteria		✓
Efficacy assessment		✓
Long term follow-up assessment		✓
Listings	✓	

* If there is a difference higher than 10% between the number of patients in AIS and in TS.

Protocol deviations

As per ICH E3 guideline, a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, with or without impact to the patient safety or the efficacy assessments. Protocol deviations are displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study. The list of protocol deviations is presented in the table below and can be updated if necessary. Protocol deviations will be gathered from monitoring files and clinical database.

Of note, if the reason of deviations is related to the COVID pandemic then it will be indicated in the Statistical Data Review Meeting Minutes (DRM) and the corresponding deviation presented apart.

The deviations are listed in the table below:

Category	Description	Source
Inclusion criteria not met/ Non-inclusion criteria met	Inclusion criteria n°01 not met	Clinical data base
	Inclusion criteria n°02 not met	Monitoring
	Inclusion criteria n°03 not met	Clinical data base
	Inclusion criteria n°04 not met	Monitoring
	Inclusion criteria n°05 not met	Clinical data base
	Non-inclusion criteria n°01 met	Monitoring
	Non-inclusion criteria n°02 met	Clinical data base
	Non-inclusion criteria n°03 met	Monitoring
	Non-inclusion criteria n°04 met	Monitoring
	Non-inclusion criteria n°05 met	Monitoring
	Non-inclusion criteria n°06 met	Clinical data base
	Non-inclusion criteria n°07 met	Clinical data base
	Non-inclusion criteria n°08 met	Clinical data base
	Non-inclusion criteria n°09 met	Monitoring
	Non-inclusion criteria n°10 met	Monitoring
	Non-inclusion criteria n°11 met	Monitoring
	Non-inclusion criteria n°12 met	Monitoring
	Non-inclusion criteria n°13 met	Monitoring

Category	Description	Source
Forbidden concomitant medication	Concomitant medication significantly impacting safety (Beta-blockers, Metformin, Interleukin II)	Clinical data base
	Concomitant medication with effective anti-coagulant therapy	Clinical data base
IMP deviation	Temperature excursion for IMP	Monitoring
	IMP management not appropriate	Monitoring
	Volume of Lipiodol® Ultra Fluid > 15 mL	Clinical data base
	Lipiodol and surgical glue mixture not administered via selective arterial catheterization	Monitoring
Missing data	Age is missing	Clinical data base
	Sex is missing	Clinical data base
	Weight is missing	Clinical data base
	Height is missing	Clinical data base
	Medical history is missing	Clinical data base
	Number of lesions to be treated is missing	Clinical data base
	Location of lesions to be treated is missing	Clinical data base
	Type of lesions to be treated is missing	Clinical data base
	Target level obliteration is missing	Clinical data base
	Name of associated surgical glue is missing	Clinical data base
	Volume of mixture used is missing	Clinical data base
	Mixture ratio is missing	Clinical data base
	Post-procedure obliteration obtained is missing	Clinical data base
	Other embolization material used is missing	Clinical data base
Non-respect of study's schedule and procedures	Enrolment visit (ICF signature date) performed more than 7 days before study procedure	Clinical data base
	Optional Second study procedure performed more than 30 days after first study procedure	Clinical data base
	Follow-up visit performed less than 27 days or more than 33 days after last study procedure	Clinical data base
	Compatibility between Lipiodol and glue not performed by site	Monitoring
GCP deviation	Deviations related to ICF signature process	Monitoring
	Source document management not appropriate	Monitoring
	SAE Management not appropriate	Monitoring

Frequency and percentages of subjects with protocol deviations will be presented. A listing of all protocol deviations will also be provided in CSR appendix 16.2.2.

5.3. Measurements of study drug compliance

Study drug in this study refers to the mixture. No analyses will be performed on study drug compliance.

5.4. Demographic and Other Baseline Characteristics

Demographic and Other Baseline Characteristics will be tabulated using the AIS and TS.

5.4.1. Demographic data

The following demographic parameters, at enrolment (Day -7 to Day 0), will be presented:

- Age (in years),
- Gender,
- Body weight (in kg),
- Height (in cm),
- BMI (in kg/m²).

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age, body weight, height and BMI. Frequency and percentages will be calculated for gender. The denominator will be the number of subjects in the set for which demographic characteristics summaries will be presented.

