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Title:	Post-marketing Surveillance of Ofev Capsules in Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype in Japan
NCT number:	NCT04559581
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This page has been added to the Statistical and Epidemiological Analysis Plan (SEAP) to reflect the requirements by ClinicalTrials.gov. This information is not part of the standard document.

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Document Number:	VV-TMF-82584
BI Study Number:	1199.402
BI Investigational Product(s)	Nintedanib
Title:	Post-marketing Surveillance of Ofev Capsules in Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype in Japan
Brief lay title:	PMS of Ofev Capsules in PF-ILD
SEAP version identifier:	Version 1.0
Date of last version of SEAP:	NA
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ONIS [redacted] [SEAP reviewer]	[redacted]
ONIS Data [redacted] [SEAP reviewer]	[redacted]

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1. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ADS	Analysis Data Set
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
CRF	Case Report Form
DMARDs	Disease Modifying Anti-Rheumatic Drugs
EDC	Electronic Data Capture
FVC	Forced Vital Capacity
HLGT	High level group term
HLT	High level term
HOT	Home Oxygen Therapy
ILD	Interstitial Lung Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NIS	Non-interventional Study
PD	Protocol deviation
PF-ILD	Chronic fibrosing Interstitial Lung Diseases with a progressive phenotype
PMS	Post-marketing surveillance
PT	Preferred term
RMP	Risk Management Plan
SMQ	Standardised MedDRA query
SOC	System organ class
TBILI	Total bilirubin
SEAP	Statistical and Epidemiological Analysis Plan
ULN	Upper Limit of Normal

2. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the Post Marketing Surveillance (PMS) tracking system which manages the contracts with site and investigators name.

3. PURPOSE AND SCOPE

The purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the PMS data.

This SEAP assumes familiarity with the Non-interventional Study (NIS) Protocol, including Protocol Amendments. In particular, the SEAP is based on the planned analysis specification as written in NIS Protocol Section 9.7 “DATA ANALYSIS”. Therefore, SEAP readers may consult the NIS Protocol for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

5. RESEARCH QUESTION AND OBJECTIVE

The primary objective is to evaluate the frequency of adverse drug reactions (focus on hepatic function disorders) of Ofev Capsules under the real world setting in patients with PF-ILD.

6. RESEARCH METHODS

6.1 STUDY DESIGN

This is a non-interventional study based on newly collected data of patients under routine care to confirm safety of Ofev Capsules in the real-world setting in Japanese patients with PF-ILD.

6.2 SETTING

6.2.1 Study sites

Sites throughout entire country will be equally listed according to the size of the hospitals or general clinics at which Ofev Capsules are available for prescription.

Planned number of sites: Approximately 100 Sites

A medical representative will explain the objective and design of this study to investigators at each study site and conclude a written contract with the head of the study site (e.g., hospital director).

6.2.2 Inclusion/ exclusion criteria

Inclusion criteria

- Patients in Japan with PF-ILD who are prescribed with Ofev Capsules and have never been treated with Ofev Capsules before enrolment will be included.

Exclusion criteria

- Diagnosis of IPF
- Patients with PF-ILD due to systemic scleroderma as the underlying disease

6.2.3 Registration period

From October 2020 to September 2022

6.2.4 Patient registration method

The registration method will be a continuous investigation system. Patients who begin treatment with Ofev Capsules after the conclusion of the contract will be registered by entering necessary information in the Electronic Data Capture (EDC) system within 14 days whenever possible from the day of treatment initiation (inclusive).

Patient registration will be stopped when the overall target number of patients for the study is reached. After the end of the registration period, investigators use a signed form to confirm that patients have been registered continuously at the site. A log of all patients included in the study will be maintained at the site.

6.3 STUDY POPULATION

Provide a table specifying the definition of all important Protocol deviations (PDs) with columns for PD category / code, PD description, additional comment/example and a column to describe which PDs will be used to exclude patients from the different patient analysis sets. The final decision about which patients will be excluded from analysis sets will be taken during the course of the study and at report planning meetings before database lock at the latest.

