NOVARTIS

Novartis Research and Development

CBYL719F12201 / NCT04589650

Clinical Trial Protocol

EPIK-P2: A Phase II double-blind study with an upfront, 16-week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS)

Clinical Trial Protocol Number: CBYL719F12201

Version number: V05 (amended protocol) (Clean)

Compound: BYL719

Brief Title: Study assessing the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS)

Study Phase: II

Study Acronym: EPIK-P2

Sponsor Name: Novartis Pharma AG or its affiliates outside of the EEA (where applicable)

Sponsor address in the EEA: Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland

Regulatory Agency Identifier Number(s): EU CT Number: 2023-508530-34-00, IND: 143387

Content final date: 21-Oct-2024

Table of contents

Table of contents 2
List of tables 6
List of figures 7
List of abbreviations 9
Glossary of terms 13
Global Protocol Amendment 05 (21-Oct-2024) 16
Global Protocol Amendment 04 (05-Oct-2023) 20
Global Protocol Amendment 03 (11-Apr-2023) 22
Global Protocol Amendment 02 (28-Sep-2022) 24
Global Protocol Amendment 01 (14-Jan-2022) 36
Protocol summary 51
1 Introduction 58
1.1 Background 58
1.2 Purpose 64
2 Objectives, endpoints and estimands 64
2.1 Primary estimands 68
2.2 Secondary estimands 69
3 Study design 69
4 Rationale 75
4.1 Rationale for study design 75
4.2 Rationale for dose/regimen and duration of treatment 77
4.3 Rationale for choice of control drugs (comparator/placebo) 79
4.4 Purpose and timing of interim analyses/design adaptations 80
4.5 Risks and benefits 80
4.6 Public health emergency mitigation procedures 81
4.7 Rationale for planned off-site procedures (for Netherlands only) 81
5 Study Population 81
5.1 Inclusion criteria 82
5.2 Exclusion criteria 84
6 Treatment 87
6.1 Study treatment 87
6.1.1 Investigational and control drugs 87
6.1.2 Additional study treatments 90
6.1.3 Treatment arms/group 90
6.1.4 Guidelines for continuation of treatment 91

6.1.5 Treatment duration 91
6.2 Other treatment(s) 93
6.2.1 Concomitant therapy 93
6.2.2 Prohibited medication 95
6.3 Participant numbering, treatment assignment, randomization 96
6.3.1 Participant numbering 96
6.3.2 Treatment assignment, randomization 96
6.4 Treatment blinding 97
6.5 Dose escalation and dose modification 98
6.5.1 Dose modifications 98
6.5.2 Follow-up for toxicities 114
6.6 Additional treatment guidance 119
6.6.1 Treatment compliance 119
6.6.2 Emergency breaking of assigned treatment code 119
6.7 Preparation and dispensation 120
6.7.1 Handling of study treatment and additional treatment 121
6.7.2 Instruction for prescribing and taking study treatment 122
7 Informed consent procedures 124
8 Visit schedule and assessments 125
8.1 Screening 147
8.1.1 Eligibility screening 148
8.1.2 Information to be collected on screening failures 149
8.2 Participant demographics/other baseline characteristics 149
8.3 Efficacy 150
8.3.1 Evaluation of response of PROS lesions 151
8.3.2 Other assessments for PROS 155
8.3.3 Blinded Independent Review Committee (BIRC) assessment 156
8.3.4 Appropriateness of efficacy assessments 156
8.4 Safety 157
8.4.1 Laboratory evaluations 158
8.4.2 Electrocardiogram (ECG) 160
8.4.3 Pregnancy and assessments of fertility 162
8.4.4 Other safety evaluations 164
8.4.5 Appropriateness of safety measurements 165
8.5 Additional assessments 165
8.5.1 Clinical Outcome Assessments (COAs) 165

8.5.2 Pharmacokinetics 170
[redacted] 173
8.5.4 Imaging 175
8.5.5 Lung function assessment 175
9 Study discontinuation and completion 176
9.1 Discontinuation and completion 176
9.1.1 Study treatment discontinuation and study discontinuation 176
9.1.2 Discontinuation from study 177
9.1.3 Withdrawal of informed consent 177
9.1.4 Lost to follow-up 178
9.1.5 Early study termination by the sponsor 178
9.2 Study completion and post-study treatment 178
10 Safety monitoring, reporting and committees 179
10.1 Definition of adverse events and reporting requirements 179
10.1.1 Adverse events 179
10.1.2 Serious adverse events 181
10.1.3 SAE reporting 182
10.1.4 Pregnancy reporting 183
10.1.5 Reporting of study treatment errors including misuse/abuse 184
10.1.6 Off-site procedures (for Netherlands only) 184
10.2 Additional Safety Monitoring 185
10.2.1 Liver safety monitoring 185
10.2.2 Data Monitoring Committee 185
10.2.3 Steering Committee 186
11 Data Collection and Database management 186
11.1 Data collection 186
11.2 Database management and quality control 187
11.3 Site monitoring 187
12 Data analysis and statistical methods 188
12.1 Analysis sets 189
12.2 Participant demographics and other baseline characteristics 190
12.3 Treatments 190
12.4 Analysis of the primary estimand(s) 190
12.4.1 Definition of primary estimand(s) 190
12.4.2 Statistical model, hypothesis, and method of analysis 191
12.4.3 Handling of remaining intercurrent events of primary estimand 191

12.4.4 Handling of missing values not related to intercurrent event 191
12.4.5 Supplementary analysis 192
12.4.6 Sensitivity analyses for primary endpoint/estimand 192
12.5 Analysis of secondary endpoints/estimands 192
12.5.1 Efficacy and/or Pharmacodynamic endpoint(s) 192
12.5.2 Safety endpoints 197
12.5.3 Pharmacokinetics 199
12.5.4 Patient reported outcomes 200
[redacted] 200
12.7 Interim analyses 203
[redacted] 203
[redacted] 203
[redacted] 206
13 Ethical considerations and administrative procedures 207
13.1 Regulatory and ethical compliance 207
13.2 Responsibilities of the Investigator and IRB/IEC 208
13.3 Publication of study protocol and results 208
13.4 Quality Control and Quality Assurance 209
13.5 Data protection 209
13.6 Participant Engagement 209
14 Protocol adherence 210
14.1 Protocol amendments 210
15 References 211
16 Appendices 215
16.1 Appendix 1: PROS diagnostic criteria 215
16.2 Appendix 2: Karnofsky performance scale index 216
16.3 Appendix 3: Lansky play performance scale 216
16.4 Appendix 4: Tanner assessment staging scale 217
16.5 Appendix 5: QT Heart rate Fridericia's Correction Formula 218
16.6 Appendix 6: List of concomitant medications 218
16.6.1 Permitted medication to be used with caution and/or action 219
16.6.2 Prohibited Medication 219
[redacted] 221
[redacted] 221
[redacted] 221
[redacted] 221

[redacted] 222

List of tables

Table 2-1 Objectives and related endpoints 66
Table 6-1 Investigational and control drug - Core period Week 1 - Day 1 to Week 16 88
Table 6-2 Investigational drug - Core period Week 17 to Week 24 89
Table 6-3 Investigational drug - Extension 1 and Extension 2 89
Table 6-4 Investigational drug - Exploratory Group 3 89
Table 6-5 Investigational drug - Exploratory Group 4 90
Table 6-6 Investigational drug - Exploratory Group 5 90
Table 6-7 Group 3 starting dose and maximum age-related dose 91
Table 6-8 Dose escalation for alpelisib in Group 1 and Group 5 99
Table 6-9 Dose escalation for alpelisib in Groups 2, 3 and 4 100
Table 6-10 Dose reduction sequential steps for alpelisib in Group 1 101
Table 6-11 Dose reduction sequential steps for alpelisib in Group 2 and 4 101
Table 6-12 Dose reduction sequential steps for alpelisib in Group 5 101
Table 6-13 Dose reduction sequential steps for alpelisib in Group 3 102
Table 6-14 Criteria for interruption and re-initiation of alpelisib/placebo treatment due to QTcF prolongation 102
Table 6-15 Criteria for interruption and re-initiation of alpelisib/placebo treatment due to skin toxicity 103
Table 6-16 Criteria for interruption and re-initiation of alpelisib/placebo treatment due to hyperglycemia 105
Table 6-17 Management of pneumonitis related to alpelisib/placebo with or without other agents in combination 107
Table 6-18 Criteria for interruption and re-initiation of alpelisib treatment due to diarrhea 107
Table 6-19 NCI CTCAE version 4.03 grading of diarrhea for participants without Colostomy 111
Table 6-20 Criteria for interruption and re-initiation of alpelisib treatment due to stomatitis 112
Table 6-21 Criteria for interruption and re-initiation of alpelisib treatment due to pancreatitis. 112
Table 6-22 Criteria for interruption and re-initiation of alpelisib treatment: Investigations (hematologic) 113
Table 6-23 Criteria for interruption and re-initiation of alpelisib treatment: Investigations (other) 113

Table 6-24 Alternative causes of liver disease 116
Table 6-25 Preparation and dispensation 121
Table 8-1 Allowable visit windows 126
Table 8-2 Assessment Schedule (≥ 2 years of age) 127
Table 8-3 Assessment schedule (less than 2 years of age) 139
Table 8-4 Imaging Assessment Collection Plan 154
Table 8-5 Assessments & Specifications 158
Table 8-6 Central clinical laboratory parameters collection plan 160
Table 8-7 Local ECG collection plan 161
Table 8-8 Daily Diary: Starting at Screening period, then at specified time points in Table 8-2 and Table 8-3 168
Table 8-9 PRO measures on ePRO Device by age range: Starting at Week 1 Day 1 then at specified time points in Table 8-2 and Table 8-3 168
[redacted] 170
Table 8-11 Pharmacokinetic blood collection log for Groups 1 and 2 171
[redacted] 172
[redacted] 172
[redacted] 173
[redacted] 174
Table 12-1 Pharmacokinetic parameters 200
[redacted] 205
[redacted] 205
[redacted] 206
[redacted] 206
[redacted] 207
Table 16-1 List of CYP450 substrates to be used with caution 219
Table 16-2 List of prohibited strong inducers of CYP3A 219
Table 16-3 List of prohibited BCRP inhibitors 220

List of figures

Figure 3-1 Study design 70
Figure 6-1 Study drug administration on scheduled visit days 124

Figure 8-1 Timing of study procedures 161
Figure 12-1 Graphical gatekeeping procedure to test procedure to test primary and key secondary endpoints in order to control overall type I error. 194
Figure 12-2 Example rejection sequences for the sequentially rejective graphical procedure 195
Figure 16-1 Sexual maturity rating (Tanner stages) of secondary sexual characteristics 217
[redacted] [redacted] 221

List of abbreviations

ADA	American Diabetes Association
ADL	Activity of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AKT	Protein Kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
ARA	Acid Reducing Agents
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under the Curve
b.i.d.	twice a day
BAL	Broncho-Alveolar Lavage
BCRP	Breast Cancer Resistance Protein
BIRC	Blinded Independent Review Committee
BMI	Body Mass Index
BPI	Brief Pain Inventory
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulation
CI	Confidence Interval
CLOVES	Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Skeletal/Scoliosis/Spinal abnormalities
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	COronaVIrus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DILI	Drug-Induced Liver Injury
DLco	Diffusing Capacity of the Lung for Carbon Monoxide
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid

DTI	Direct Thrombin Inhibitors
DXA	Dual-energy X-ray Absorptiometry
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
EM	Erythema Multiforme
EMA	European Medicines Agency
EoS	End of Study
EOT	End Of Treatment
ePRO	electronic Patient Reported Outcomes
[redacted]	
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FCT	Film-Coated Tablets
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
FFPE	Formalin Fixed Paraffin Embedded
FPG	Fasting Plasma Glucose
Fr	French scale (used to measure the size of a catheter)
FSH	Follicle Stimulating Hormone
FVC	Full Vital Capacity
FVCPP	Percent Predicted Forced Vital Capacity
[redacted]	
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
h	Hour
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B virus surface Antigen
HBV	Hepatitis B Virus
HDL	High Density Lipoprotein
HER	Human Epidermal Growth Factor Receptor
HR	Hormone Receptor
HRQoL	Health-Related Quality of Life
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDFU	Investigational directions for use
IEC	Independent Ethics Committee
IPTW	Inverse Probability of Treatment Weighting

IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
KTS	Klippel-Trenaunay Syndrome
LCMS/MS	Liquid Chromatography-tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
LPLV	Last Participant Last Visit
LVEF	Left Ventricular Ejection Fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
ml	milliliter(s)
MRI	Magnetic Resonance Imaging
mTOR	mammalian Target Of Rapamycin
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
NTI	Narrow Therapeutic Index
OHP	Off-site Health Provider
OL	Open-Label
p.o.	oral
PAS	Pharmacokinetic Analysis Set
PBPK	Physiologically Based Pharmacokinetic
PDCO	Pediatric Committee
PIP	Pediatric Investigation Plan
PI3K	Phosphatidylinositol-3-Kinase
PIK3CA	Phosphoinositide-3-Kinase Catalytic subunit Alpha
PK	Pharmacokinetic(s)
PLT	Platelets
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcome Measurement Information System
PROS	PIK3CA-Related Overgrowth Spectrum
PS	Proteus Syndrome
PSDS	Post-Study Drug Supply
PTA	Post-Trial Access
PTT	Partial Thromboplastin Time
QD	Once a Day
QMS	Quality Management System
QOD	Every Other Day

QTcF	QT interval corrected by Fridericia's formula
RDI	Relative Dose Intensity
REB	Research Ethics Board
RNA	Ribonucleic Acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Standard Deviation
SDS	Standard Deviation Scores
SJS	Stevens-Johnson Syndrome
SMT	Safety Management Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
t.i.d	ter in die (3 times a day)
T1/2	Half Life
tbd	to be discussed
TBIL	Total Bilirubin
TEN	Toxic Epidermal Necrolysis
TFQ	Trial Feedback Questionnaire
Tmax	Time to maximum concentration
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
US	United States
VES	Visual Evaluation Scale
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
XR	Extended Release
yr	year

Glossary of terms

ARAs	Acid Reducing Agents
Assessment	A procedure used to generate data required by the study.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives.
Clinical Trial Team	Group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed up or traced over time.
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant may agree to the other protocol required assessments including Safety follow-up.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis and other oversight authorities, as appropriate.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug	The study drug whose properties are being tested in the study.

Medication number	A unique identifier on the label of medication kits.
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy).
Participant	A trial participant (patient). “Participant” terminology is used in the protocol whereas term “Subject” is used in data collection.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis/Sponsor for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant.
Remote	Describes any trial activities performed at a location that is not the investigative site where the Investigator will conduct the trial, but is for example a home or another appropriate location.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s).
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Subject number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data / biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Global Protocol Amendment 05 (21-Oct-2024)

At the time of this amendment, 188 participants have been either randomized or enrolled in EPIK-P2 (81 in Group 1 [≥ 18 years of age]; 84 in Group 2 [6-17 years of age]; 7 in Group 4 [2-5 years of age] and 16 in Group 5 [6-17 years of age]). Enrollment in Groups 1, 2, 4 and 5 has been completed. The primary analysis for this study was conducted after all participants from Groups 1 and 2 completed at least 48 weeks of treatment or discontinued earlier; the data cut-off date for the primary analysis was 20-Mar-2024. The main purpose of this amendment is to open Group 3 for enrollment following completion of the primary analysis as per plan.

Amendment rationale

[redacted]

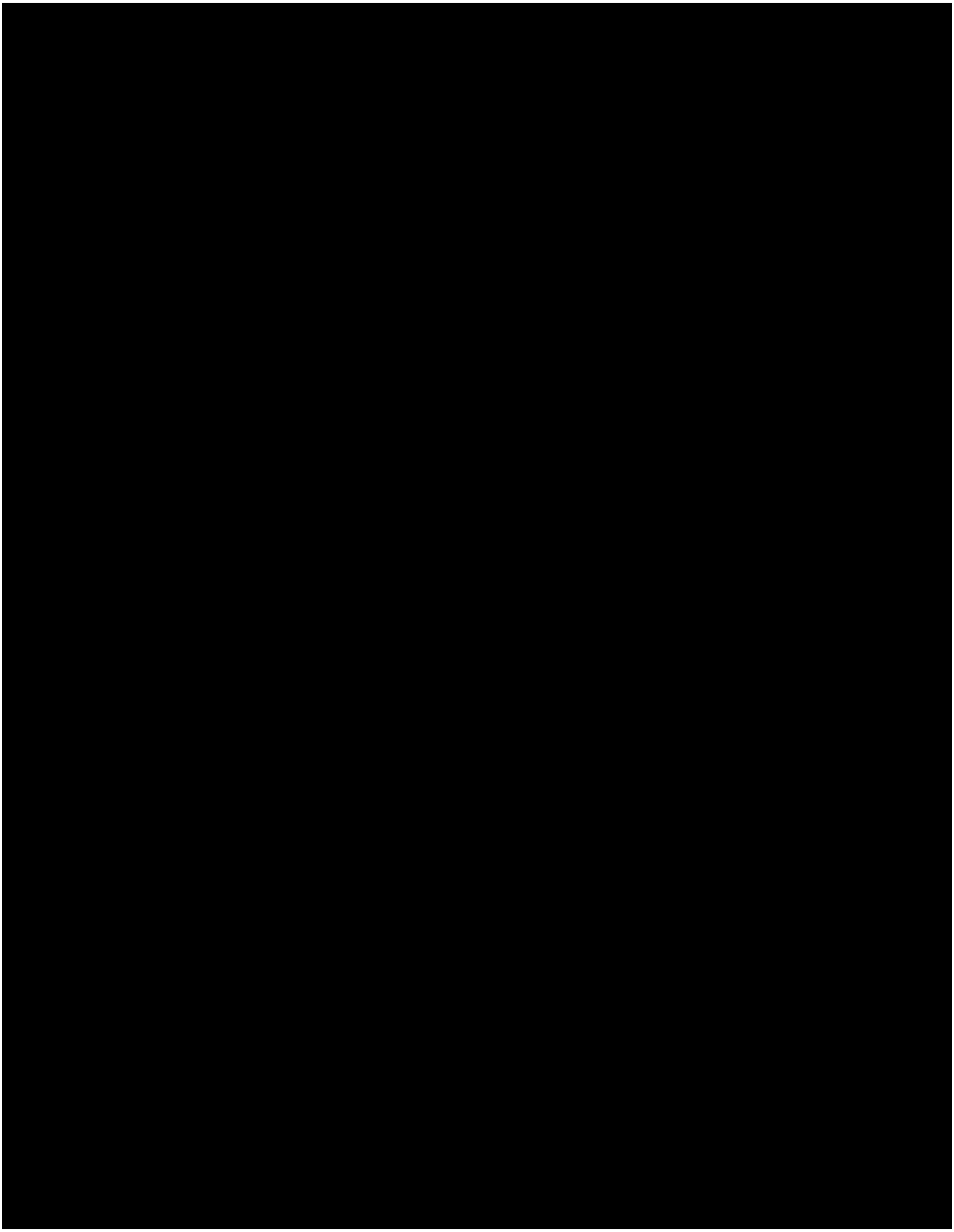
Given the expansion of the population to be included in Group 3 from participants 2 to 5 years of age to participants 0 to 5 years of age, the study will target enrollment of approximately 15 participants in Group 3 (vs. approximately 12 participants previously anticipated).