Listing of all demographic parameters will be presented in CSR Appendix 16.2.4.

5.4.2. Study disease

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for the number of lesions to be treated with the mixture. Number and frequency of the variable "number of lesions to be treated" categorized in class will be also tabulated (1 lesion, 2 lesions, 3 lesions and > 3 lesions).

The main lesions (up to three) to be treated with the mixture will be described in terms of location and type. Summary tables will present these characteristics by subject (number and % of subjects) and by lesion (number and % of lesions).

5.4.3. Risk factors

Not Applicable.

5.4.4. Medical history and concomitant diseases

Medical History and associated diseases will be coded in System Organ Class (SOC) and Preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) latest version in force at the date of data base lock.

Summary tables (number and % of subjects) grouped by SOC and PT will be presented for Medical History firstly (past) then for concomitant diseases (present). Medical histories are those "Not Ongoing" and concomitant diseases are those "Ongoing" at the enrolment visit. The number and % of subjects presenting with at least one Medical History under medication will be presented.

Listing of all diseases, with a flag for ongoing diseases, will be presented in CSR Appendix 16.2.4.

5.4.5. Clinical laboratory evaluation at baseline

Not Applicable.

5.4.6. Vital signs, physical findings and other observations related to safety at baseline

Not Applicable.

5.4.7. Prior therapies

Subjects' prior medications within 7 days prior to the first study procedure will be coded in Anatomic Therapeutic Chemical (ATC) using the WHO Drug dictionary latest version in force at the date of data base lock.

Summary tables (number and % of subjects) grouped by the first and the last level of ATC codes will be presented for prior medications (those with "End of Treatment" coded 1, 2 or 3).

Listing of all prior medications will be presented in CSR Appendix 16.2.4.

5.4.8. Other baseline characteristics

5.4.8.1 Therapeutic/Palliative strategy at enrolment

Summary tables will present the number of subjects with at least one previous procedure and one next scheduled procedure, together with the type of procedure (number and % of subjects). Previous and next type of procedure will also be presented by lesion (number and % of lesions).

5.4.8.2 Second vascular embolization at enrolment

A summary table will display the number of subjects with at least one second procedure using the mixture scheduled within the next 30 days, (number and % of subjects).

Listing of all other baseline characteristics will be presented in CSR Appendix 16.2.4.

5.5. Efficacy evaluation

All efficacy analysis will be conducted using the TS. Descriptive statistics will be summarized per lesion and per procedure (if applicable) on all available efficacy data.

The following parameters will be presented:

- Number and frequency of the target obliteration scores defined before any procedure,
- Number and frequency of the post-procedure obliteration scores (including for the lesions not targeted initially),
- Number and frequency of lesions embolization.

These analyses will be repeated according to the surgical glue (Histoacryl®, Endoacryl®, Other) associated to Lipiodol® Ultra Fluid.

In case of second procedure, the following analyses will be presented:

- Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for the number of lesions to be treated with the mixture,
- Number and frequency of the variable "number of lesions to be treated" categorized in class will be also tabulated (1 lesion, 2 lesions, 3 lesions and > 3 lesions),
- The main (up to three) and new lesions to be treated with the mixture will be described in terms of location and type, separately. Summary tables (number and % of subjects) will be tabulated. Description will be also presented by lesion (number and % of lesions).

Listings of all efficacy data will be presented in CSR appendix 16.2.6.

5.6. Safety Evaluation

All safety analyses will be performed using the TS except otherwise specified.

5.6.1. Extent of Exposure

Extent of exposure will be summarized per subject, per procedure and if necessary, per administration (e.g. injection). The following parameters will be tabulated:

Per subject:

- Duration between first Study Procedure and "ICF signature" (in days, calculated as the difference between the date of "First Study Procedure" and "ICF signature"),
- Duration of subject's participation (in days, calculated as the difference between the date of "End of study" and "ICF signature"),
- Number of procedures (presented as quantitative and categorical data [Only one procedure/2 procedures]),
- Number of subjects having a second procedure during the study (number of subjects and percent [n row / N subjects) * 100]),
- Reason for having a second procedure (number of subjects and percent [n row / N subjects having a second procedure) * 100]),
- Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) on the time interval (in days) between second and first study procedure.