Table 6.3: 1 Important protocol deviations

Category / Code		Description	Requirements	Method	Excluded from
A		**Entrance criteria not met**			
	A1	Patient of non-PF-ILD	Reason of use is not PF-ILD Patients who correspond the below exclusion criteria ・ Diagnosis of IPF ・ Patients with PF-ILD due to systemic scleroderma as the underlying disease	Automated	Effectiveness
	A2	Patient received Ofev ® treatment before registration	See Previous Medication code:3999039 (include 9 digits code)	Automated	Safety/ Effectiveness
B		**Trial medication**			
	B1	No treatment with Ofev® Capsules	No treatment status	Automated	Safety/ Effectiveness
C		**Missing data**			
	C1	No effectiveness outcomes	No effectiveness outcomes at baseline and/or post treatment (FVC, FVC% predicted, FEV1, FEV1% predicted, DLco% predicted, SpO2 and time to first acute ILD exacerbation)	Automated	Effectiveness
D		**Invalid registration**			
	D1	No patient visit after entry	Administration status is “No visit since the first visit”	Automated	Safety/ Effectiveness
	D2	Multiple registration	Pick out patients that falling under all of the following: ・ Sex, birthday, Ofev start date and site name are the same ・ Height is within ± 2 cm ・ Weight is within ± 5 kg	Manual	Safety/ Effectiveness
	D3	Registration rule not followed	See NIS Protocol section 9.2.2.2 and 9.2.2.3	Manual	Safety/ Effectiveness
	D4	Patient started Ofev ® treatment out of registration period	See NIS Protocol section 9.2.2.2	Automated	Safety/ Effectiveness

Category / Code		Description	Requirements	Method	Excluded from
	D5	Not continuous investigation	See NIS Protocol section 9.2.2.3	Manual	Safety/ Effectiveness

The safety set will be the basis of all demographic, baseline and safety analyses. Effectiveness analysis will be on basis of the effectiveness set.

- Safety set:
  This patient set includes all patients who didn't have important PDs regarding safety and regulatory issues as marked as "Safety" in Table 6.3: 1.
- Effectiveness set:
  This patient set includes all patients in safety set with PF-ILD and have effectiveness information. (Patients marked "Effectiveness" in Table 6.3: 1 should be excluded from effectiveness analysis.)

6.4 STUDY VISITS

The study will consist of a baseline visit and further visits in a 104-week follow-up for patients who have initiated Ofev Capsules treatment.

With regard to effectiveness and safety endpoints, the term "baseline" refers to the last observed measurement before the first administration of Ofev® Capsules. The first date of the administration of Ofev® Capsules is included in "baseline".
Effectiveness analyses will be performed based on calculated visits as shown in Table 6.4: 1. If two or more data points of a patient fall into the same interval, the closest value to the planned day will be selected. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used.

Table 6.4: 1 Baseline, time windows and calculated visits

		Time window (actual days on treatment)	
Week label	Planned days	Start	End
Baseline	1	The last observed measurement before administration of Ofev® Capsules	
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	308
Week 52	364	309	434
Week 72	504	435	546
Week 84	588	547	630

		Time window (actual days on treatment)	
Week label	Planned days	Start	End
Week 96	672	631	700
Week 104	728	701	End of study

7. VARIABLES

7.1 EXPOSURES

Exposure to Ofev Capsules is estimated as time from the day Ofev Capsules is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).
Patients newly initiating Ofev Capsules will be followed up to 104 weeks.

7.2 OUTCOMES

7.2.1 Primary outcomes

The primary outcome of this study is the frequency of adverse drug reactions (ADRs).
There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety.

7.2.2 Secondary outcomes

None

7.3 COVARIATES

The covariates included in the model analysis is described in Section 10.2.4.

8. DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the EDC system.

In EDC system, three casebooks will be set:
- Book 1 includes baseline, 4 and 12 weeks.
- Book 2 includes 24, 36 and 52 weeks.
- Book 3 includes 72, 84, 96 and 104 weeks.

The data are to be transmitted immediately after being entered into EDC at 12 weeks (Book 1), 52 weeks (Book 2) and 104 weeks (Book 3) after the start of treatment or at discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9. DATA MANAGEMENT AND SOFTWARE/TOOLS

9.1 SOFTWARE/TOOLS

SAS® Version 9.4 or later will be used for all analyses.

9.2 HANDLING OF MISSING VALUES

Safety:
Missing or incomplete AE dates are imputed according to [redacted]

Missing or partial date information will be replaced according to following rules.