[redacted] An age-dependent starting dose and maximum dose levels ranging from 20 mg every other day to 50 mg once daily are being introduced for Group 3 participants below 2 years of age to reflect metabolic enzyme ontogeny. [redacted]

[redacted]

Changes to the protocol

[redacted]



Made clerical updates throughout the amendment, such as revising patients to participants and updating table numbers.

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Global Protocol Amendment 04 (05-Oct-2023)

As of the release of this Global Protocol Amendment, 186 participants have been either randomized or enrolled in EPIK-P2 (81 in Group 1 [≥ 18 years of age]; 84 in Group 2 [6-17 years of age]; 7 in Group 4 [2-5 years of age] and 14 in Group 5 [6-17 years]). Enrollment in Groups 1, 2, and 4 has been completed.

This protocol amendment is being implemented to change the timing of the primary analyses which will occur after all ongoing participants from Groups 1 and 2 have completed at least 48 weeks (instead of at least 24 weeks) of treatment or discontinued earlier. In line with the change in the timing of the primary analyses, the durability of the confirmed objective response will be assessed when all participants from Groups 1 and 2 have reached at least 48 months (instead of at least 42 months) of treatment or discontinued earlier to characterize the duration of response (DOR).

Amendment rationale:

In the context of the review of pooled blinded EPIK-P2 data (i.e., combined blinded data for participants randomized to alpelisib and placebo) in preparation for a regularly scheduled data monitoring committee (DMC) meeting which took place on 30-Jun-2023, Novartis identified that 66% (29/44) of adult participants randomized in Group 1 and 72% (41/57) of pediatric participants randomized in Group 2 who were eligible for alpelisib dose escalation for response optimization as per protocol (i.e., after Week 28) had at least one dose increase. Furthermore, 42% (8/19) of adult participants randomized in Group 1 and 38% (9/24) of pediatric participants randomized in Group 2 who were eligible for a second dose escalation (i.e., after Week 40) had a second dose increase.

Given the higher-than-expected rates of participants with dose escalation(s), modification to the timing of the primary analyses for Groups 1 and 2 to occur after all ongoing participants from these groups have completed at least 48 weeks, instead of at least 24 weeks, of treatment or discontinued earlier is warranted. This change will capture additional data from participants with dose escalation(s) and consequently allow for the more comprehensive assessment of the impact of dose escalation(s) on efficacy.

This protocol amendment only impacts the timepoint of the data cut-off for the primary analyses; it does not result in changes to individual participant care (e.g., no changes will be made to participant visits, clinical assessments, blinded independent review committee [BIRC] assessments, etc.). Besides the timing of the primary analysis, there is no impact on any other component of the study design or the analyses. Additionally, no impact on the integrity of the trial is expected based on the modification to the timing of the primary analyses.

List of modified Protocol Amendment 04 sections:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The following sections have been modified in the amended protocol:

[redacted]

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Global Protocol Amendment 03 (11-Apr-2023)

As of the release of this Global Protocol Amendment, 39 sites have been initiated and 177 participants have been either randomized or enrolled (81 in Group 1 [≥18 years of age]; 84 in Group 2 [6-17 years of age]; 7 in Group 4 [2-5 years of age] and 5 in Group 5 [6-17 years of age]).

The main changes implemented in this amendment are:

a. Inclusion of a new exclusion criterion # 23.
b. A mandate for a physical examination on Day 1 of the trial, prior to the start of study treatment.

Amendment rationale:

Addition of a new exclusion criterion and physical examination on Day 1

An ad hoc Safety Data Monitoring Committee (DMC) Meeting was held on 27-Jan-2023 to discuss on the death of a study participant that occurred [redacted].

Subsequently on the same day, the DMC held a closed session to review unblinded data for the same study participant.

The fatal case concerned a pediatric participant who was taken off treatment with an inhibitor of the PI3K/AKT/mTOR pathway prior to the start of study treatment and died on Study Day 4 due to a massive embolism of leg/vena cava/heart/pulmonal and haemolytic streptococcus group A infection. These events were deemed unrelated to study treatment by the investigator.

After reviewing the case, the DMC recommended inclusion of the following new exclusion criterion to help further strengthen the existing exclusion criterion #16 (Participant with other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate administration of alpelisib) and call for particular attention on evolving signs and symptoms in those patients who washed out of another inhibitor of the PI3K/AKT/mTOR pathway:

Participants with clinically significant worsening of PROS-related laboratory anomalies, physical signs and symptoms (such as, but not limited to increase of D-dimers, worsening of underlying pain, newly occurring swelling or redness) indicating an uncontrolled condition during the screening phase, particularly if systemic treatment with any other inhibitor of the PI3K/AKT/mTOR pathway was stopped prior to the start of study treatment. This includes but is not limited to hypercoagulability state in participants not receiving prophylactic treatment.

The DMC has also recommended to mandate a physical examination on Day 1 of the trial, prior to the start of study treatment.

In addition, the following changes are implemented:

[redacted]

List of modified Protocol Amendment 03 sections:

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Global Protocol Amendment 02 (28-Sep-2022)

As of the release of this Global Protocol Amendment, 37 sites have been initiated and 110 participants have been randomized/enrolled (47 in Group 1 [≥18 years]; 58 in Group 2 [6-17 years] and 5 in Group 4 [2-5 years).

The main changes implemented in this amendment are:

a. Modification of the primary objective and related endpoint from a response at Week 24 to a confirmed objective response by a blinded independent review committee (BIRC).
b. Addition of a secondary objective and related endpoint to reflect the response at Week 24 (by BIRC).
c. Inclusion of an additional analysis to characterize the durability of confirmed objective response at the time that participants from Groups 1 (≥18 years), 2 (6-17 years), 4 (2-5 years) and 5 (6-17 years) have reached at least 42 months (i.e., 36 months after the Week 24 time-point) of treatment or discontinued earlier to characterize the duration of response (DOR).

[redacted]

e. Update of the imaging assessment (whole-body MRI and photography) frequency for Groups 1, 2, 4 and 5 by adding a new imaging assessment at Week 72.
f. Clarification on the whole-body MRI requirement and the timing of the mandatory unscheduled whole-body MRI prior to a surgery due to PROS.

Amendment rationale:

Modification of the primary objective and related endpoint, addition of a secondary objective and related endpoint, and an additional analysis

The Food and Drug Administration (FDA) granted accelerated approval for alpelisib under the tradename Vijoice® on 05-Apr-2022 for the following indication: *"Vijoice is indicated for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)."* In accordance with this accelerated approval, Novartis agreed to a Post Marketing Requirement (PMR) (4260-1) which necessitates that the primary objective and related endpoint of EPIK-P2 be modified to allow for a more precise estimation of confirmed objective response rate and mature response duration per BIRC in EPIK-P2.

As such, the purpose of this Global Protocol Amendment 02, is to modify the primary objective and related endpoint previously defined as the proportion of participants randomized to alpelisib film-coated tablets (in Groups 1 and 2) with a response at Week 24 (a fixed timepoint) to the proportion of participants randomized to alpelisib film-coated tablets (in Groups 1 and 2) with confirmed objective response by BIRC at any time during the treatment period of this study. Considering data from Study [CBYL719F12002 (EPIK-P1)], in which most participants with a response experienced early reduction in target lesion volume which was subsequently sustained,

it is anticipated that most of the responses in EPIK-P2 will be associated with an onset within the first 24 weeks of treatment and subsequently sustained. Hence, the expected confirmed response rate of alpelisib is anticipated to be similar to the expected response rate at Week 24 and the analysis of this primary objective will be performed around this timeframe (i.e., at the time all participants in Groups 1 and 2 reached at least 24 weeks of treatment or discontinued earlier). Of note, the specification of the primary hypothesis tests as well as the sample size for the primary analysis remain unchanged.

Subsequently, a secondary endpoint has been added to assess the efficacy of alpelisib as measured by the proportion of participants with a response by BIRC at Week 24 in Groups 1 and 2.

Additionally, all the responses reported in Groups 1, 2, 4 and newly added Group 5 as of the Week 24 cut-off date (i.e., at the time all participants reached at least 24 weeks of treatment or discontinued earlier) will be followed for at least 36 months to characterize the duration of response and therefore an additional analysis will be performed.

Addition of exploratory group (i.e., Group 5)

In accordance with FDA's accelerated approval of alpelisib for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy, Novartis agreed to a Post Marketing Commitment (PMC) (4260-6) to assess a starting dose of alpelisib 125 mg (in addition to the alpelisib 50 mg starting dose) in pediatric patients 6 to 17 years of age to evaluate the pharmacokinetics, safety, and clinical outcomes for dose optimization in this patient population. As such, an exploratory group, Group 5, has been added to the study design.

In EPIK-P1, 28 of 57 participants were 6 to 17 years of age; 12 participants were 6 to 11 years of age and 16 participants were 12 to 17 years of age. Per the Study [CBYL719F12002 (EPIK-P1) CSR], the median duration of exposure was 13.6 months for the participants aged 6 to 11 years and 19 months for those aged 12 to 17 years, with a median relative dose intensity (RDI) of 100% and 112.6%, respectively, providing a long period of observation for safety. No life-threatening treatment related events or adverse events (AEs) leading to discontinuations or deaths were observed. There were no unique toxicities noted in these age groups. Additionally, one participant in the 6 to 11 years age group started alpelisib at 100 mg, two participants in the 12 to 17 years age group started alpelisib at 150 mg, and one participant in the 12 to 17 years age group started alpelisib at 250 mg. Lastly, ten out of 28 (35.7%) pediatric participants had at least one dose increase of alpelisib during the study, without safety concerns, of which five participants were in 6 to 11 years age group and the other five in the 12 to 17 years age group.

As such, the purpose of this Global Protocol Amendment 02 is to open an exploratory group (i.e., Group 5) which will include approximately 15 participants 6 to 17 years of age who will start treatment with alpelisib 125 mg film-coated tablets.

Enrollment of Group 5 participants will start after the approval of this Global Protocol Amendment 02 and immediately after the enrollment of Group 2 participants has been completed in order to avoid competition of enrollment amongst these two groups.

Data from the participants included in Group 5 will support the following objectives:

- Provide efficacy and safety information of a higher starting dose in participants 6 to 17 years of age.
- Contribute to the totality of PROS information and further evaluate the pharmacokinetics, safety, and clinical outcomes for dose optimization in this age group.

Addition of an imaging assessment at Week 72 for Groups 1,2,4, and 5

Based on the modification of the primary objective and related endpoint, i.e., to demonstrate the efficacy of alpelisib as measured by the proportion of participants randomized to alpelisib film-coated tablets (in Groups 1 and 2) with a confirmed objective response by BIRC, an MRI at Week 72 (i.e., 24 weeks after the Week 48 efficacy assessment) will be performed to allow for a more precise assessment of the efficacy and more specifically document confirmation of response for participants who may have a late response to treatment.

Clarification regarding whole-body MRI requirement

Whole-body MRI is the primary and preferred method of response evaluation. However, undergoing this procedure requires multiple hours and is creates a heavy burden for participants, especially children. These concerns were raised by several study Investigators, including Steering Committee members. To decrease this burden the MRI schedule requirements have been adjusted as follows: it is mandatory that a whole-body MRI be performed at baseline; if at the subsequent timepoints whole-body MRI is not feasible, at least the lesions identified at baseline by the Investigator should be captured. In addition, focused MRI imaging may be required to adequately assess small anatomic areas with PROS lesions.

Clarification regarding the mandatory unscheduled whole-body MRI prior to a surgery due to PROS

In protocol Section 8.3.1 about "Evaluation of response for PROS lesions": it has been clarified that the Investigator must perform a whole-body unscheduled MRI prior to any surgical procedure if a surgery due to PROS is deemed necessary. No additional unscheduled whole-body MRI is required if an existing MRI was already performed within 4 weeks prior to the surgical procedure. This clarification is applicable to participants in all Groups and at any time point in the study in order to support the assessment of the PROS lesions.

In addition, the following change is implemented:

- Revision added to specify Walking Distance Test is not applicable for Groups 3 and 4 participants (2-5 years of age).

List of modified Protocol Amendment 02 sections:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The following sections have been changed in the amended protocol:

Section 1.1: Abbreviation of "Food and Drug Administration" has been specified (FDA). Section updated to specify that data from EPIK-P1 were submitted to the US FDA and resulted in the FDA granting an accelerated approval on 05-Apr-2022 for Vijoice® (alpelisib) tablets for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations

of PIK3CA-related Overgrowth Spectrum (PROS) who require systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

[redacted]

The other secondary objectives and endpoints were modified. A new other secondary objective was added as "To assess the efficacy of alpelisib as measured by the proportion of participants with a response at Week 24 (by BIRC) in Groups 1 and 2". The corresponding other secondary endpoint was added as "Response at Week 24 (by BIRC)". The other modification to this section included an update to the already existing secondary objective to assess the rate of overall clinical response, in order to specify the additional scheduled protocol visits for disease evaluation at Weeks 72 and 96.

[redacted]

Section 2.1: Section was updated to add "confirmed" and remove "at Week 24" with regards to the proportion of confirmed responders; In addition, "by BIRC" has been specified with proportion of confirmed responders, considering participants that discontinue treatment prior to confirmation of response and participants that receive surgery as rescue therapy for any PROS lesions prior to confirmation of response as non-responders.

- Primary estimants #1: “Randomized” has been specified.
- Primary estimands #3: Replaced Week 24 with confirmation of response.
- Primary estimands #4: Removed Week 24 and specified that confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response.
- Primary estimands #5: Updated as “proportion of participants (children/adolescents aged 6 to 17 years and adults) achieving confirmed response by BIRC”. Removed response at Week 24.

Section 3: Specified that three additional groups with a total of approximately 33 participants will be enrolled for exploratory purposes and added a description of Groups 3, 4 and 5. Updated the entire section to include Group 5, including Figure 3-1 (study design).

Section 4.1: Added a statement to specify there is no approved pharmacological treatment for PROS outside the US.

Response rate was also updated in this section with the removal of “achieving response at Week 24” and updated to the following language:

Response rate (based on pre-defined volumetric reduction of target lesions) has been selected as a primary endpoint in pivotal studies to demonstrate treatment efficacy and has been used as the basis for regulatory approval of agents in different indications in a number of therapeutic areas such as oncology and neurology. The primary endpoint of this study is the proportion of participants randomized to alpelisib with a confirmed objective response.

Section 4.2: The entire section was updated to include Group 5. Group 5 rationale for dose/regimen and duration of treatment was provided for the alpelisib starting dose of 125 mg FCT once daily (taken with food) for pediatric participants from age 6 to 17 years based on the data available from the EPIK-P1 study results.

Description of Group 5 dose escalation for long-term extension periods to optimize the dose for all participants for long-term efficacy and safety was added to the section.

Section 4.5: It was specified that PROS is a serious condition with no approved pharmacological treatment targeting the underlying cause of the disease outside the US.

Section 4.6: This section had a minor update based on the most recent Clinical Trial Protocol template V05. The first sentence now states, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol.

Section 5: Study enrollment figures were updated with the addition of Group 5. The section now states; 189 participants in total, 78 adults and 111 children and adolescents.

A description of Group 5 was added to the section; Specified that, following the implementation of Global Protocol Amendment 02 and once enrollment of Group 2 is completed, exploratory Group 5 will be opened to enroll approximately 15 additional pediatric participants with PROS, treated with alpelisib FCT at a higher starting dose: Group 5: 6 to 17 years old.

Section 5.1: Inclusion criteria #2 was updated to add Group 5 and mention Group 3; Inclusion Criteria #5; Inclusion criteria #9 were updated to add Group 5.

Section 5.2: Exclusion criteria #8 and #9 were updated with the addition of Group 5.

A sentence within the exclusion criteria #18 was changed to ensure if local regulations are more stringent than the contraception methods listed to prevent pregnancy, local regulations apply and will be described in the ICF.

Section 6.1: Within the section, core period Week 0 was corrected to Core period Week 1.