Per subject and per procedure:

- Number of injections (presented as quantitative and categorical data [Only one injection/2/3/4/5/6 injections]),
- Punctures sites (number and % of subjects),
- Glues brand name (number and % of subjects),
- Duration of the procedure (in minutes, calculated as the difference between "Time leaving the catheterization laboratory" and "Time of first injection").

Per subject, procedure and injection:

- Total volume and ratio of mixture,
- Volumes of Lipiodol® Ultra Fluid and of the glues will be calculated,
- Catheter flush done.

Per subject, procedure and lesion:

- Number of lesions treated (presented as quantitative and categorical data [Only one lesion/2 lesions/3 lesions/4 lesions]),
- Other embolization material used,
- Type of embolization material.

Listing of exposure will be presented in CSR appendix 16.2.7.

5.6.2. Adverse Events

Adverse events (AEs) will be coded in System Organ Class (SOC) and Preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) latest version in force at the date of data base lock.

AEs with missing relationship will be considered related to the mixture (except if date of onset is before date of first procedure) and to the study procedure.

5.6.2.1 Primary analysis of the primary criteria

The following parameters will be described on ADRs occurring, per study procedure, after administration of Lipiodol® Ultra Fluid in association with surgical glues and before catheterization laboratory discharge (i.e

ADR start date is greater or equal to time of first injection and lower or equal to time leaving the catheterization laboratory):

- Number and percentage of subjects experiencing at least one ADR,
- Number of ADRs,
- Distribution of number of ADRs per subject (1/2/3 or more),
- Number and percentage of subjects presenting with at least one ADR per intensity,
- Number of ADRs according to their intensity,
- Number and percentage of subjects presenting with at least one ADR per outcome,
- Number of ADRs according to their outcome,
- Number and percentage of subjects presenting with at least one ADR requiring an ADR-targeted medication,
- Number of ADRs requiring an ADR-targeted medication,
- Number and percentage of subjects presenting with at least one ADR requiring another ADR-targeted action,
- Number of ADRs requiring another ADR-targeted action,
- Number and percentage of subjects presenting with at least one ADR per lesion location,
- Number of ADRs per lesion location,
- Number and percentage of subjects presenting with at least one ADR per lesion type,
- Number of ADRs per lesion type,
- Number and percentage of subjects with mixture administration withdrawal due to at least one ADR,
- Number of ADRs leading to discontinuation of mixture administration,
- Number of ADRs leading to premature discontinuation,
- Number and percentage of subjects presenting with at least one serious ADR, whatever the seriousness criteria,
- Number of serious ADRs, whatever the seriousness criteria,
- Number and percentage of subjects presenting with at least one serious ADR per seriousness criteria,
- Number of serious ADRs per seriousness criteria.

The following distributions, by SOC and PT, will be tabulated on ADRs occurring, per study procedure, after administration of Lipiodol® Ultra Fluid in association with surgical glues and before catheterization laboratory discharge (i.e ADR start date is greater or equal to time of first injection and lower or equal to time leaving the catheterization laboratory):

- Number and percentage of subjects experiencing at least one ADR and number of ADRs,
- Number and percentage of subjects experiencing at least one ADR requiring an ADR-targeted medication and number of ADRs,
- Number and percentage of subjects experiencing at least one ADR requiring another ADR-targeted action and number of ADRs,
- Number and percentage of subjects experiencing at least one ADR leading to discontinuation of mixture administration and number of ADRs,
- Number and percentage of subjects experiencing at least one serious ADR and number of serious ADRs.

Parameters and distributions will also be presented according to the surgical glue (Histoacryl®, Endoacryl®, Other) associated to Lipiodol® Ultra Fluid.

5.6.2.2 Supportive analyses of primary criterion

None.

5.6.2.3 Additional analyses of primary criterion

None.

5.6.2.4 Analysis of secondary criteria

The primary analysis of the primary criteria will be repeated with all ADRs occurring between catheterization laboratory discharge (the last one, if applicable) and end of follow-up period (see 5.6.2.1). The same analysis will be performed with all ADRs occurring from the first administration of the mixture up to the end of follow-up period. (see also 5.6.2.1).