YEAR	MONTH	DAY	YMD	DT
"Unknown" (tick-box)			UNKNOWN	.
yyyy	Null or "Unknown"	Null	Yyyy	yyyy/01/01
yyyy	mm	Null or "Unknown"	Yyyymm	yyyy/mm/01

Effectiveness:
Missing effectiveness data will not be imputed.
Missing or partial date information will be replaced according to safety rules.

Note that in general when tabulating AEs, and/or demographic and baseline characteristics variables reported as unknown will be treated as such; otherwise treated as missing data.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Outliers will not be excluded from analyses unless otherwise noted.

10. DATA ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max.

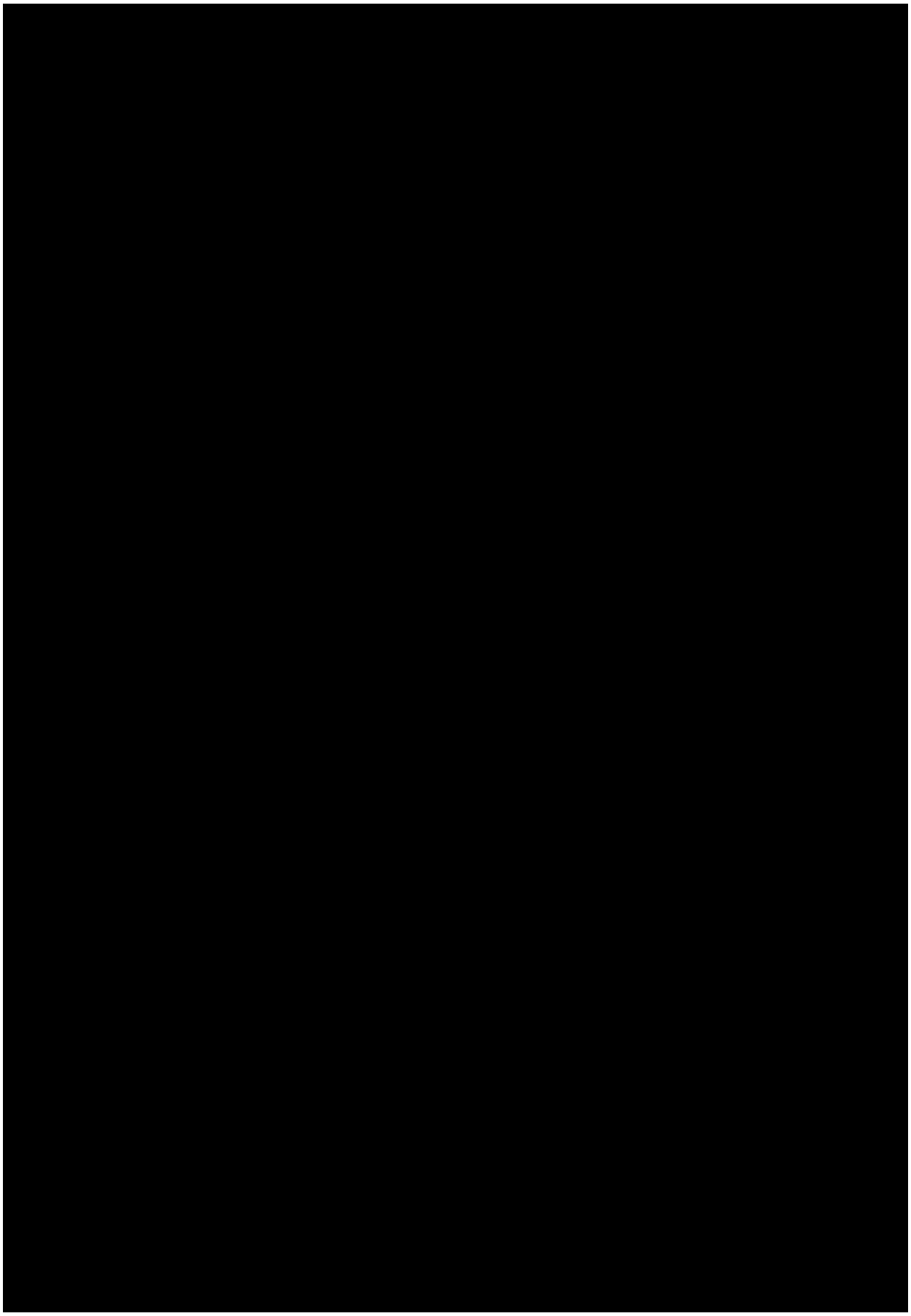
For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