Section 6.1.1: Three sections were updated to include Group 5 and to specify that, Group 5 will start after implementation of Global Protocol Amendment 02 and enrollment in Group 2 is completed. The participants in Group 5 will receive alpelisib FCT 125 mg once daily in an open-label setting.

A new table (Table 6-6) labeled “Investigational drug- Exploratory Group 5” was also added to the section to provide details on age range, investigational drug, dosage form, route, strength and supply type. The subsequent numbering of tables was revised accordingly.

The footnote “c” in Table 6-4 has been updated concerning granules under development for Group 3, that “additional data from Groups 4 and 5 as available” will be used in addition to the data of Group 1 and 2 into the primary analysis to determine Group 3 dose strengths.

In addition, the Table 6-5 has been updated to specify the other possible dose strengths 125 and 200 mg.

Section 6.1.3: Group 5 was added and specified for those participants they will receive 125 mg alpelisib FCTs once daily in an open-label setting. Once a participant has reached at least Week 25, dose escalation will be allowed.

Section 6.1.5: The section was updated to include Group 5. It was specified in Section 6.1.5.1 that participants of Group 1, Group 2 and Group 5 with BIRC- confirmed disease progression by Week 24 and later, who do not have safety/tolerability issues, may remain on study therapy at the discretion of the Investigator; they will also have the option to undergo dose escalation after 28 weeks for Groups 1 and 2 and after 24 weeks for Group 5 of study treatment.

Section 6.2.1: The following language was added based on Clinical Trial Protocol template V5.0:

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Section 6.3.1: Within the section, “Center Number (Center No.)” was replaced with “Site Number (site No.)”.

Section 6.3.2: The entire section was updated to include Group 5.

Section 6.4: The section was updated to include Group 5.

Section 6.5.1 (dose escalation): The section was updated in 4 locations to include Group 5.

- Dose escalation is allowed for Group 5 once the participant has reached at least Week 25.
- In Group 5, dose escalations are possible from Week 25 onwards as follows: from 125 mg to 200 mg, from 200 mg to 250 mg once daily p.o.
- Table 6-7 was updated to include dose escalation for alpelisib in Group 5.
- For those participants from Group 5, who receive the lower dose because of safety/tolerability concerns, re-escalation of the dose is possible starting from Week 25 in certain conditions as defined in the dose modification guidance below. The Investigator should consult Novartis to make a decision to re-escalate the dose.

Clarification also added for Group 4 that, dose escalations are possible from Week 25 onward.

Section 6.5.1 (dose reduction): The dose reduction sequential steps for alpelisib in Group 5 were added in Table 6-11. The dose reduction sequential steps for alpelisib in Groups 2 and 4 have been grouped in Table 6-10.

Section 6.7 Table 6-23 (preparation and dispensation): Updated to include Group 5.

Section 8: Group 5 was added to the following visit names in Table 8-2 (assessment schedule):

- Addition of Group 5 concerning the exception regarding IRT randomization
- Whole-body MRI, Digital photography of PROS related lesions with corresponding imaging timepoints for Group 5 added
- Overall clinical response assessment with corresponding imaging timepoints for Group 5 added
- Spirometry
- Table 8-11 added for Blood sample for alpelisib PK sampling in Group 5
- Footnote 5 was updated with the following text to include Group 5. If archival block or slides is not available, a fresh biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated.

In Table 8-2 the footnote 9 has been modified to specify Bone development assessments are required per scheduled protocol timepoints. In addition, the footnote 13 has been added to specify that Walking distance test will not be performed in Groups 3 and 4.

For assessments, whole-body MRI, digital photography of PROS related lesions as well as overall clinical response assessment for Groups 1, 2 and 4, the Week 72 timepoint has been added.

Performance Status assessment has been updated as “Karnofsky (in patients > 16 years old / Lansky ≤ 16 years old)” consistently with Inclusion Criteria#6.

Section 8.1: A sentence has been added to specify that technical aspects on imaging are provided in the Vendor Site Manual.

The following 2 sentences were also updated to include Group 5.

It is strongly recommended to provide a tissue sample and/or slides in which the initial PIK3CA determination was made by the local laboratory, when an archival tissue sample is not available, a fresh biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated, and tissue to be sent to the central laboratory.

Participants from Groups 3, 4, and 5 meeting all inclusion and none of exclusion criteria will be enrolled to receive alpelisib treatment in an open-label fashion.

Section 8.1.2: Updates added in this section to specify that data and samples collected from participants prior to screen failure may still be analyzed.

Section 8.2: Group 5 added in the sentence "When archival tissue sample is not available, a fresh biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated".

Section 8.3: The language concerning the "Selection of target and non-target lesions at screening" has been revised to indicate that whole-body MRI is mandated at baseline; in addition, focused MRI imaging may be required to adequately assess small anatomic areas with PROS lesions; all images (MRI, digital photography) will be submitted to BIRC and reviewed centrally.

Section 8.3.1: For "Definitions of response and progression of PROS lesions" the following changes were implemented:

- For primary efficacy, the language for response of PROS lesions evaluated by BIRC was revised to specify it is to be confirmed by a subsequent imaging assessment.
- For secondary efficacy, the language for the response of PROS lesions evaluated by BIRC was revised to add Week 24, 72 and 96 timepoints (i.e., they will be evaluated at Weeks 16, 24, 40, 48, 72, 96 and then every 48 weeks during the study).

[redacted]

For the progression of PROS lesions, one criterion has been revised to remove "at Week 16 and 24" and instead specify "at any timepoint of efficacy evaluation". The updated criteria is "Increase of ≥ 20 % of the volume of target and/or MRI-measurable non-target PROS lesions relative to baseline at any timepoint of efficacy evaluation, otherwise to nadir (defined as best achieved response)".

Section 8.3.1 For "Evaluation of overall clinical response (by Investigators)" the following changes were implemented:

In the sentence "If Investigator suspect a radiological progression of the PROS lesions as defined above at any timepoint of efficacy evaluation, Investigator must require BIRC to confirm the radiological progression in an expedited fashion", the original language "at week 16 and/or week 24" has been replaced with "at any timepoint of efficacy evaluation".

Section 8.3.1 For "Magnetic resonance imaging (MRI)" the following changes were implemented:

Language was revised to indicate that "Whole-body MRI is mandatory at baseline. Whole-body MRI is also recommended to be performed at all scheduled imaging time points". Language also added to indicate "If this is not feasible, at least the lesions identified at baseline by the

Investigator should be captured. Additionally, focused MRI imaging may be required to adequately assess small anatomic areas with PROS lesions."

It was specified in this sub-section that, technical aspects on imaging are provided in the Vendor Site Manual.

For Groups 1 and 2, the Week 72 and 96 imaging assessment timepoints were added concerning the MRI of the whole-body to be performed (i.e., MRI will be performed at screening, at Week 16, 24, 40, 48, 72, 96 and then at other time points of response assessment).

Similarly for Groups 4, the Week 72 and 96 imaging assessment timepoints were added concerning the MRI of the whole-body to be performed (i.e., MRI will be performed at screening, at Week 24, 48, 72, 96 and then at other time points of response assessment).

Group 5 specifications were added and indicate MRI will be performed at screening, at Week 16, 24, 48, 72, 96 and then at other time points of response assessment. At the End of treatment, an MRI will also be performed for all participants if not performed within last 8 weeks during Year 1 (until visit Week 48 included), and within last 3 months during Year 2 - Year 5.

Lastly, language was added in this sub-section to indicate, in the event of a surgery due to PROS lesions, an MRI must be performed, prior to the procedure. No additional MRI is required if an existing MRI was already performed within 4 weeks of the surgical procedure.

Section 8.3.1 and Table 8-3 (Imaging assessment collection plan): table was updated to add the new mandated MRI assessment at Week 72 and to specify the originally existing assessment timepoint planned at Week 96 for Groups 1, 2 and 4. The imaging assessments collection plan has been added for Group 5.

Section 8.3.2 and Table 8-2: Revision added for Walking Distance Test to specify it will not be performed in Groups 3 and 4.

Section 8.3.4: Section was revised to remove "at week 24" for the proportion of participants with confirmed response. As a result, the revised text is "The primary/key secondary objectives are to demonstrate the efficacy of alpelisib as measured by the proportion of participants with confirmed objective response (primary) and response at Week 16 (key secondary) by BIRC for Group 2 (6 - 17 yr-old) and for Group 1 (≥ 18 yr-old)".

Section 8.4.1: Added the following sentence based on the Clinical Trial Protocol template version 5.0: "Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples".

Section 8.5.2: Group 5 was added to the section as well as the new related Table 8-11 for pharmacokinetic blood collection log. A revision has also been added into the footnote of Table 8-9 to clarify, concerning participants who had dose escalation after Week 28 that, PK sample is expected on the next scheduled visit after each dose escalation.

Sentence was added to specify for standard pharmacokinetic abbreviations and definitions, to refer to the list of abbreviations.

Section 8.5.3: Group 5 was added in the following text related to tissue sampling:

"A tissue sample (fresh or archival) is to be sent to Novartis designated central Laboratory. If archival tissue is not available, collection of a fresh tissue biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated."

Section 8.5.5: Section updated to specify that spirometry will be applicable for participants in Group 5.

Section 9.1.3: Revisions added to bring clarifications on the procedures for Withdrawal of consent/opposition to use of data and/or biological samples, in alignment with Novartis Protocol template v5.0 language

Section 10.1.5: Updated in alignment with Novartis Protocol template v5.0 language to align to current safety guidance.

Section 11.3: Site monitoring information updated in alignment with Novartis Protocol template v5.0 language.

Section 12: Specified that an additional CSR will be developed once all participants in Groups 1, 2, 4 and 5 have reached at least 42 months (i.e., 36 months after the Week 24 timepoint) of treatment or discontinued earlier to characterize the durability of response. Revision also added to indicate any additional data for participants continuing to receive study treatment past the data cutoff date in Groups 1, 2, 4 and 5 as well as new data collected from participants in Group 3, as allowed by the protocol, will be reported at completion of the study in a final CSR.

- Section 12.1
  - Group 5 added to the analysis sets.
- Section 12.4, Section 12.4.1, Section 12.4.2
  - Modified the primary endpoint/estimand to confirmed objective response.
- Section 12.4.3
  - Updated the intercurrent events of the primary estimand with regards to confirmation of response.
- Section 12.4.4
  - Updated the handling of missing values not related to intercurrent events with regards to confirmation of response.
- Section 12.5.1.1
  - Clarified the description of the key secondary efficacy variable due to the modification of the primary efficacy variable.
- Section 12.5.3
  - Revision added for T1/2 in the Table 12-1 to remove "Use qualifier for other half-lives".
- Section 12.6
  - Added details on the statistical analysis for the exploratory Group 5.
- Section 12.7
  - Introduced an additional CSR once all participants in Groups 1, 2, 4 and 5 have reached at least 42 months (i.e., 36 months after the Week 24 timepoint) of treatment or discontinued earlier to characterize the durability of response. It was also specified

that additional reports may also be developed prior to the final clinical study report in order to respond to Health Authority requests or to support Health Authority submissions.

- Section 12.8.1
  - Revisions added in this section considering data from Study [CBYL719F12002 (EPIK-P1)], in which most participants with a response experienced early reduction in target lesion volume which was subsequently sustained, and that it is anticipated that most of the responses in EPIK-P2 will be associated with an onset within the first 24 weeks of treatment and subsequently sustained.
  - Modified the sample size calculation with regards to confirmed objective response for the primary endpoint, and added details about sample size/operating characteristics for Group 5. Table 12-3: '95% Confidence interval for the difference in confirmed response rates (Group 5 vs Group 2)'and Table 12-4: 'Operating characteristics for Group 5' have been newly added in Section 12.8.1.
- Section 12.8.2
  - Header of the Table 12-6 updated with regards to confirmation of response for the primary endpoint.

Section 13.1: Language on Regulatory and ethical compliance has been updated in alignment with Novartis Protocol template v5.0.

Section 13.3: Language into this section about Publication of study protocol and results has been revised in alignment on Novartis Protocol template v5.0.

Section 13.5: New section entitled "Data Protection" was added in alignment with Novartis Protocol template v5.0.

Section 15: Added two references "Hernán MA and Robins JM (2020)" and "Vijoice® (alpelisib) United States Prescribing Information (2022)". Two references also moved to the appropriate place in alphabetic order: "(2007) Patient-reported outcomes to support medical product labeling claims: FDA perspective" and "The EuroQol Group (1990) EuroQol--a new facility for the measurement of health-related quality of life. Health Policy;16(3):199-208".

In addition, the following editorial changes are implemented within the protocol sections:

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Global Protocol Amendment 01 (14-Jan-2022)

As of the release of this Global Protocol Amendment, 24 sites have been initiated, 11 participants are in screening and 43 have been randomized.

The main purposes of this amendment are:

1. To update elements of the study design based on the recent results from Study [CBYL719F12002] (hereafter referred to as EPIK-P1 entitled "Retrospective chart review study of adult or pediatric patients ≥ 2 years of age, with severe or life|-threatening PIK3CA-Related Overgrowth Spectrum (PROS), who have received alpelisib as part of a compassionate use program"). This specifically concerns the hypothesis to be tested for the primary endpoint, the sample size and the addition of a secondary objective to assess the "Time to Treatment Failure".

[redacted]

3. To adapt the global study protocol to the changes requested by HAs/ECs/IRBs or other regulatory institutions, that were already implemented through local protocol amendments in Germany, the United Kingdom (UK) and China.
4. To modify the imaging assessment (MRI and photography) frequency of Groups 1 and 2, add a new imaging assessments frequency for Group 4, and clarify the timing of the mandatory unscheduled MRI following a suspected disease progression.
   - Revisions to a number of eligibility criteria
   - Correction of discrepancies and typos throughout the protocol.

Amendment rationale:

1. To update elements of the study design based on the recent results from EPIK-P1. [redacted]

Rationale:

At the time of the development of the original EPIK-P2 protocol, limited information regarding the efficacy of pharmacological treatment in PROS was available. Specifically, two publications were considered for estimation of alpelisib efficacy in PROS; one reported efficacy results of alpelisib treatment effect in 19 PROS patients treated at a single site (Venot et al 2018) and the other one the efficacy of sirolimus (an mTOR inhibitor) treatment effect in 57 patients with vascular anomalies only (Adams et al 2016). Response criteria and assessment of response were not standardized across these trials and less stringent to what is proposed in EPIK-P2.

In EPIK-P2, response is planned to be derived from the change in the sum of target lesion volumes (1 to 3 lesions) as assessed by an independent central radiological review (ICRR) and taking into account rescue surgeries and progression of non-target lesions. No data with a similar approach to derive response at Week 24 were available at the time of the development of the original EPIK-P2 protocol.

The hypothesis to be tested was therefore determined based on a case series of patients with PROS published in Venot et al (2018), where: response was derived from changes in the volume of a single target lesion, as assessed by the investigator. It is expected that selecting up to 3 target lesions to assess the radiological response may result in different findings. It is also well known from the oncology setting that lack of concordance in response status may be observed between local assessments and independent, blinded central assessments.

The futility threshold was based on results of a study of sirolimus in patients with complicated vascular anomalies Adams et al (2016). A 35% response rate was considered as an appropriate surrogate estimation of sirolimus efficacy in PROS and was selected as the futility threshold. Of note, none of the patients in Adams et al (2016) had a diagnosis of PROS and the response criteria were based on changes in the size of a single lesion and not on volumetric changes in up to 3 lesions (as in EPIK-P2).

Since the release of the original EPIK-P2 protocol, additional data for alpelisib in the treatment of PROS became available from EPIK-1. This new information is relevant and must be considered in determining efficacy assumptions. It further triggered the revision of the futility threshold to be based on the Parker et al (2019) publication.

The results from EPIK-P1 in 57 patients ≥ 2 years of age with severe or life-threatening complications of PROS recently became available (Jul-2021). The efficacy results in EPIK-P1 are based on the same assessment approach as that considered in EPIK-P2 (i.e., up to 3 clinically relevant lesions selected as target and response status at Week 24 assessed based on ICRR) and allowed to obtain more accurate information regarding a clinically significant response rate at Week 24.

In EPIK-P1 (Canaud et al 2021), 37.5% (95% CI: 21.1 to 56.3) of patients (12/32) included in the complete case analysis had a radiological response at Week 24 based on independent central radiological review (ICRR). Most of the 57 patients included in the study reported clinical benefit (e.g., signs and symptoms improvement, no rescue surgery). Based on the primary efficacy endpoint, none of the patients had radiologically confirmed progression of disease.

EPIK-P1 results demonstrate a meaningful, compelling, and sustained clinical benefit for PROS patients treated with alpelisib. This triggered a review of the efficacy assumptions used for the EPIK-P2 study design as data from EPIK-P1 support the notion that a lower response rate at Week 24 (than expected based on data from Venot et al 2018 publication) is associated with clinically meaningful benefit.

Furthermore, the futility threshold has been revised from 35% to 15% based on published results with sirolimus treatment in a PROS population exclusively (Parker et al 2019), allowing a more accurate estimation of the treatment effect with sirolimus using similar response rate criteria as in EPIK-P2. Among the 22 participants with evaluable volume for affected tissue at the end of 26 weeks of treatment, none (0% of participants, 95% CI: 0 to 15.4%) achieved ≥ 20% reduction (derived from supplementary material Table S2 in Parker et al 2019). The upper limit of the confidence interval of 15.4% is now considered as a more suitable threshold to define the insufficient level of activity for the EPIK-P2 sample size calculation.