Moreover, the following parameters will be described on AEs occurring, per study procedure, after administration of Lipiodol® Ultra Fluid in association with surgical glues and before catheterization laboratory discharge:

- Number and percentage of subjects experiencing at least one AE,
- Number of AEs,
- Distribution of number of AEs per subject (1/2/3 or more),
- Number and percentage of subjects presenting with at least one AE per intensity,
- Number of AEs according to their intensity,
- Number and percentage of subjects presenting with at least one AE per outcome,
- Number of AEs according to their outcome,
- Number and percentage of subjects presenting with at least one AE requiring an AE-targeted medication,
- Number of AEs requiring an AE-targeted medication,
- Number and percentage of subjects presenting with at least one AE requiring another AE-targeted action,
- Number of AEs requiring another AE-targeted action,
- Number and percentage of subjects experiencing at least one AE leading to discontinuation of mixture administration,
- Number of AEs leading to discontinuation of mixture administration,
- Number of AEs leading to premature discontinuation,
- Number and percentage of subjects presenting with at least one AE related to the mixture (ADR), at least one AE related to the study procedure and at least one AE related to the mixture and related to study procedure,
- Number of AEs related to the mixture (ADR), related to the study procedure and related to the mixture and to study procedure,
- Number and percentage of subjects presenting with at least one serious AE, whatever the seriousness criteria,
- Number of serious AEs, whatever the seriousness criteria,
- Number and percentage of subjects presenting with at least one serious AE per seriousness criteria,
- Number of serious AEs per seriousness criteria.

The following distributions, by SOC and PT, will be tabulated on AEs occurring, per study procedure, after administration of Lipiodol® Ultra Fluid in association with surgical glues and before catheterization laboratory discharge:

- Number and percentage of subjects experiencing at least one AE and number of AEs,
- Number and percentage of subjects experiencing at least one AE requiring an AE-targeted medication and number of AEs,
- Number and percentage of subjects experiencing at least one AE requiring another AE-targeted action and number of AEs,
- Number and percentage of subjects experiencing at least one AE leading to discontinuation of mixture administration and number of AEs,
- Number and percentage of subjects experiencing at least one AE related to the study procedure and number of AEs,

- Number and percentage of subjects experiencing at least one AE related to the mixture and to study procedure and number of AEs,
- Number and percentage of subjects experiencing at least one serious AE and number of serious AEs.

The same analyses will be performed, on one hand, on all AEs occurring between catheterization laboratory discharge (the last one, if applicable) and end of follow-up period and on all AEs occurring from the first administration of the mixture up to the end of follow-up period, on the other hand.

Data listings will present all AEs reported, including AEs occurring between date of ICF signature and date of first procedure (ICF date ≤ AEs onset date < 1st procedure date). Adverse event listings will be sorted by site and subject number and will display also the study procedure, surgical glue, puncture site, body system, and preferred term, time of onset (by convention, from the time of the first injection), duration, intensity, seriousness, outcome, action taken and causal relationship to IMP/procedure (presented in CSR appendix 16.2.7).

5.6.3. Deaths, serious adverse events and other significant adverse events

All deaths and all serious adverse events experienced during the study will be separately listed per subject number, presenting:

- Procedure number,
- Date of first and second (if applicable) study procedure,
- Visit,
- Surgical glue,
- Puncture site,
- Description (Diagnosis or if unknown, nature),
- SOC,
- PT,
- Date and Time of onset,
- End date,
- Time between the last procedure and date of onset,
- Duration (in days),
- Relationship to the mixture,
- Relationship to the study procedure,
- Outcome,
- Intensity,
- Action taken,
- Seriousness criteria.

5.6.4. Clinical laboratory evaluation

Not Applicable.

5.6.5. Vital signs, physical findings and other observations related to safety

Data collected at the end of the safety follow-up period (30 days after the last study procedure [30 days]) will be presented:

- Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) on the time interval (in days) between date of follow-up and date of last study procedure,
- Kind of follow-up (number of subjects and percent [n row / N subjects) * 100]),

- Number and percentage of subjects undergoing a new therapeutic/palliative procedure for the study disease,
- Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) on the time interval (in days) between first procedure after last study procedure and last study procedure,
- Reason of procedure (number of subjects and percent [n row / N subjects having a new procedure) * 100]),
- Type of procedure (number of subjects and percent [n row / N subjects having a new procedure) * 100]).