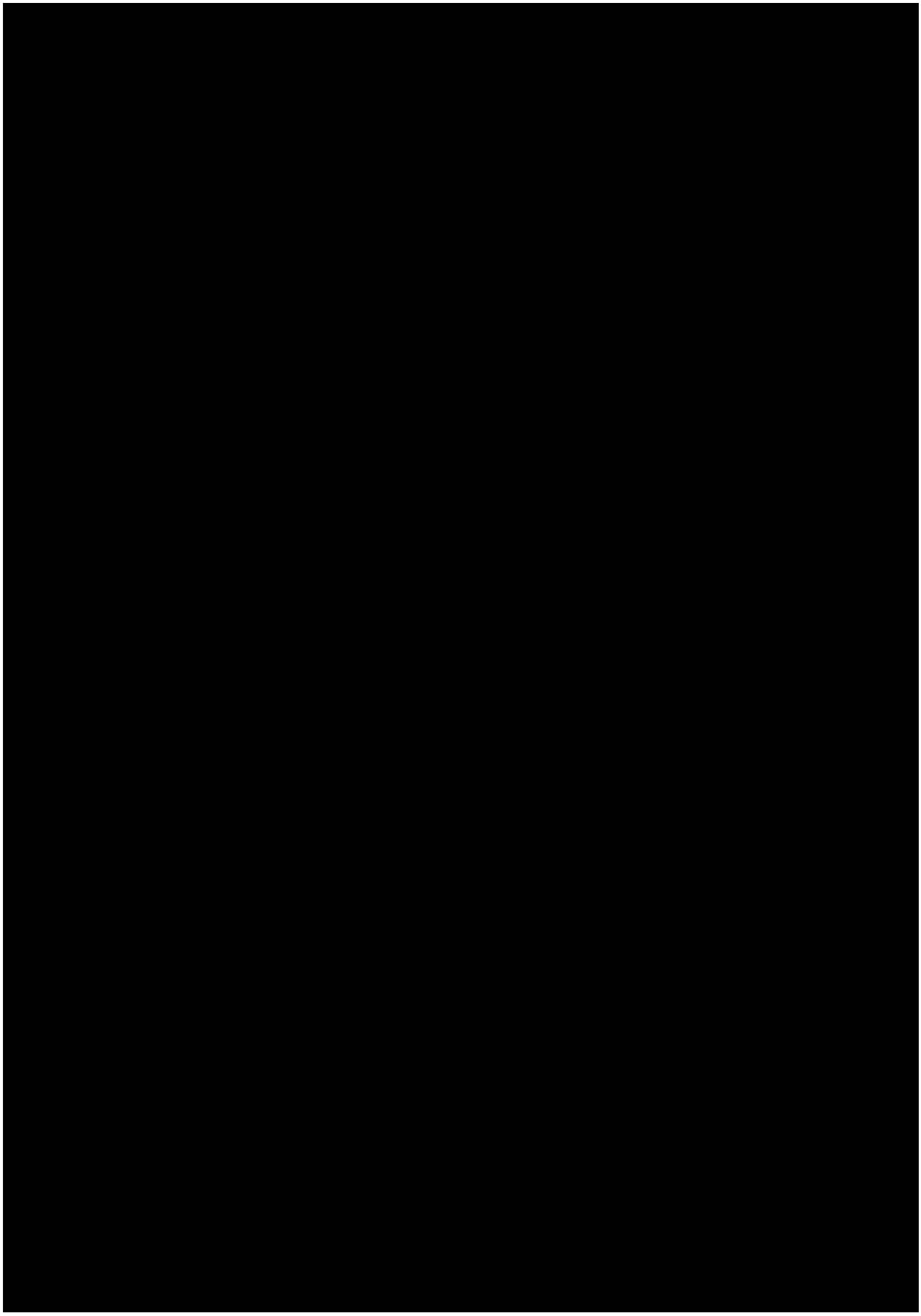
Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to two decimal places. The category missing will be displayed only if there are actually missing values.

10.1 MAIN ANALYSIS

The analysis of the primary outcomes is described in Section 10.3.1.