As a result of the revised primary hypothesis test, approximately 52 participants are now required in the alpelisib arm of each age group (i.e., Groups 1 and 2) to achieve 86.0% power

(with a one-sided α of 1.25%). With randomization to alpelisib or placebo in a 2:1 ratio, approximately 78 participants are planned to be randomized for each age group (i.e., Groups 1 and 2). This sample size also provides adequate operating characteristics for the key secondary objectives, even if the conditional power (conditional on the primary endpoint being met in the respective age group) has decreased.

The revision of the EPIK-P2 design results in a sample size increase of 18 patients. The change in EPIK-P2 sample size has been performed based only on information external to EPIK-P2 (i.e., results from EPIK-P1 and the Parker et al 2019 publication). This change does not affect the validity of statistical interference and it is not expected to have an impact on trial integrity.

In addition, based on EPIK-P1 study results and the clinical benefit observed on this trial, an additional secondary objective and the related endpoint was added to assess the "time to treatment failure". Time to treatment failure will be assessed in participants who are on treatment with alpelisib in order to measure the duration of the stabilization of disease.

[redacted]

Rationale:

[redacted]

The emerging data from EPIK-P1 in this group of patients support the inclusion of an additional exploratory group of participants 2 to 5 years of age treated with the film-coated tablet formulation (Group 4) in the EPIK-P2 study protocol.

Results from EPIK-P1 in 57 patients ≥ 2 years of age with PROS (including 39 pediatric patients) have become available (Canaud et al 2021). Of the 39 pediatric patients enrolled in EPIK-P1, 11 were 2 to 5 years of age and all were treated with alpelisib 50 mg film-coated tablets. The median duration of exposure to alpelisib in this age group was 18.1 months (range: 11.5 to 36.6). As of the cut-off date for the primary analysis (09-Mar-2020), 92.3% of pediatric patients (36/39) continued to receive alpelisib.

The data collected in the group ages 2 to 5 years demonstrate a positive meaningful clinical benefit/risk ratio including a response rate (proportion of patients with at least 20% reduction in the sum of target lesion volumes, without disease progression from the index date) at Week 24 (± 4 weeks) of 28.6% (95% CI: 3.7 to 71.0) (2/7 patients (complete case analysis)) and an improvement in the severity of the signs and/or symptoms related to the PROS disease (e.g., fatigue, vascular malformation, lipomatosis).

The safety profile of alpelisib in patients 2 to 5 years was acceptable and consistent with the known safety profile of alpelisib established in adult cancer patients. Notably, a low frequency and severity of treatment-emergent adverse events was reported in patients 2 to 5 years of age with no patient requiring treatment interruption or discontinuation.

Furthermore, as of 30-Aug-2021, a total of 189 requests have been approved for pediatric patients with PROS to receive alpelisib via compassionate use programs (under the Novartis Managed Access Program [MAP; CBYL719F12001M], individual patient request (IPR)/nominative Temporary Authorisation for Use (ATU) [CBYL719X2001I], and or the

cohort ATU in France [CBYL719F12001M]). As of the aforementioned cut-off date, approximately 60 patients from 2 to 5 years of age received treatment with alpelisib for a duration ranging from 0 to approximately 55 months. The compassionate use programs recommend that patients be treated with alpelisib 50 mg film-coated tablets. Review of safety data reported to the Novartis Safety Database in patients 2 to 5 years of age treated under compassionate use is in line with that reported in EPIK-P1 and supports an acceptable and manageable safety profile in this patient population. The totality of available data demonstrate that alpelisib 50 mg film-coated tablets can be used to treat patients 2 to 5 years of age.

As such, another purpose of this Global Protocol Amendment 01 is to open an exploratory group (i.e., Group 4) which will include approximately 6 participants (based on feasibility considerations) of age 2 to 5 years treated with 50 mg film-coated tablets. In participants who have difficulty swallowing, alpelisib film-coated tablets can be administered as drinkable suspension by crushing tablets under water with a spoon. Refer to preparation details in Section 6.7 (Table-6-23).

[redacted]

3. **To reflect or implement changes to the study protocol requested by HAs/ECs/IRBs or other regulatory institutions, that were implemented through local protocol amendments in Germany, the United Kingdom (UK) and China.**

Rationale:

[redacted]

[redacted]

4. **To modify the imaging assessment (MRI and photography) frequency in Groups 1 and 2, add a new imaging frequency for Group 4 and clarify the timing of the mandatory unscheduled MRI following a suspected disease progression.**

Rationale:

Following the initial implementation of this Global Protocol original version 00, several study Investigators, including Steering Committee members, raised concerns about the need for repeated whole-body MRI after 48 weeks of treatment. This is supported by the heavy burden for patients, especially children, to undergo such procedure and the absence of strong justification for this high MRI assessments frequency once the treatment is efficacious and given the known evolution of the underlying disease. The MRI schedule that was proposed in Global Protocol original version 00 is seen as a serious risk for patients' retention in this study after 48 weeks of treatment. Therefore, it has been decided to decrease the MRI assessments frequency to closer follow the current medical practice in PROS patients (once yearly in absence of sign or symptoms suggestive of a negative evolution). Thus, for Groups 1 and 2: MRI of the whole-body will be performed at screening, Weeks 16, 24, 40, and 48 as well as every 48 weeks thereafter until Week 264 (End of Treatment). Thus, this amendment decreases the frequency of MRI after Week 48 for patients from Groups 1 and 2 from every 24 weeks to every 48 weeks. Given that the primary and main secondary analyses are based on data collected up to Week 48, the frequency of MRI could be decreased following these milestones.

For the newly introduced Group 4: MRI of the whole-body will be performed at screening, Weeks 24 and 48 as well as every 48 weeks thereafter until Week 264 (End of Treatment). Given that all participants from Group 4 will receive alpelisib and that none will receive placebo, there is no need to perform imaging assessments at Week 16 or at Week 40. Week 16 assessments are used to assess efficacy in Groups 1 and 2 only, as part of the key secondary objective (comparison of the response rate between the placebo and the alpelisib arms), whereas Week 40 will assess the effect of alpelisib on participants originally randomized to the placebo arm and who have then been treated with alpelisib for 24 weeks. Thus, only the main analysis milestone, at Weeks milestones: Week 24 and 48, followed by a yearly assessment thereafter, are applicable for participants of Group 4.

In protocol Section 6.1.5.1 about "Treatment beyond disease progression": it has been clarified that if disease progression is suspected for any patient, the Investigator must perform an

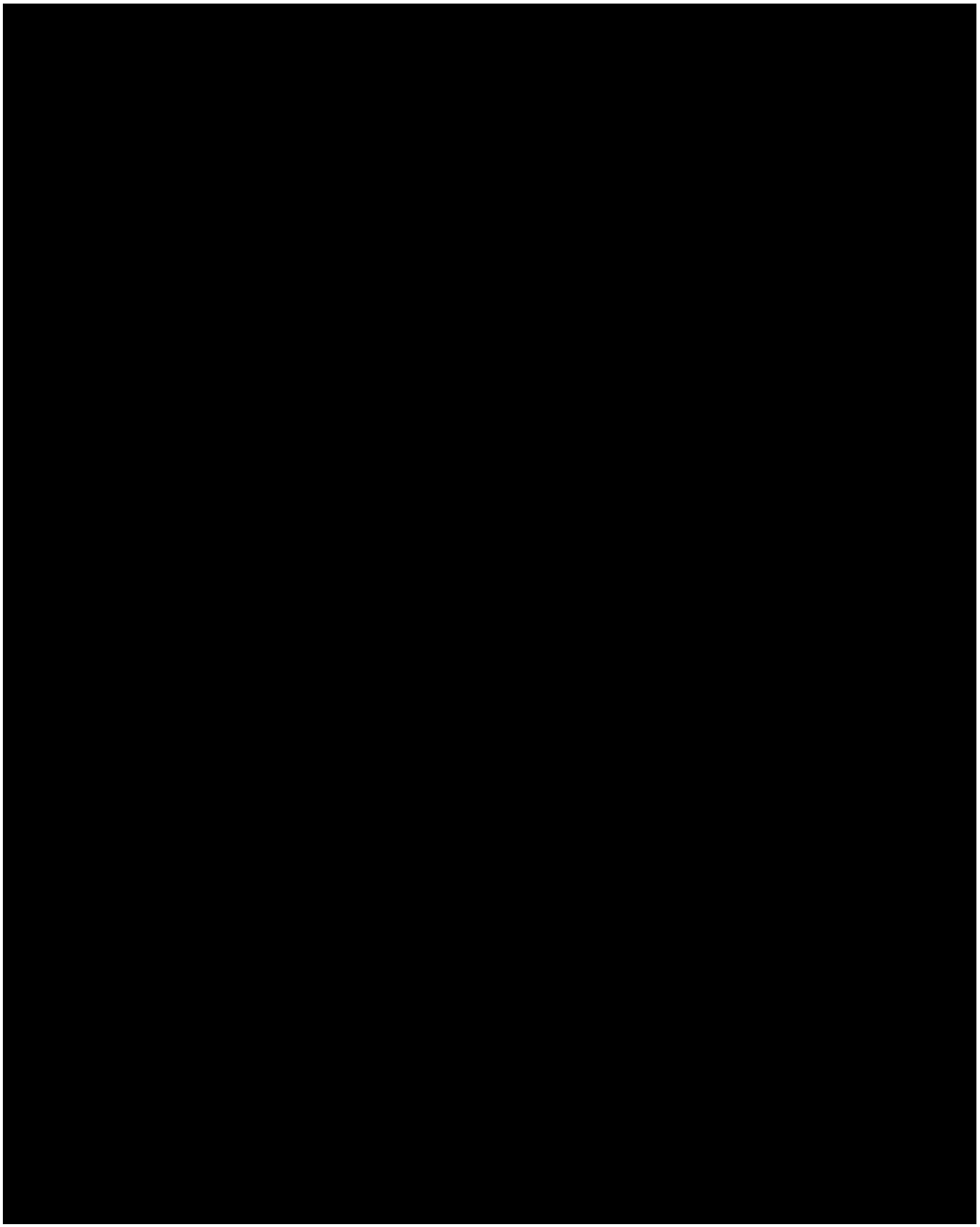
unscheduled MRI as soon as feasible and within the coming 3 months maximum. This is applicable to participants of all groups at any time point in the study in order to support assessment of duration of response.

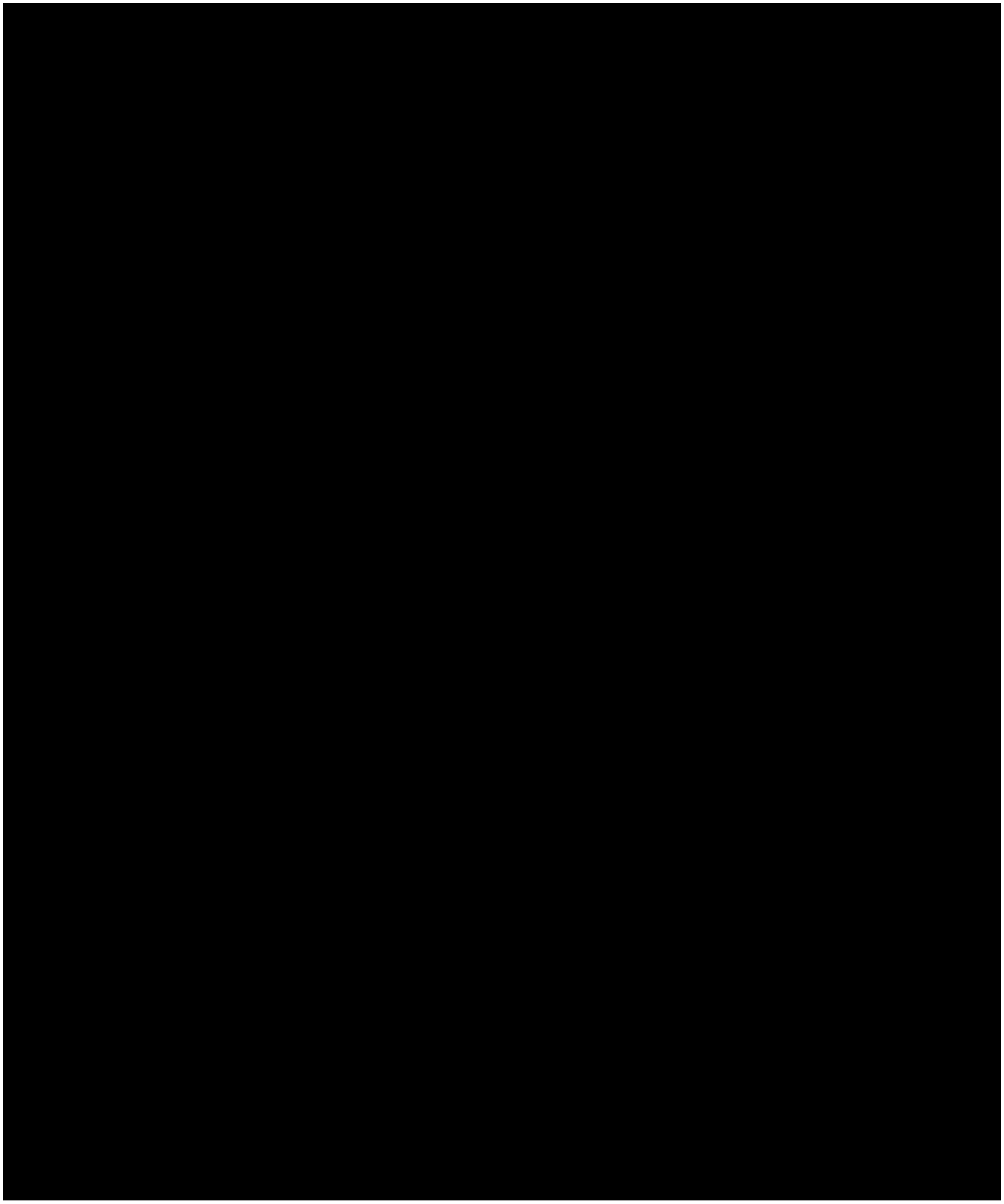
In addition, the following changes are implemented:

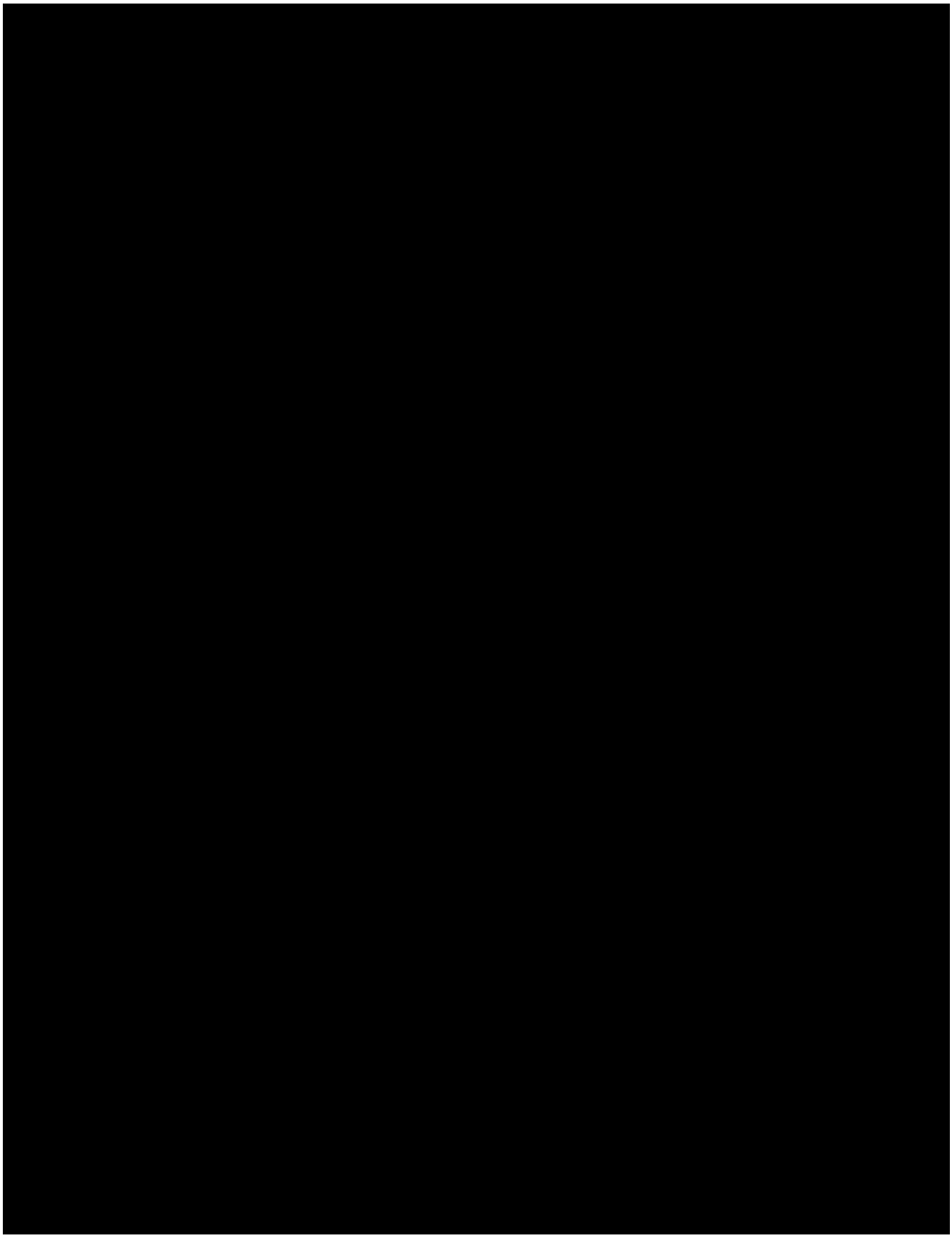
[redacted]