Listings on data collected at the end of the safety follow-up period will be presented in CSR appendix 16.2.7

5.6.6. Concomitant medications

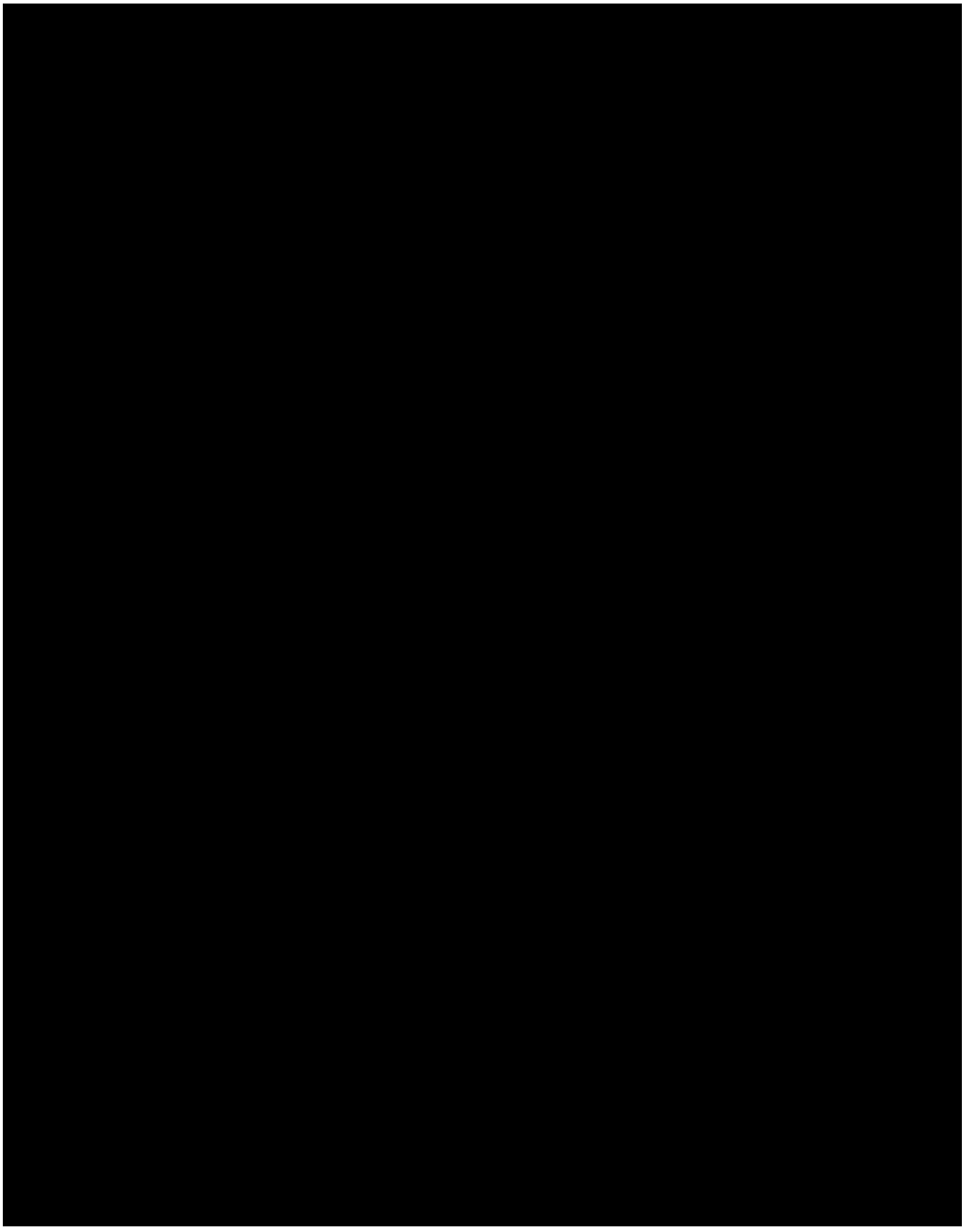
Concomitant medications will be coded using the latest WHO Drug dictionary version in force at the date of data base lock. Incidence of concomitant medications will be tabulated. The number and percent of subjects taking concomitant medications will be presented. The denominator will be the number of subjects in the TS.