[redacted]





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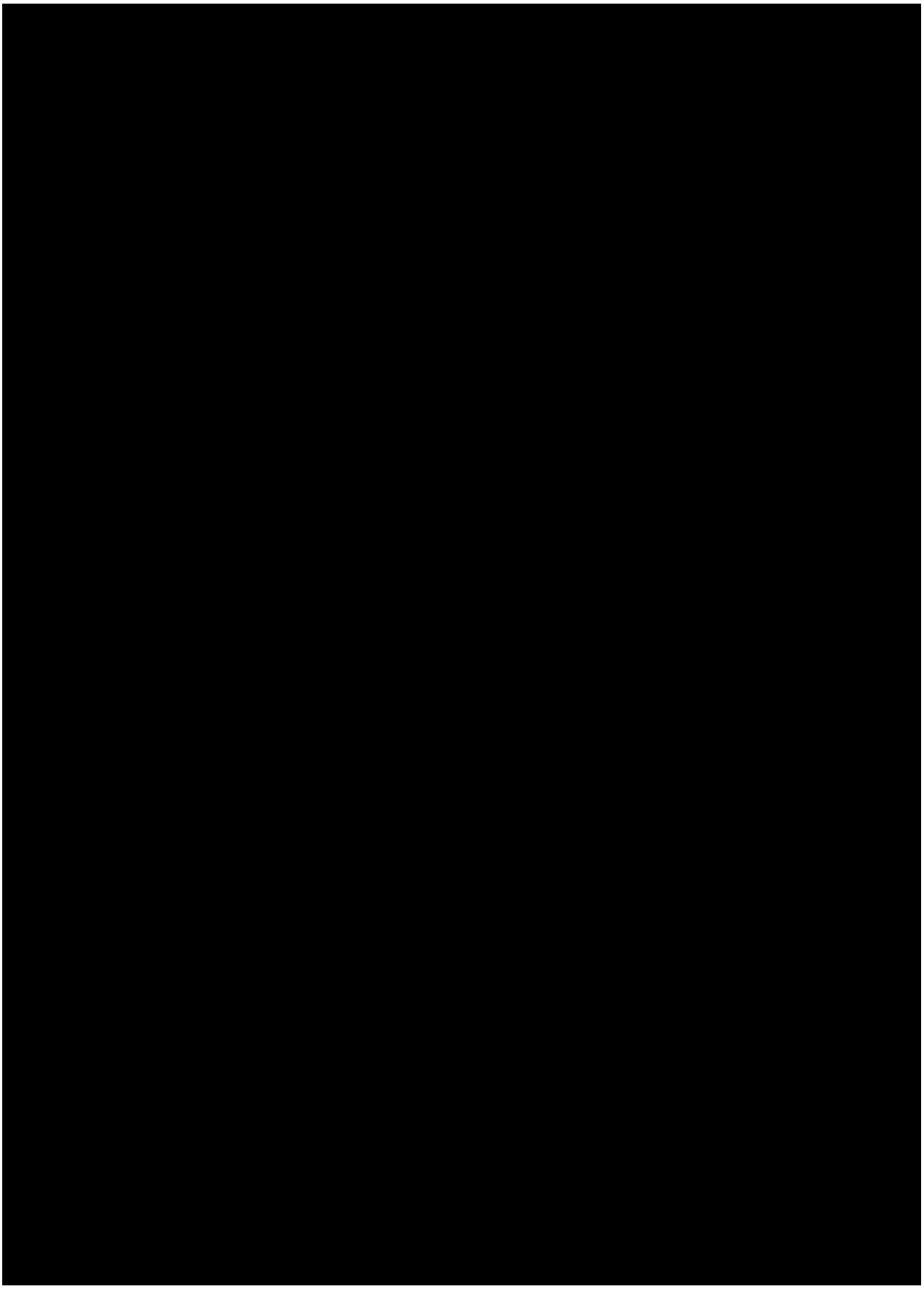