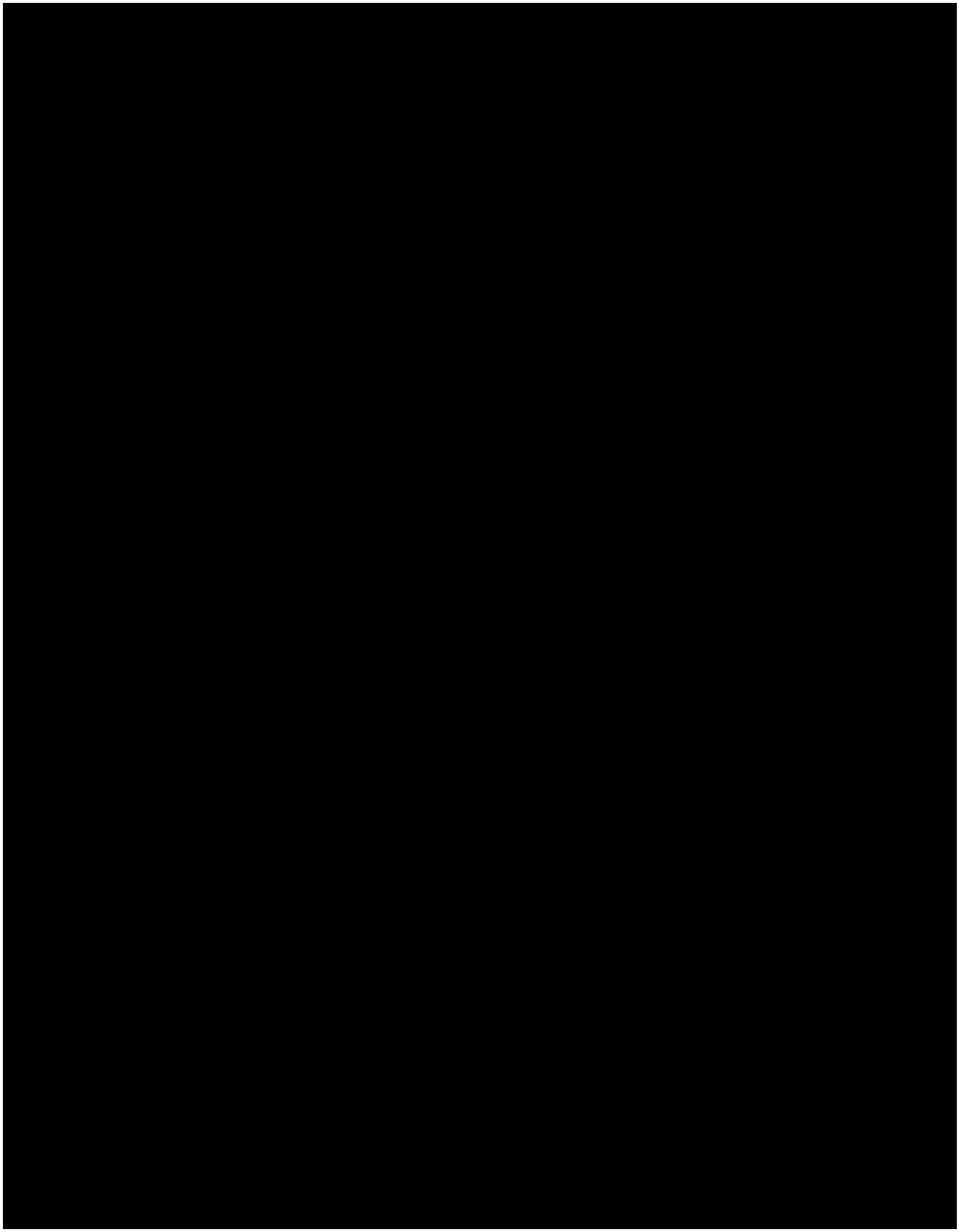
List of modified Protocol Amendment 01 sections:

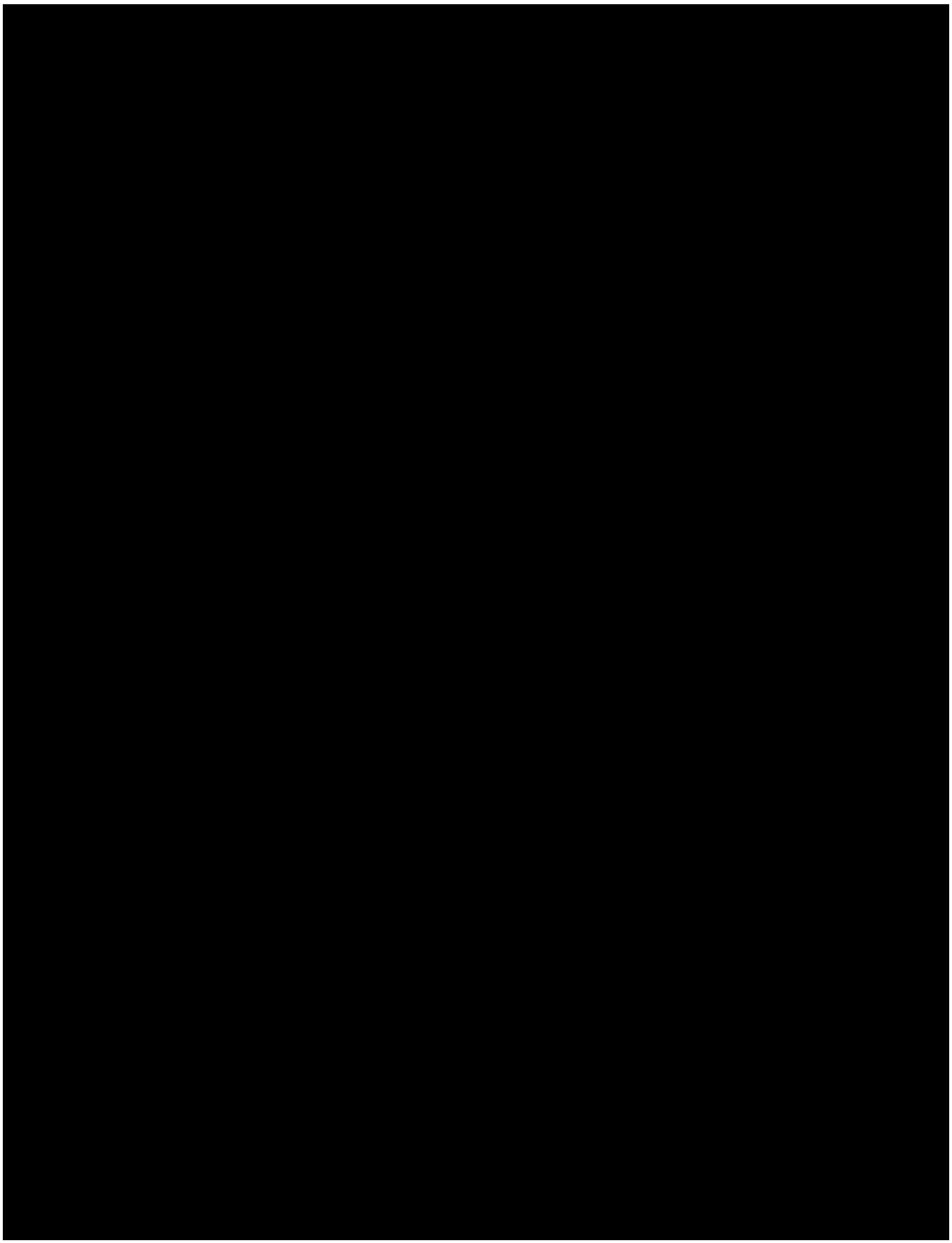
[redacted]

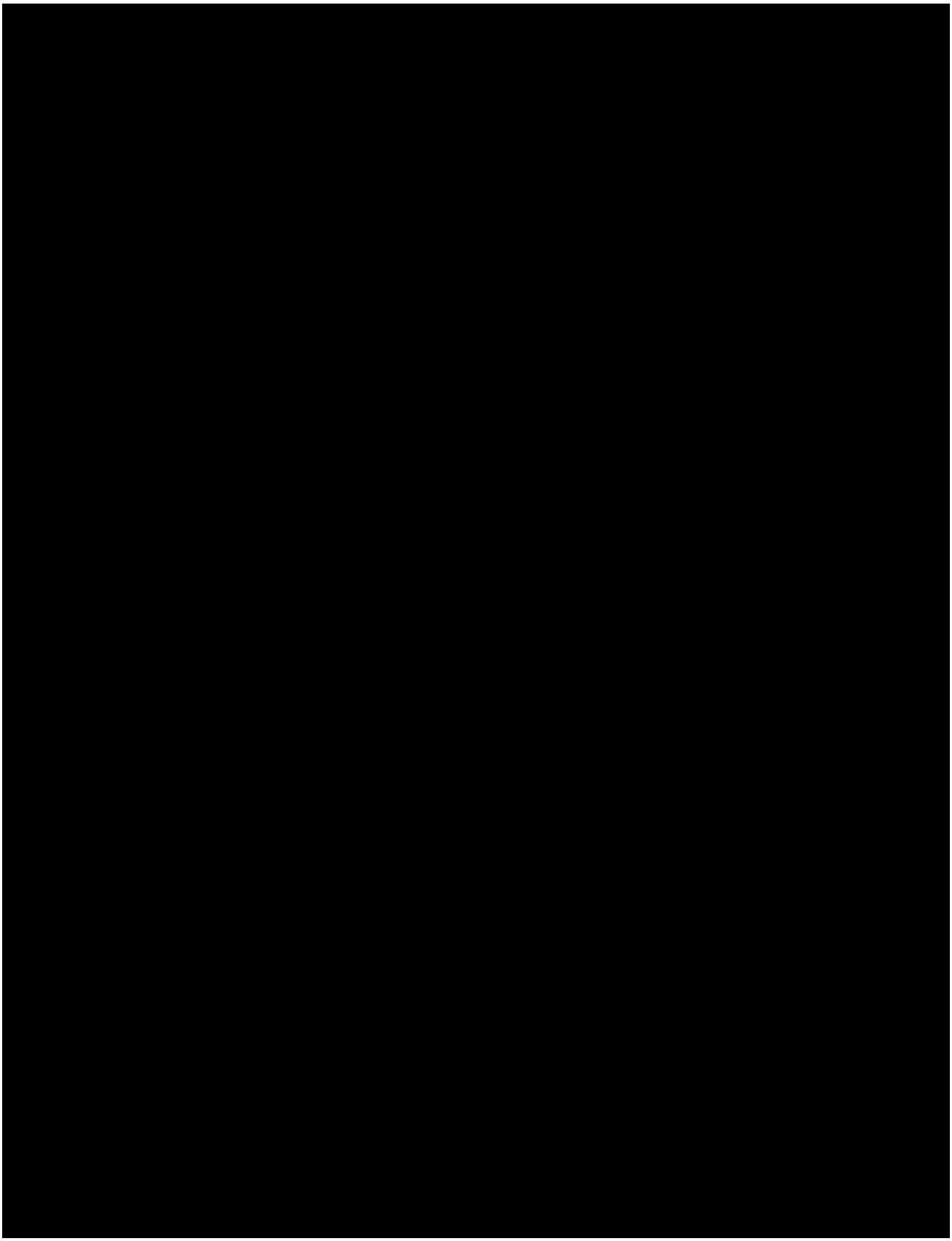


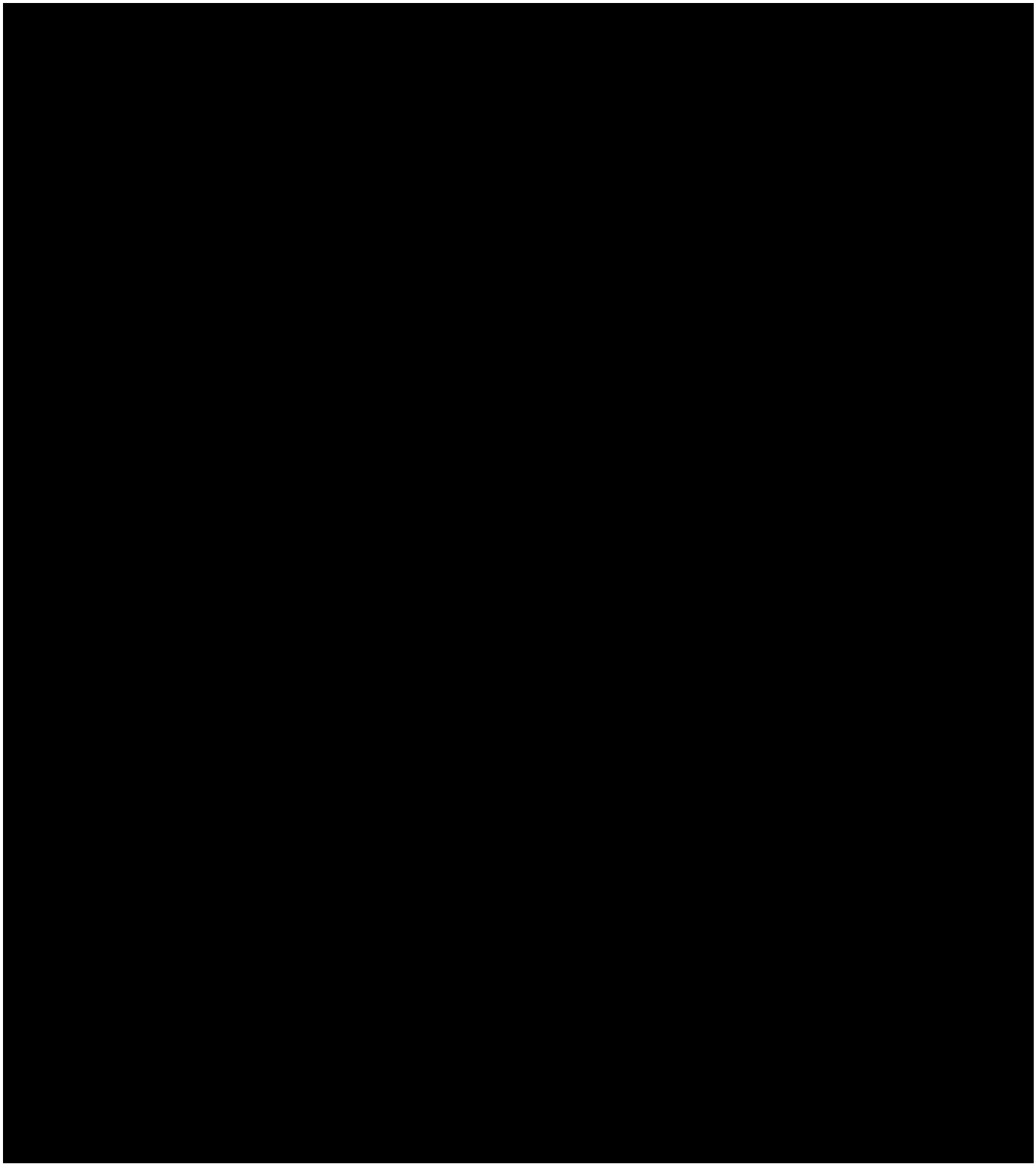












In addition, the following editorial changes are implemented within the protocol sections:

[redacted]

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CBYL719F12201
Full Title	EPIK-P2: A Phase II double-blind study with an upfront, 16-week randomized, placebo-controlled period to assess the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS)
Brief title	Study assessing the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS)
Sponsor and Clinical Phase	Novartis Pharma AG Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study will be the first prospective study of alpelisib in participants with PROS. Local overgrowth or hemihypertrophy, mostly progressive, is the most frequently observed manifestation of the disease, often causing functional and/or mobility impairment and reduction in health related quality of life. The first experience with alpelisib in overgrowth related to mutation in PIK3CA gene provides the direct evidence of clinical improvement in participants supporting PIK3CA inhibition as a promising therapeutic strategy in participants with PROS. PROS is a serious condition with no approved pharmacological treatment targeting the underlying cause of the disease. Current therapy includes debulking surgery, amputation, and/or endovascular occlusive procedures and mainly addresses symptoms and complications of the disease. There is a high unmet medical need for an effective systemic treatment. The purpose of this study is to assess the efficacy, safety/tolerability and evaluate pharmacokinetics (PK) of alpelisib in participants of different ages with confirmed diagnosis of PROS. As the disease continues throughout the participant life and may be diagnosed at different time points (Keppler-Noreuil et al 2014), the study will enroll adult participants (Group 1; treated with film-coated tablets (FCT)), 6 to 17 years old pediatric participants (Group 2; treated with FCT), two exploratory groups of pediatric participants less than 6 years old (Group 3, 0-5 years old treated with granules and Group 4, 2-5 years old treated with FCT) and an exploratory group of 6 to 17 years old pediatric participants (Group 5, treated with FCT [at a higher starting dose than Group 2]). Group 3 will be enrolled after the completion of the primary analysis when the efficacy, safety and PK data will be available from the participants in Groups 1 and 2 in addition to the data from Groups 4 and 5 as available, in order to select the recommended dose for participants in Group 3. Recruitment of participants in Group 3 will start only after implementation of Global Protocol Amendment 05. Group 4 will be enrolled before Group 3 and immediately after implementation of Global Protocol Amendment 01. Group 5 will be open to enrollment after implementation of Global Protocol Amendment 02 and immediately after enrollment of Group 2 has been completed.
Primary Objective(s)	The primary objective of this study is to demonstrate the efficacy of alpelisib as measured by the proportion of participants randomized to alpelisib with a confirmed objective response by BIRC in at least one of the following groups: • *Group 1 (≥ 18 yr-old)* • *Group 2 (6 - 17 yr-old)* The primary scientific question of interest is, for children/adolescents aged 6 to17 years (in Group 2) and adults (Group 1: ≥ 18 years) with PROS, to assess the benefit of alpelisib with regards to the proportion of confirmed responders by BIRC, considering participants that discontinue treatment prior to confirmation of response and participants that receive surgery as rescue therapy for any PROS lesions prior to confirmation of response as non-responders.
Secondary Objectives	Key secondary objective: • To demonstrate the efficacy of alpelisib vs placebo based on the comparison of the proportion of participants with response at Week 16 in Group 1 or Group 2