Summary tables (number and % of subjects) grouped by the first and the last level of ATC code will be presented whatever the purpose and when purpose is only for AEs (purpose coded 2), respectively. Concomitant medications are those ongoing (“Start Period” coded 1,2 AND “End of Treatment” coded 4, 5, 6) or started (“Start Period” coded 3,4) after the first study procedure.

Listing of all concomitant medications will be presented in CSR appendix 16.2.4.

[redacted]

[redacted]



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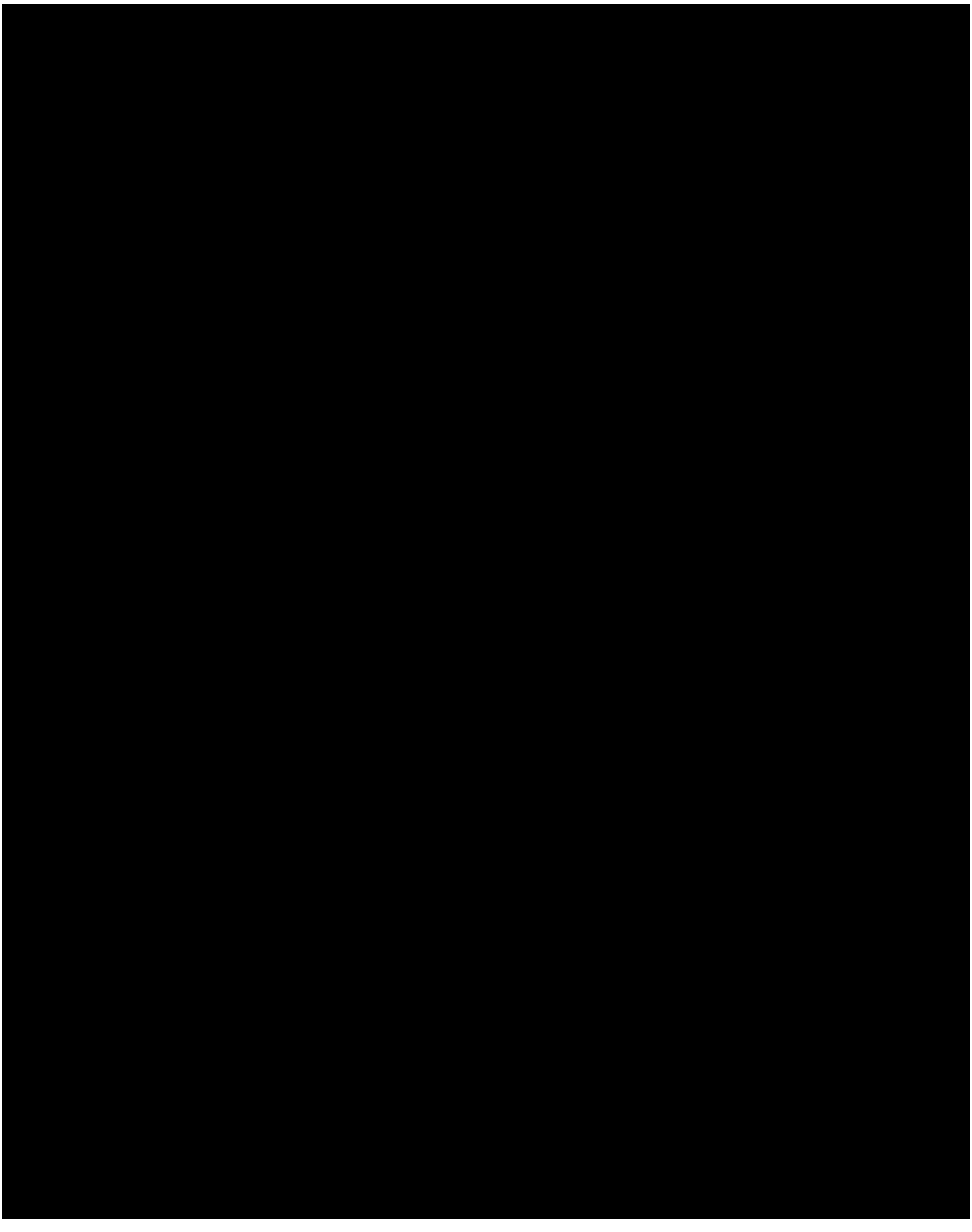

7. **REFERENCES**

Not Applicable.

8. **APPENDICES**

Not Applicable.