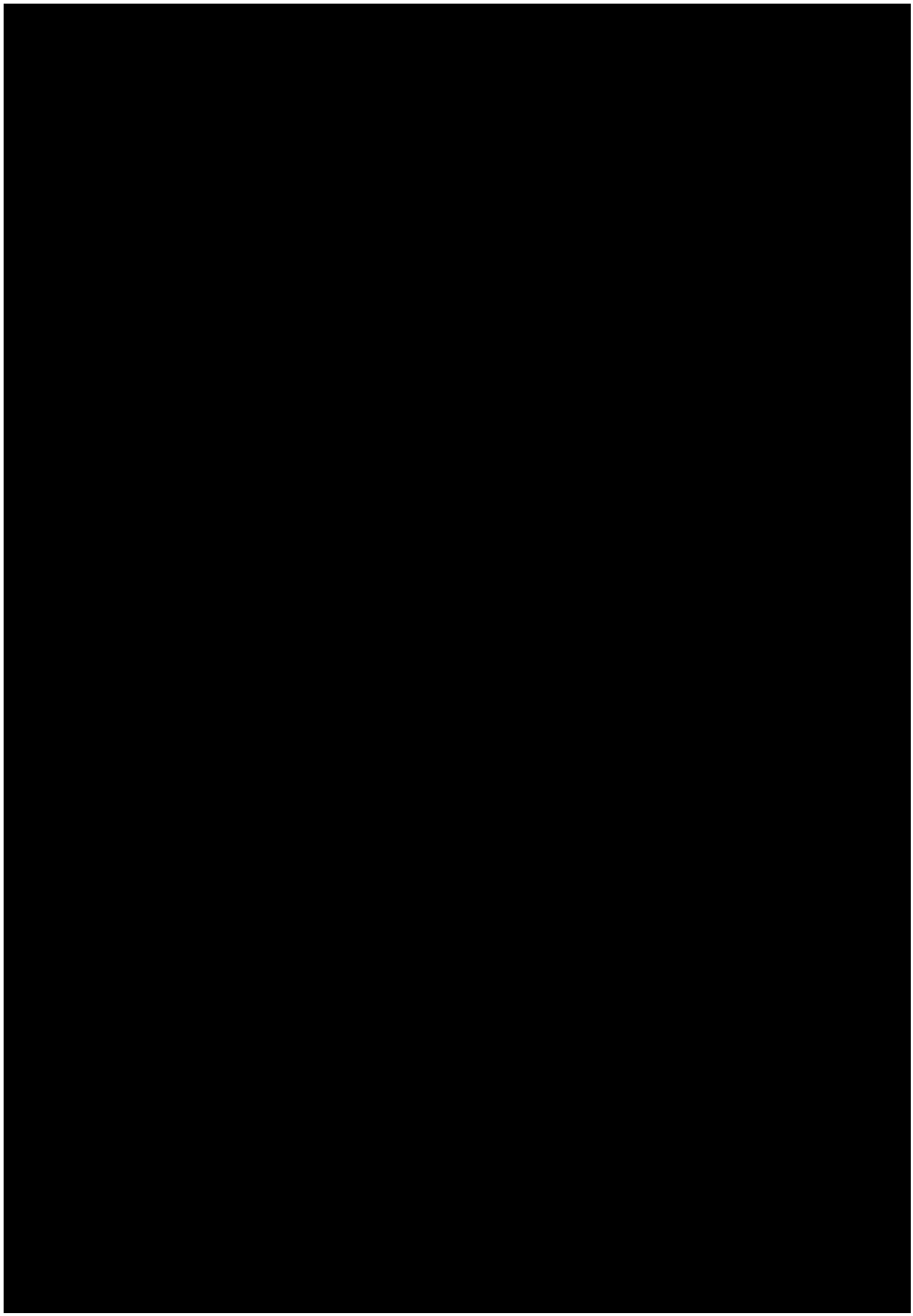

[redacted]

10.3 SAFETY ANALYSIS

All safety analyses will be performed on the safety set.

10.3.1 Adverse Events

Unless otherwise specified, the analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer to [redacted]

Unless otherwise specified, AE analyses will be performed by AE data from Safety data.

An Adverse Drug reaction (ADR) is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Ofev® Capsules as “Yes“. A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness as “Serious”.

The SOCs will be sorted according to the standard sort order specified by European Medicines Agency, PTs will be sorted by frequency (within SOC).

The frequency of patients with the following items will be summarized.

- AEs
- ADRs

[redacted]

- AEs leading to death

[redacted]

- Serious AEs

[redacted]

The frequency of patients with the following items will be summarized by primary SOC and PT.

- AEs
- ADRs

[redacted]

- AEs leading to death

[redacted]

- Serious AEs

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11. QUALITY CONTROL

All processes are conducted according to [redacted]
Appropriate records and documents are stored based on the [redacted] and these processes are checked by internal self-check.

12. REFERENCES

12.1 PUBLISHED REFERENCES

Not applicable.

[redacted]