	Other secondary objectives: • To assess the efficacy of alpelisib as measured by the proportion of participants with a response at Week 24 (by BIRC) in Groups 1 and 2 • To assess the safety and tolerability of alpelisib as compared to placebo in Groups 1 and 2 up to week 16 • To assess the overall safety and tolerability of alpelisib in participants with PROS over time • To assess changes in patient-reported pain intensity and overall severity of symptoms at week 16 on treatment with alpelisib as compared to placebo in pediatric and adult populations • To assess changes in target and non-target lesions over time and appearance of new lesions on treatment from baseline over time • To assess the PK of alpelisib in adult and pediatric patients with PROS • To assess changes in patient-reported pain, health-related quality of life and overall impression of symptoms in pediatric and adult populations over time • To assess the duration of response in participants who receive alpelisib • To assess the time to treatment failure in participants who are on treatment with alpelisib • To assess the rate of overall clinical response as assessed by Investigator at the scheduled protocol visits for disease evaluation (e.g., week 16, 24, 40, 48, 72, 96 and thereafter every 48 weeks) • To assess the proportion of participants with a response at the scheduled protocol visits for disease evaluation during the extension periods • To assess changes in symptoms and complications/comorbidities up to week 16 on treatment with alpelisib as compared to placebo • To assess changes in symptoms and complications/comorbidities associated with PROS over time • To assess the frequency of healthcare visits/hospitalizations due to PROS, rescue surgeries for PROS (incl. avoidance/delay in planned disease-related surgery) over time·
Study design	This is a Phase II multi-center study with an upfront 16-week, randomized, double-blind, placebo-controlled period, and extension periods, to assess the efficacy, safety and PK of alpelisib in pediatric and adult participants with PROS. **Study period 1 - Core Period: Double-blind treatment, with an upfront 16-week placebo-controlled period (From Randomization to the end of Week 24) – Groups 1 and 2** At study start, participants in Group 1 and Group 2 will be enrolled and randomized in a 2:1 ratio (104 participants in the active arms and 52 participants in the placebo arms) to alpelisib or matching placebo. The upfront placebo-controlled period will continue for the first 16 weeks. At the conclusion of week 16, those participants who were randomized to receive placebo will be switched to active treatment with alpelisib in a blinded fashion at the dose level received at the end of the placebo period. Those participants who were randomized to receive alpelisib, will continue their treatment at the same dose level. During the initial 16 weeks of the Core period, study treatment will be given in a blinded fashion, starting from week 17 of the Core period in open label fashion. The randomized treatment assignment to the treatment arms will remain blinded to participants, Investigators and the study team until the time of the primary analysis, when the last participant reaches week 48 from randomization or discontinues earlier. **Study period 1 – Exploratory; Group 4, open label treatment with the alpelisib FCT formulation** After the implementation of Global Protocol Amendment 01, approximately 6 participants 2 to 5 years of age will be enrolled in exploratory Group 4. These participants will receive alpelisib FCT in an open label setting.

	Study period 2 - Extension 1: treatment with alpelisib (week 25 up to the end of week 48) – Groups 1 and 2 Participants (Group 1 and Group 2) will continue their treatment during this study period. For Groups 1 and 2, dose escalation is NOT allowed during first 4 weeks of Extension 1 period (weeks 25-28). Once a participant (Groups 1 and 2) has completed initial 24 weeks of study treatment and reached Week 29, dose escalation will be allowed (Refer to Section 6.5.1): • Group 1: Alpelisib (125mg, or 200mg, or 250 mg QD) • Group 2: Alpelisib (50mg, or 125mg, or 200mg, or 250 mg QD) **Study period 2 – Exploratory: Group 4, open label treatment with the alpelisib FCT formulation** For Group 4 dose escalation is allowed once participant has reached the age of 6 years old, has completed the initial 24 weeks of study treatment, and has reached week 25: • Group 4: Alpelisib (50 mg, or 125 mg, or 200 mg, or 250 mg QD) **Study period 3 - Extension 2: long-term treatment with alpelisib (Week 49 up to 5 years) – Groups 1 and 2** Groups 1 and 2 participants who continue the study until Week 48 and have clinical benefit from the study treatment, will enter a long-term extension period. Dose escalation and treatment beyond progression are allowed in both Group 1 and Group 2. **Study period 3 – Exploratory: Group 4, open label treatment with the alpelisib FCT formulation** Group 4 participants who continue the study until Week 48 and have clinical benefit from the study treatment, will enter a long-term extension period. Dose escalation is allowed once a participant has reached the age of 6 years old, has completed the initial 24 weeks of study treatment, and has reached Week 25. **Exploratory study part: Group 3, open label treatment with the alpelisib granules formulation** Group 3 will be an exploratory group of participants who are 0 to 5 years old and will receive the alpelisib granules formulation with an age-dependent starting dose and maximum dose levels ranging from 20 mg every other day to 50 mg once daily. Group 3 will be open to enrollment only after implementation of Global Protocol Amendment 05. Dose escalation is allowed once a participant has reached the age of 6 years, has completed the initial 24 weeks of study treatment, and has reached Week 25. **Group 5 open-label treatment with the alpelisib FCT formulation:** Participants of Group 5 will be enrolled after implementation of Global Protocol Amendment 02 and immediately after enrollment of Group 2 has been completed and will receive a starting dose of 125 mg alpelisib FCT formulation once daily in an open-label setting. Dose escalation is allowed for those who did not derive sufficient clinical benefit at the Investigator's discretion and once participant has reached at least Week 25.
Study population	It is planned to enroll approximately 192 participants in total, 78 adults and 114 children and adolescents. A total of approximately 156 male or female participants (of age ≥ 6 years) with PROS will be randomized in a 2:1 ratio in Groups 1 and 2 (approximately 78 participants per age group). Additional exploratory groups (Group 3, Group 4 and Group 5) will include approximately a total of 36 participants (approximately 15 in Group 3, 6 in Group 4 and 15 in Group 5).
Key Inclusion criteria	• Signed informed consent and assent (when applicable) from the patient, parent, legal authorized representative or guardian prior to any study related screening procedures are performed. • Patients with diagnosis of PROS with symptomatic and /or progressive overgrowth and at least one measurable PROS-related lesion confirmed by BIRC assessment.

	• Documented evidence of a somatic mutation(s) in the PIK3CA gene performed in local laboratories. • A tissue sample (fresh or archival) is to be sent to a Novartis-designated central Laboratory. If archival tissue is not available, collection of a fresh tissue biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated. For participants in Groups 3 and 4, a fresh tissue biopsy is not mandatory. [redacted] For Germany only: If archival tissue is available, it must be sent to a Novartis-designated central laboratory. If no archival tissue is available, obtaining a fresh tissue biopsy is recommended, if it is not clinically contraindicated, but is not mandatory. • Karnofsky (in patients > 16 years old at study entry)/Lansky (≤16 yrs of age at study entry) performance status index ≥50. • Adequate bone marrow and organ function including Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L) and Glycosylated hemoglobin (HbA1c) ≤ 6.5% (both criteria have to be met) (as assessed by central laboratory for eligibility). • Presence of at least one PROS-related measurable lesion defined as a lesion with longest diameter ≥2 cm, when the volume can be accurately and reproducibly measured by MRI (Magnetic resonance imaging), and associated with complaints, clinical symptoms or functional limitations affecting the patient's everyday life. Measurability must be confirmed by BIRC before randomization. For the full inclusion criteria, please refer to Section 5.1.
Key Exclusion criteria	• Participant with only isolated macrodactyly, epidermal nevus/nevi and macroencephaly (the only clinical feature or a combination of any of three of them), in absence of other PROS-related lesions at the time of informed consent. • Previous treatment with alpelisib and/or any other PI3K inhibitor(s) (except treatment attempt, defined as the attempt to treat PROS with any of PI3K inhibitors, with treatment duration less than 2 weeks and stopped at least 4 weeks prior to the first dose of study medication with alpelisib). • Radiation exposure for PROS treatment purpose within the previous 12 months on those PROS areas which are expected to qualify for target lesions (except lesion(s) progressing after completion of radiotherapy) at time of informed consent. • Debulking or other major surgery performed within 3 months at time of informed consent. • Clinically meaningful PROS-related thrombotic event (Grade 2 and more as per CTCAE v.4.03) within 30 days before informed consent, and/or sclerotherapy/embolization for vascular complications performed within 6 weeks before informed consent. Note: Participants receiving anticoagulants for PROS-related coagulopathy, primary or secondary prophylaxis of thrombosis may be included in the study. • Participants in Groups 1, 2 and 5 with documented pneumonitis or interstitial lung disease at time of informed consent and with impaired lung function (e.g., FEV1 or DLCO ≤ 70% of predicted) that is not related to PROS. Participants in Groups 3 and 4 with documented or suspicious pneumonitis or interstitial lung disease based on MRI images at time of informed consent. • History of acute pancreatitis within 1 year before informed consent or past medical history of chronic pancreatitis at time of informed consent. • Participants with an established diagnosis of type I diabetes mellitus or uncontrolled type II diabetes mellitus at time of informed consent. • Known history of seizure, or epilepsy, regardless of relatedness to PROS spectrum at time of informed consent, when epilepsy is not controlled and/or the patient may not be switched to non-enzyme inducing antiepileptic drug(s) at time of informed consent.

	• Participants with clinically significant worsening of PROS-related laboratory anomalies, physical signs and symptoms (such as, but not limited to increase of D-dimers, worsening of underlying pain, newly occurring swelling or redness) indicating an uncontrolled condition during the screening phase, particularly if systemic treatment with any other inhibitor of the PI3K/AKT/mTOR pathway was stopped prior to the start of study treatment. This includes but is not limited to hypercoagulability state in participants not receiving prophylactic treatment. For the full exclusion criteria, please refer to Section 5.2.
Study treatment	**Study treatment in Group 1 and Group 2** Alpelisib/matching placebo FCT will be administered immediately after food at the assigned starting doses based on the age groups: • 125 mg alpelisib/matching placebo once daily p.o. in Group 1 • 50 mg alpelisib/matching placebo once daily p.o. in Group 2. After Week 16 those participants who were randomized to receive placebo will be switched to active treatment with alpelisib in a blinded fashion at the dose level received at the end of the placebo period. Those participants who were randomized to receive alpelisib will continue their treatment at the same dose level. Participants (Group 1 and Group 2) will continue their treatment at the randomized dose unless the dose is reduced for safety reason. When the dose was reduced because of toxicity, the participant remains on reduced dose at least until end of Week 28, when escalation becomes allowed. **Study treatment in Group 4** The participants in Group 4 will receive 50 mg alpelisib (FCT) once daily, administered immediately after food, in an open-label setting. **Study treatment in Group 5** The participants in Group 5 will receive 125 mg alpelisib (FCT) once daily, administered immediately after food, in an open-label setting. **Study treatment in Group 3** The participants in Group 3 will receive alpelisib (granules) administered with food in an open-label setting. Group 3 dosing will be age-based with starting dose and maximum dose levels ranging from 20 mg every other day to 50 mg once daily.
Treatment of interest	Randomized treatment with daily alpelisib, regardless of dose changes, in absence of rescue surgery for PROS lesions. Further details are provided in Section 6.
Efficacy assessments	Refer to Section 8 for more details. • For Groups 1 and 2: MRI of the whole-body will be performed at screening, Weeks 16, 24, 40, 48, 72, 96 as well as every 48 weeks thereafter, until Week 264 (End of Treatment). For Group 4: MRI of the whole-body will be performed at screening, Weeks 24, 48, 72, 96 as well as every 48 weeks thereafter until Week 264 (End of Treatment). For Group 3: MRI of the whole-body will be performed at screening, Weeks 24, 48, 72, 96 as well as every 48 weeks thereafter until Week 264 (End of Treatment). For Group 5: MRI of the whole-body will be performed at screening, Weeks 16, 24, 48, 72, 96 as well as every 48 weeks thereafter until Week 264 (End of Treatment). • For Groups 1 and 2: Digital photography (images of the whole-body; images of the body parts changed due to PROS when applicable; Images of PROS-related skin/superficial visual lesions) will be performed at screening, at Week 16, 24, 40, 48, 72 and 96 as well as every 48 weeks thereafter until Week 264 (End of Treatment). For Group 4: Digital photography will be performed at screening, at Weeks 24, 48, 72 and 96, as well as every 48 weeks thereafter until Week 264 (End of Treatment). For Group 5: Digital photography will be performed at screening, at Weeks 16, 24, 48, 72 and 96, as well as every 48 weeks thereafter until Week 264 (End of Treatment).

	For Group 3: Digital photography will be performed at screening, at Weeks 24, 48, 72 and 96, as well as every 48 weeks thereafter until Week 264 (End of Treatment). • Assessment of changes in symptoms and complications/comorbidities associated with PROS over time, will be collected at baseline and then at every time point for response assessment. • Assessment of patient-reported pain, overall symptom severity, impacts and health-related quality of life will be collected with patient-reported outcomes measures throughout the study. • Assessment of the frequency of hospitalizations/surgeries will be collected at baseline and then at every time point for response assessment. • Assessment of mobility will be performed at screening and then for those participants who have PROS-related impairment of mobility after 4 and 8 weeks of initial treatment, and then at efficacy assessment time points.
Pharmacokinetic assessments	Blood samples for alpelisib PK evaluation will be collected from all participants who receive at least one dose of study treatment.
Key safety assessments	Safety assessments will be conducted through the study (according to the assessment schedule – Table 8-2) • Monitoring of adverse events (AEs) and serious adverse events (SAEs) • Physical examination • Body weight and vital signs • Karnofsky/Lansky performance status • Laboratory assessment including hematology, biochemistry and coagulation • Serum pregnancy test for women of child-bearing potential • Electrocardiogram (ECG) • Echocardiography • Spirometry • Height and Body Mass Index (BMI) • Growth, bone/dental development and sexual maturation in pediatric participants. For more details, please refer to Section 8.
Other assessments	The patient-perceived effects of treatment with alpelisib will be assessed through changes in patient-reported outcomes measures (PROMs), as the basis of secondary endpoints in this study. These PROMs will assess concepts including pain intensity, overall symptom severity, physical functioning, mental health, social functioning, fatigue, sleep, and shortness of breath. PROMs will be implemented on electronic patient-reported outcomes (ePRO) devices given to each participant (or caregiver) and include, depending on age of the participant: • Worst Pain Intensity, pain interference, location and type of pain, derived from the Brief Pain Inventory (for adults and children 12 and over) • Wong-Baker FACES® Pain Rating Scale (For children 3-11 years of age) • Dyspnea Severity (for adults and children 12 and over) • Patient Global Impression of Symptom Severity (for adults, children 12 and over and parents for children under 12) • The PROMIS-29 plus 2 Profile v2.1 (adults only) • The PROMIS Pediatric-25 Profile v2.0 (children 12 and over) • The PROMIS Pediatric and Parent-Proxy Sleep Disturbance Short Form 4a (Parents to answer for children under 12) [redacted]

	[redacted]
Data analysis	The primary efficacy variable of the study is the proportion of participants randomized to alpelisib achieving confirmed objective response (by BIRC). Response is defined by achieving at least 20% reduction in the sum of target lesion volumes (1 to 3 lesions), assessed by MRI by a blinded independent review committee, provided that none of the individual target lesions has ≥ 20% increase from baseline and in absence of progression of non-target lesions and without new lesions. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response. Participants that discontinue treatment prior to confirmation of response and participants that receive surgery as rescue therapy for any PROS lesions prior to confirmation of response are considered as non-responders. The primary analysis will be based on the FAS-BYL719 (i.e. all participants to whom alpelisib has been assigned by randomization) for Groups 1 and 2, respectively. A confirmed response rate of 15% or less is considered "as insufficient" level of efficacy for the proposed participant population. The primary statistical null hypotheses state that the confirmed objective response rate in each group is ≤ 0.15. In order to conserve the overall type-1 error (one-sided level of significance of α=0.025) in testing multiple primary and key secondary hypotheses, an alpha split with a graphical gate-keeping approach will be implemented based on the graphical multiple testing procedure. Confirmed objective response rates in Groups 1 and 2 will be summarized using descriptive statistics along with 2-sided exact 100(1-2α_i) % confidence interval (CI) (Clopper-Pearson exact method), where α_i corresponds to the appropriate α-level adjusted for multiple testing. The study will be declared positive if at least one of the two primary null hypotheses can be rejected, i.e. if the lower bound of the 100(1-2α_i) % CI for the response rate exceeds 15% in Groups 1 or 2. The key secondary objective is to demonstrate the efficacy of alpelisib based on the comparison of the proportion of participants achieving response at Week 16 with alpelisib versus placebo in Groups 1 or 2. The key secondary analysis will be based on the FAS (i.e. all randomized participants) for Groups 1 and 2, respectively. The key secondary statistical null hypotheses in Groups 1 and 2 state that the response rates at Week 16 in participants randomized to alpelisib are the same (or lower) than in participants randomized to placebo. The analysis to test these hypotheses will consist of a Fisher's exact test at the appropriate α-level governed by the graphical gatekeeping procedure. The testing of key secondary hypothesis will be carried out only if the primary null hypothesis is rejected in the respective age group. Response rates at Week 16 in Groups 1 and 2 will be summarized using descriptive statistics along with 2-sided exact 95% Clopper-Pearson CI. The difference between treatment arms (alpelisib - placebo) in response rates at Week 16 will be presented together with 2-sided 95% confidence interval (unadjusted for multiple testing), separately for Groups 1 and 2.
Key words	PIK3CA-related overgrowth spectrum (PROS), alpelisib, Phase II.

1 Introduction

1.1 Background

The PI3K/AKT/mTOR pathway in PIK3CA-related overgrowth spectrum (PROS):

Tissue proliferation is a tightly regulated process in the organism from embryonic development to adult life. One of the main regulators of cell proliferation is the PI3K/AKT/mTOR signaling pathway, which is a well-known target of multiple therapeutic strategies. The hyper-activation of the PI3K/AKT/mTOR pathway results in significant dysregulation of cellular functions, which in turn leads to a competitive growth advantage. Somatic mutations and gains or losses in these genes are linked to many different solid and hematological tumors (De Santis et al 2017). In addition to the well-characterized role of PIK3CA in cancer, post zygotic somatic mutations in PIK3CA have also been identified in a spectrum of overgrowth disorders comprising a wide group of clinically recognizable mutation-driven malformations referred to as PIK3CA-related overgrowth spectrum (PROS) (De Santis et al 2017).

PIK3CA-Related Overgrowth Spectrum (PROS) designates a heterogeneous group of rare, asymmetric overgrowth disorders caused by post zygotic variants in the gene PIK3CA (Keppler-Noreuil et al 2014). PIK3CA encodes the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which transduces activation of tyrosine kinase growth factor and hormone receptors into activation of Protein Kinase B (AKT) and Mammalian Target of Rapamycin (mTOR) signaling to promote tissue growth. In PROS, activation of this pathway is associated with overgrowth which may include adipose tissue, muscle, skin, bone, blood or lymph vessels, or neural tissue (Kurek et al 2012, Lindhurst et al 2012).

The prevalence of PROS is difficult to estimate because of its rarity, its recent characterization (i.e., in 2014 by the National Institutes of Health), variation in ascertainment, the broad phenotypic spectrum, and the occurrence of atypical or mild phenotypes leading to misdiagnosis (Keppler-Noreuil et al 2014, Mirzaa et al 2013). The incidence rate was estimated by medical experts to be approximately 1 in 70,000; essentially based on the number of patients they see.

PROS is characterized by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. Segmental overgrowth is often congenital at onset, but it is usually noted by 1 year of age with progressive overgrowth of tissues persisting in some cases into adulthood. Though some genotype–phenotype correlation in PROS has been suggested (Mirzaa et al 2016, Keppler-Noreuil et al 2014), the main determinant of phenotype is the timing and location of the pathogenic mutation. Consequently, PROS is characterized by a high degree of interindividual phenotypic heterogeneity. The overgrowth features vary greatly for reasons which are unknown: some lesions exhibit excess growth which is limited to childhood, while other individuals have progressive soft tissue overgrowth during adult life. Complications of PROS depend on the anatomical site and extent of overgrowth, but may include functional impairment (e.g., of walking or swallowing), pain, cardiac function impairment, pulmonary hypertension, seizures, impaired neurological development, recurrent superficial infections, thromboembolism, and/or hemorrhage, amongst other manifestations all of which may be debilitating, and cause early mortality. Current treatment relies on surgery primarily with debulking objectives - amputation, and/or endovascular occlusive procedures. Regrowth

following surgery frequently occurs and often requires repeated surgery. There is large unmet need for targeted, new therapeutic approaches and effective treatments to combat PROS.

Disorders that lead to inappropriate activation of the PI3K/AKT/mTOR pathway have been shown to result in tissue overgrowth in association with vascular anomalies. Inhibitors targeting different components of the PI3K/AKT/mTOR signaling pathway are/were under clinical investigation (Keppler-Noreuil et al 2016, Suzuki et al 2017, Venot et al 2018). However only a very limited number of clinical studies were conducted with medical treatment in the PROS population.

Development of PI3K/AKT/mTOR inhibitors in PROS indication:

Investigation of efficacy and safety of mTOR inhibitor sirolimus (rapamycin) was first conducted in vascular anomalies, a spectrum of the rare diseases classified into vascular tumors and malformations. A prospective study enrolled children and young adults (n=61). They received up to 12 courses of 28 days, sirolimus was administered orally at a starting dose of 0.8mg/m² twice daily, then the levels were maintained between 10 and 15 ng/ml. In terms of efficacy, at the end of course 6 no complete response was seen, a total of 47 participants had a partial response, 3 participants had stable disease, and 7 participants had progressive disease (57 participants were evaluable for efficacy). Grade 3 and higher toxicities attributable to sirolimus included blood/bone marrow toxicity in 27% of participants, gastrointestinal toxicity in 3%, and metabolic/laboratory toxicity in 3%; 2 participants were taken off of study medicine secondary to persistent adverse effects; no toxicity-related deaths occurred. It was concluded that sirolimus demonstrated activity in participants with complicated vascular anomalies, and further investigations are needed to evaluate specific disease phenotypes (Adams et al 2016). Another sirolimus study was conducted in patients with PROS. Thirty-nine participants with PROS and progressive overgrowth (22 children < 16 years old, 17 adults ≥16 years old) were included in an open-label study (with a 26 weeks run-in period) of efficacy and safety of low-dose sirolimus. The dose of sirolimus was titrated to achieve a target plasma concentration of 2-6 ng/ml (based on renal transplants dosing algorithms). Evaluations for efficacy were done at Weeks 0 (before the run-in phase), Week 26 (after the run-in phase and before treatment), and at Week 52 (after 26 weeks of treatment) with use of dual energy X-ray absorptiometry (DXA) scans (quantification for primary outcome) and MRI without contrast. Sirolimus led to a change in mean percentage total tissue volume of –7.2% (SD 16.0, p = 0.04) at affected sites affected by PROS, but not at unaffected sites (+1.7%, SD 11.5, p = 0.48) (completed the study: n=30, evaluable: n = 23). The adverse-effect profile was interpreted as significant: twenty-eight of 39 (72%) participants had ≥1 adverse event related to sirolimus of which 37% were grade 3 or 4 in severity and 7/39 (18%) participants were withdrawn consequently; in the opinion of the Investigators, treatment of PROS with sirolimus mandates individualized risk-benefit evaluations (Parker et al 2019).

The results of sirolimus studies in participants with vascular anomalies and PROS support the hypothesis that the agents targeting PI3K/AKT/mTOR pathway may be good candidates to be further explored (Adams et al 2016, Parker et al 2019).

The pan-AKT inhibitor, miransertib (ARQ 092), is known to decrease pAKT and pPRAS40 in PROS and PS (Proteus Syndrome) participant-derived cells (primarily fibroblasts) in a dose-dependent manner (Lindhurst et al 2015, Ranieri et al 2018). Miransertib was investigated in

phase 1/2 non-randomized open-label study in participants with PROS and PS. Preliminary results from dose escalation and signal finding Part A of the study are available. Children (n=13), young adults (n=2) and adults (n=2) were enrolled in Part A of the study, 5 of 17 previously received Sirolimus. They received miransertib at the recommended dose of 15 mg/m² with subsequent dose increase to 25 mg/m². Median time on treatment in the study was 54 weeks (7 to 91 weeks). Miransertib demonstrated preliminary evidence of clinical activity (n=17): radiologic (MRI) response to treatment as assessed by Investigators has been reported for 10 participants (stable disease over one year – 9, reduction in lesions by 15 % - 1), response by clinical assessments has included reduction in lesion sizes in 2 participants, decrease in nevi pigmentation and lip angioma in 1 participant, decrease in pain in 11 participants, improved walking in 2 participants, epilepsy control in 1 participant, normalized hemoglobin (with no more blood transfusions) in 1 participant, started eating by mouth in 1 participant.

All participants experienced at least one adverse event; 5 (29%) of participants had at least one drug-related adverse event, all Grade 1 or 2. Two Grade 3 adverse events (pyrexia, cellulitis) were interpreted as non-related to miransertib. Two participants discontinued the study because of adverse events (1 Grade 5 non drug-related suspected dehydration, 1 Grade 1 drug-related thrombocytopenia). Summary of safety findings (n=17) include the following adverse events interpreted as related to the drug and assessed as being Grade 1 or 2 of severity: diarrhea, stomatitis, vomiting, anemia, lymphocytopenia, neutropenia, thrombocytopenia, white blood cells (WBC) decrease, hypercholesterolemia, hyperinsulinemia. Each of these adverse events were reported in 1 (6%) of 17 participants. The most common reported adverse events of any Grade of severity (≥3 participants) regardless their relation to study drug included pyrexia (82%), vomiting (53%), cough (41%), abdominal pain (29%), diarrhea (29%), constipation (24%), pharyngitis (18%), rhinitis (18%), upper respiratory infection (18%), neutropenia (18%), gastroenteritis (18%), pain in extremity (18%), headache (18%), maculopapular rash (18%). Based on preliminary results of Part A of the study, miransertib has been considered to be a potential drug to provide a molecularly targeted treatment for participants with rare PI3K/AKT driven overgrowth diseases with a manageable safety profile; Part B of the study is ongoing (Leoni et al 2019).

Identification of gain-of-function mutations in PI3K has raised the possibility to treat PROS with drugs that inhibit PIK3CA. Taselisib is a selective inhibitor of class I PI3Ks with direct inhibitory activity of the p110α isoform. An open-label, single-arm, Phase IB/IIA study was started in participants with PROS. Occurrence of dose limiting toxicities was a primary outcome. The study was stopped early for safety reasons (clinicaltrials.gov/ct2/show/record/NCT03290092?view=record).

Overview of alpelisib:

Alpelisib (BYL719) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. In biochemical assays, alpelisib potently inhibits the p110α subunit of PI3K (IC50 = 4.6 nM) ≥ 50-fold compared to the other class I PI3K isoforms (e.g., p110β IC50 = 1156 nM, p110δ IC50 = 290 nM, p110γ IC50 = 250 nM), and is inactive against most other kinases (Fritsch et al 2014).

Non-clinical experience with alpelisib:

Alpelisib has demonstrated antitumor activity in a variety of cancer cell lines, particular those harboring PIK3CA mutations and in xenograft models with mutated or amplified PIK3CA (Keegan et al 2018).

Clinical studies also demonstrated the antitumor activity of alpelisib, especially in tumors with PIK3CA alterations, with a favorable safety profile (Juric et al 2018, Hoste et al 2019).

Based on the efficacy shown in participants carrying tumors with PIK3CA mutations, it was hypothesized that alpelisib could be an effective treatment for PROS due to the similarities related to the presence of somatic mutation in the same gene, causing cell proliferation. To demonstrate the efficacy of alpelisib in preventing and improving organ dysfunction in PROS, Venot and co-Investigators developed a postnatal mouse model of PROS/CLOVES (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Skeletal/Scoliosis/Spinal abnormalities) that partially recapitulates the human disease. The transgenic mouse strain, *R26Stop^{FL}P110* after breeding with Cre recombinase mice expressed a dominant active *PI3KCA* transgene. *R26Stop^{FL}P110* mice were crossed with *CAGG-CreER* mice to generate *PIK3CA$^{CAGG-CreER}$* animals that ubiquitously express *PIK3CA*. As a next step, the effect of alpelisib on *PIK3CA$^{CAGG-CreER}$* mice was studied. First, alpelisib was administered orally each day starting on the day of *Cre* induction. Whereas all placebo-treated *PIK3CA$^{CAGG-CreER}$* mice died within 15 days, all alpelisib-treated *PIK3CA$^{CAGG-CreER}$* mice were alive after 40 days and had an overtly normal appearance. Histological examination at 40 days showed that the alpelisib treated mice had preserved tissues and normal vessels. *PIK3CA$^{CAGG-CreER}$* mice treated with alpelisib had a strong reduction of proliferation, but senescence and apoptosis did not change. Western blot and immunofluorescence analyses confirmed that PI3KCA pathway activation was effectively inhibited. However, interruption of treatment 40 days after *Cre* recombination led to the rapid death of all *PIK3CA$^{CAGG-CreER}$* mice (median survival 9.8 days after withdrawal of the drug). During the next part of experiment, either placebo or alpelisib were administered to *PIK3CA$^{CAGG-CreER}$* mice seven days after *Cre* induction, when tissue abnormalities were already detected by MRI. Alpelisib treatment improved the survival of the *PIK3CA$^{CAGG-CreER}$* mice. MRI performed 12 days after the start of treatment (19 days after *Cre* induction) showed improvements in scoliosis, muscle hypertrophy, and vessel malformations; histological analysis of alpelisib-treated mice revealed only minor tissue changes compared to wild-type mice. Alpelisib administration strongly reduced cell proliferation in all affected organs, and western blot and immunofluorescence analyses confirmed PIK3CA pathway inhibition (Venot et al 2018). In comparison with rapamycin (Sirolimus), alpelisib notably blocked phosphorylation of AKT on both Thr308 and Ser473 in the *PIK3CA$^{CAGG-CreER}$* mouse model. These pre-clinical results confirmed that alpelisib could be a good therapeutic option even for participants for whom rapamycin is not an effective option (Venot et al 2018).

Clinical experience with alpelisib in PROS:

Alpelisib was administered to participants with PROS under a compassionate use program.

It was first administered to two participants (one adult and one child), who had confirmed PIK3CA mutations and suffered from severe clinical manifestations of PROS.

The adult participant was a [redacted]-year-old [redacted] who was previously treated with [redacted] and progressed. [redacted] had confirmed *PIK3CA c.3140A>G* (H1047R) mutation and presented with a [redacted]; PROS-related complications included spinal cord compression, heart and renal failure. [redacted] received alpelisib at 250 mg p.o. daily. After the first 4 weeks of treatment heart and renal function improved, at 6 months reduction in [redacted] hypertrophy and improvement in skin lesions were observed, after 18 months of alpelisib the participant had meaningful (72%) reduction of total volume of vascular lesions, reduction of thorax and abdomen circumferences.

The pediatric participant was a [redacted]-year-old [redacted] with confirmed *PIK3CA c.3140A>G* (H1047R) mutation who had not received any targeted systemic treatment for [redacted] PROS/CLOVES syndrome. [redacted] received alpelisib at 50 mg p.o. daily. First improvement (reduction of muscle hypertrophy, reverse of scoliosis) was noticed after the first 6 months of treatment. Remarkable clinical improvement was observed after 12 months and included reduction of volumes of PROS-related masses and reduction in abdomen circumferences. Both participants tolerated treatment well and had no adverse effects with the exception of hyperglycemia which was experienced by the adult participant and was well controlled with nutrition therapy; alpelisib did not affect growth of the pediatric participant. In both participants shrinkage of volume of PROS lesions were clearly associated with improved functions of affected organs and improved performance status.

After the first results of treatment became available, the Investigators treated 17 additional participants with PROS (14 – children, 3 – adults). They all had gain-of-function mutations in the *PIK3CA* gene, clinically meaningful signs of the disease, 8 of 17 were previously treated with Sirolimus, 9 were treatment-naive. Children received alpelisib at the lowest available dosage of 50 mg per day orally; adult participants received 250 mg per day orally. Disease evaluation was performed at baseline, then after 3 and 6 months of treatment. Treatment results were positive in all participants, the Investigators registered progressive reduction in volumes and circumferences of the body parts affected by PROS, improvement in skin lesions and capillary anomalies. Substantial clinical improvement was associated with partial or complete recovery from PROS-related complications (for instance, chronic gastrointestinal bleeding, disseminated intravascular coagulation, scoliosis, cognitive function and changed behavior) and with changes in concomitant medication (for instance, cessation of strong analgesics, heparin, steroid treatment in participants who received these medications because of PROS-related complications). As a result of the positive effect of alpelisib, it became possible to avoid rescue surgery in a few participants when surgery was considered as an option before treatment start. Alpelisib was well tolerated, the Investigators reported the low rate of adverse effects (few cases of Grade 1 stomatitis, single case of transient hyperglycemia). In consistency with first results, decrease of PROS lesions volume was associated with improved performance, improvement in signs and symptoms of the disease, recovery from complications (Venot et al 2018).

On 24 May 2019, the Food and Drug Administration (FDA) approved Piqray (alpelisib) film-coated tablets (300 mg taken once daily with food) to be used in combination with the endocrine

therapy fulvestrant, to treat postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer (as detected by an FDA-approved test) following progression on or after an endocrine-based regimen.

Please refer to the latest version of [Alpelisib (BYL719) Investigator's Brochure] for additional information pertaining to alpelisib.

The results described in preclinical studies including a mouse model have shown that alpelisib inhibits the PI3K/AKT/mTOR signaling pathway and rescues the PROS phenotype in the mouse model efficaciously. The first reported case series demonstrated that alpelisib is clinically effective and well tolerated by both pediatric and adult participants with PROS. The drug improved the disease symptoms in all 19 participants treated in a single center over a variable period of time (beyond 18 months for some participants) (Venot et al 2018). Alpelisib demonstrated therapeutic activity in participants with PROS regardless of the type of *PIK3CA* mutation and was effective in treatment naive participants and those who previously received mTOR inhibitor Sirolimus.

In Aug-2021, results from EPIK-P1 [CBYL719F12002] study, a retrospective non-interventional study of 57 patients with PIK3CA Related Overgrowth Spectrum (PROS) were available and later presented at the European Society for Medical Oncology (ESMO) congress 2021 (Canaud et al 2021). This study's results provide evidence of meaningful clinical benefit of alpelisib for the treatment of patients aged 2 years and older with PROS. Compelling response at Week 24 showed that 37.5% (12/32, 95% CI: 21.1 to 56.3%) of patients (30.4% (7/23, 95% CI: 13.2 to 52.9%) in pediatric and 55.6% (5/9, 95% CI: 21.2 to 86.3%) in adult patients) achieved at least 20% reduction in the sum of target lesion volumes, without disease progression from the index date (complete case analysis). In addition, 74.2% (23/31) of patients with imaging assessments at the index date and at Week 24 had any reduction in sum of target lesion volume indicating that alpelisib can control the overgrowth of PROS lesions. Patients had clinically meaningful benefit as demonstrated by the early improvement in PROS related signs and symptoms in the full population, irrespective of whether the patient was considered a responder, non-responder, or had missing assessment. No patient required rescue surgery by Week 24 due to disease progression. The safety profile of alpelisib observed in EPIK-P1 was consistent with the mechanism of action of alpelisib and compares favorably with prior experience in clinical studies and post marketing exposure in the oncology setting. Diarrhea (reported in 15.8% of all patients), hyperglycemia (12.3%) and aphthous ulcer (10.5%) were the most common AEs. All events were of grade 1/2 in severity and were effectively managed with appropriate treatment. No AEs led to treatment discontinuation and no deaths were reported during the study. No new safety concerns have emerged with the administration of alpelisib to patients with PROS. Notably, the low frequency and generally mild severity of AEs suggest good tolerability and an acceptable and manageable safety profile in pediatric and adult patients.

The EPIK-P1 data supports the first direct evidence of clinical improvement in PROS participants reported by Venot et al (2018) and confirms that PIK3CA inhibition is a promising therapeutic strategy in participants with PROS.

Of note, data from EPIK-P1 were submitted to the US FDA and resulted in the FDA granting approval on 05-Apr-2022 for Vijoice® (alpelisib) tablets for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Purpose

This study will be the first prospective study of alpelisib in participants with PROS. It will assess the efficacy, safety and PK of alpelisib in participants of different ages with confirmed diagnosis of PROS. As the disease continues throughout the participant life and may be diagnosed at different time points (Keppler-Noreuil et al 2014), the study will enroll adult participants (Group 1), 6 to 17 year old pediatric participants (Group 2), two exploratory groups of less than 6 year old pediatric participants (Group 3: 0-5 years old and Group 4: 2-5 years old) and an exploratory group of 6 to 17 years old pediatric participants (Group 5).

This study is randomized and includes an upfront 16-week placebo-controlled period for Group 1 and Group 2 treated with the alpelisib FCT formulation. Groups 3, 4 and 5 will be exploratory in nature and will be based on a small number of participants; in Groups 3, 4 and 5, participants will not be randomized and instead will be treated with the alpelisib granules formulation (Group 3) and FCT formulation (Groups 4 and 5) in an open-label fashion. Group 4 will be open to enrollment immediately after the implementation of Global Protocol Amendment 01. Group 5 will be open to enrollment after implementation of Global Protocol Amendment 02 and immediately after enrollment of Group 2 has been completed. Group 3 will be open to enrollment after the primary analysis of participants in Group 1 and Group 2 will be available in addition to the data from Groups 4 and 5 as available and only after implementation of Global Protocol Amendment 05.

Local overgrowth or hemihypertrophy, mostly progressive, is the most frequently observed manifestation of the disease, often causing functional and/or mobility impairment and reduction in health related quality of life (HR-QoL). The principal PROS overgrowth lesions will be measured in an objective way, the changes in the volume of the lesions will be considered as the main efficacy measure in the study. Whole-body MRI has been selected as the primary method of disease evaluation. This is in line with the clinical endpoints which have been used in clinical studies in PROS and similar syndromes for efficacy assessment [recently completed or ongoing studies with sirolimus, miransertib, taselisib etc. (Parker et al 2019, Adams et al 2016, NCT03290092, NCT03094832)].

Functional impairment and HR-QoL will also be assessed as secondary endpoints.

2 Objectives, endpoints and estimands

Objectives and related selected endpoints are described in Table 2-1 below. More details are described in Section 8 and Section 12.

Primary, secondary and some exploratory objectives will be applicable for participants in Groups 1 and 2; [redacted].

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the efficacy of alpelisib as measured by the proportion of participants randomized to alpelisib with a confirmed objective response (by BIRC) in at least one of the following groups: • Group 1 (≥ 18 yr-old) • Group 2 (6 - 17 yr-old)	• Response (yes/no) defined by achieving at least 20% reduction from baseline in the sum of target lesion volumes (1 to 3 lesions, assessed by MRI by a blinded independent review committee (BIRC)), provided that none of the individual target lesions has ≥ 20% increase from baseline and in absence of progression of non-target lesions and without new lesions. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response. See Section 2.1 for Primary Estimands and Section 8.3 for response definition.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Key secondary objective	**Endpoint for key secondary objective**
• To demonstrate the efficacy of alpelisib vs placebo based on the comparison of the proportion of participants with response at Week 16 in Group 1 or Group 2	• Response at Week 16 (by BIRC): See Section 2.2 for secondary Estimands and Section 8.3 for response definition.
Other secondary objectives	**Endpoints for other secondary objectives**
• To assess the efficacy of alpelisib as measured by the proportion of participants with a response at Week 24 (by BIRC) in Groups 1 and 2	• Response at Week 24 (by BIRC). See Section 8.3 for response definition.
• To assess safety and tolerability of alpelisib as compared to placebo in Groups 1 and 2 up to Week 16	• Incidence, type, and severity of treatment-emergent adverse events per CTCAE v4.03 criteria and other safety data including changes in laboratory values, vital signs, assessments of cardiac and lung functions.
• To assess the overall safety and tolerability of alpelisib in participants with PROS over time	• Incidence, type and severity of treatment-emergent adverse events per CTCAE v4.03 criteria and other safety data including changes in laboratory values, vital signs, assessments of cardiac and lung functions, growth, bone/dental development and sexual maturation (for applicable age).
• To assess changes in patient-reported pain intensity and overall severity of symptoms at Week 16 on treatment with alpelisib as compared to placebo in pediatric and adult populations	• Change from baseline to Week 16 in Brief Pain Inventory (BPI) Worst Pain Intensity Item of the PRO (Patient Reported Outcomes) diary and Patient Global Impression of Symptom Severity in pediatric (12 to17 yr old) and adult populations (≥ 18 yr-old). See Section 8.5.1 for more details on Clinical Outcome Assessments.

• To assess changes in target and non-target lesions over time and appearance of new lesions on treatment from baseline over time	• Change from baseline (as assessed by BIRC) in the:
	  • Sum of target lesion volume
	  • Sum of MRI-measurable non-target lesion volume
	  • Sum of all MRI-measurable (target and non-target) lesion volume
	• Change in other non-target lesions (by BIRC)
	• Appearance of new lesions (by BIRC).

• To assess the PK of alpelisib in adult and pediatric patients with PROS	• PK parameters (e.g., Cmax, Ctrough) in Groups 1 and 2.

Objective(s)	Endpoint(s)
• To assess changes in patient-reported pain, health-related quality of life and overall impression of symptoms in pediatric and adult populations over time	• Change in scores from BPI items, or Wong-Baker Faces Scale (age appropriate), PROMIS-profile (Patient Reported Outcome Measurement Information System) and Patient Global Impression of Symptom Severity.
• To assess the duration of response in participants who receive alpelisib	• Duration of response (see Section 12.5.1.2) in participants who receive alpelisib and who satisfy the response criteria (by BIRC).
• To assess the time to treatment failure in participants who are on treatment with alpelisib	• Time to treatment failure (see Section 12.5.1.2) in participants who are on treatment with alpelisib.
• To assess the rate of overall clinical response as assessed by Investigator at the scheduled protocol visits for disease evaluation (e.g., Week 16, 24, 40, 48, 72, 96 and thereafter every 48 weeks)	• Overall clinical response as assessed by Investigator (see Section 8.3 for definition).
• To assess the proportion of participants with a response at the scheduled protocol visits for disease evaluation during the extension periods (See Section 3 for extension periods definition).	• Response (yes/no) at scheduled protocol visit. (See Section 8.3 for response definition).
• To assess changes in symptoms and complications/comorbidities up to Week 16 on treatment with alpelisib as compared to placebo.	• Change in PROS-related symptoms and complications/comorbidities up to Week 16 among participants with symptoms and complications/comorbidities present at baseline.
• To assess changes in symptoms and complications/comorbidities associated with PROS over time	• Change in PROS-related symptoms and complications/comorbidities among participants with symptoms and complications/comorbidities present at baseline.
• To assess the frequency of healthcare visits/hospitalizations due to PROS, rescue surgeries for PROS (incl. avoidance/delay in planned disease-related surgery) over time	• Number/percentage of participants with healthcare visits/hospitalized due to PROS; number of hospitalizations. • Number/percentage of participants with surgeries required to manage PROS; number of surgeries.

[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary scientific question of interest is, for children/adolescents aged 6 to 17 years (in Group 2) and adults (Group 1: ≥ 18 years) with PROS, to assess the benefit of alpelisib with regards to the proportion of confirmed responders (see Section 8.3 for definition) by BIRC, considering participants that discontinue treatment prior to confirmation of response and participants that receive surgery as rescue therapy for any PROS lesions prior to confirmation of response as non-responders.

The primary estimands are characterized by the following 5 attributes:

1. Treatment: The randomized treatment with daily alpelisib, regardless of dose changes, in absence of rescue surgery for PROS lesions (see Section 6.2).
2. Population: Children/adolescents aged 6 to 17 years and adults aged ≥ 18 years with PROS (as per the inclusion/exclusion criteria)

3. Intercurrent events
   - participants discontinuing treatment prior to confirmation of response: Classified as a non-responder
   - participants receiving surgery as rescue therapy for any PROS lesions (target or other) prior to confirmation of response: Classified as a non-responder
4. Variable: response (yes/no) defined by achieving ≥ 20% reduction from baseline in the sum of target lesion volumes (1 to 3 lesions, assessed by MRI by BIRC), provided that none of the individual target lesions has ≥ 20% increase from baseline and in absence of progression of non-target lesions and without new lesions. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response.
5. Summary Measure: Proportion of participants (children/adolescents aged 6-17 years and adults) achieving confirmed objective response (by BIRC).

2.2 Secondary estimands

The key secondary scientific question of interest is, for children/adolescents aged 6 to 17 years (in Group 2) and adults (Group 1: ≥ 18 years) with PROS to assess the benefit of alpelisib as compared to placebo with regards to the proportion of responders (see Section 8.3 for definition) at Week 16, considering participants that discontinue treatment prior to Week 16 and participants that receive surgery as rescue therapy for any PROS lesions as non-responders.

The key secondary estimands are characterized by the following 5 attributes:

1. Treatment: the randomized treatment (daily alpelisib or placebo), regardless of dose changes, in absence of rescue surgery for PROS lesions (as defined in Section 6.2).
2. Population: Children/adolescents aged 6 to 17 years and adults aged ≥ 18 years with PROS (as per the inclusion/exclusion criteria)
3. Intercurrent events
   - participants discontinuing treatment prior to Week 16: Classified as a non-responder
   - participants receiving surgery as rescue therapy for any PROS lesions (target or other) prior to Week 16: Classified as a non-responder
4. Variable: response (yes/no) defined by achieving ≥ 20% reduction from baseline in the sum of target lesion volumes (1 to 3 lesions, by BIRC) at Week 16, provided that none of the individual target lesions has ≥ 20% increase from baseline at Week 16 and in absence of progression of non-target lesions and without new lesions
5. Summary Measure: Difference in proportion of participants (children/adolescents aged 6-17 years and adults) achieving response at Week 16.

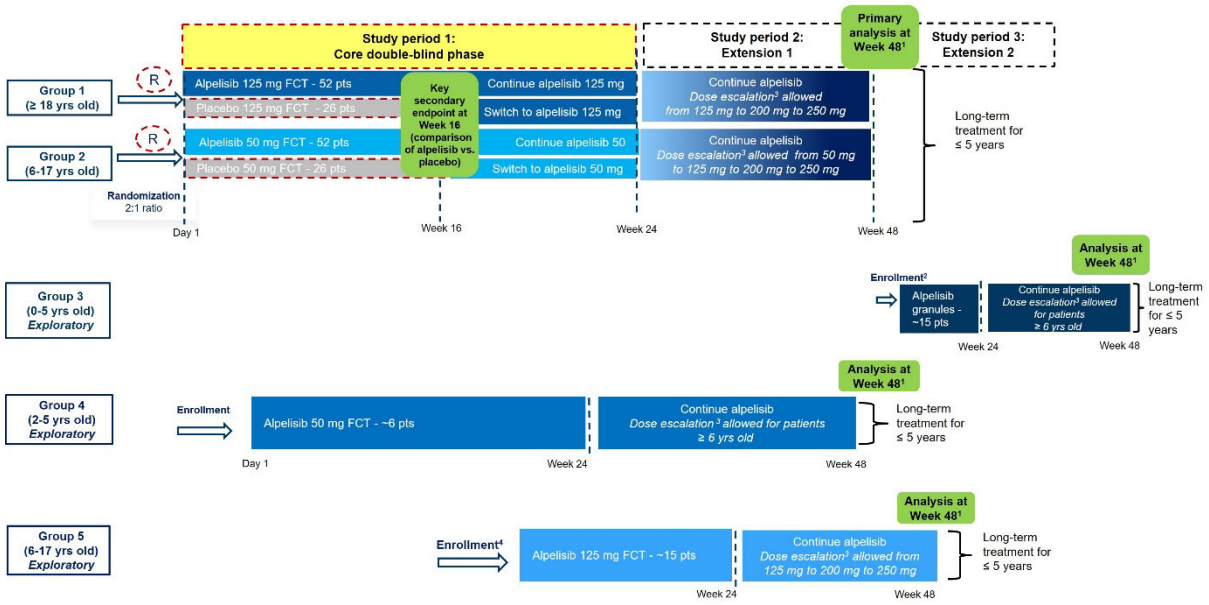
3 Study design

The study is a Phase II multi-center study with an upfront 16-week, randomized, double-blind, placebo-controlled period, and extension periods, to assess the efficacy, safety and PK of alpelisib in pediatric and adult participants with PROS.

A total of approximately 156 participants (of age ≥ 6 years) will be randomized in the study from Groups 1 and 2. Three additional groups with a total of approximately 36 participants will be enrolled for exploratory purposes:

- Group 3 (0 to 5 years old) of approximately 15 participants will receive the alpelisib granules formulation in an open-label setting with age-based dosing. For additional details, including the recommended dosing for Group 3, see Section 6.1.3 and Table 6-7.
- Group 4 (2 to 5 years old) of approximately 6 participants will receive a starting dose of 50 mg alpelisib FCT formulation once daily in an open-label setting.
- Group 5 (6 to 17 years old) of approximately 15 participants will receive a starting dose of 125 mg alpelisib FCT formulation once daily in an open-label setting.

Figure 3-1 Study design



[1] Study level milestones once all participants have completed the specified time point or discontinued earlier.
[2] All participants from Groups 1 and 2 have completed 48 weeks of treatment or discontinued earlier and the alpelisib dose is defined based on data from the primary analysis from Groups 1 and 2 in addition to the data from Groups 4 and 5 as available and only after implementation of Global Protocol Amendment 05.

[3] Decision on dose escalation will be taken by the Investigator based on local assessment of PROS lesions response, overall clinical response, and safety/tolerability concerns which may preclude from treatment continuation at higher dose level. For Groups 1 and 2, dose escalation is allowed starting at Week 29. For Group 3 and 4, dose escalation is allowed once participant has reached the age of 6 years old and has reached at least Week 25. For Group 5, dose escalation is allowed starting from Week 25. Refer to Section 6.5 for details on alpelisib dose escalation and dose modification.

[4] Enrollment in Group 5 will start after implementation of Global Protocol Amendment 02 and enrollment into Group 2 has been completed.

Core, Extension 1 and Extension 2 periods will be applied to the participants ≥6 years old (Group 1 – adults, Group 2 – participants 6 to 17 years old).

Group 3 will include participants who are 0 to 5 years old and will be an exploratory group.

Group 4 will include the participants who are 2 to 5 years old and will be an exploratory group.

Group 5 will include participants who are 6 to 17 years old and will be an exploratory group.

Group 1 and Group 2 will be enrolled in parallel.

Group 3 will be open to enrollment after the primary analysis of participants in Groups 1 and Group 2 will be available in addition to the data from Groups 4 and 5 as available and only after implementation of Global Protocol Amendment 05.

Group 4 will be open to enrollment immediately after the implementation of Global Protocol Amendment 01.

Group 5 will be open to enrollment after implementation of Global Protocol Amendment 02 and immediately after enrollment of Group 2 has been completed.

Study period 1 - Core Period:

Double-blind treatment, with an upfront 16-week placebo-controlled period (From Randomization to the end of Week 24) – Groups 1 and 2

At study start, the participants of Group 1 and Group 2 will be enrolled. Screening starts upon signature of the Informed Consent Form by the study participant. The screening assessments will be performed during a maximum of 42 days screening period (Day -42 to Day -1) to confirm participant's eligibility (Refer to Section 8.1 for more details on Screening). Eligible participants aged ≥6 years old will be randomized in a 2:1 ratio to alpelisib or matching placebo; the starting dose will be 125 mg once daily p.o. in Group 1, and 50 mg once daily p.o. in Group 2. The upfront placebo-controlled period will continue for the first 16 weeks. At the conclusion of Week 16, those participants who were randomized to receive placebo will be switched to active treatment with alpelisib and will receive 125 mg once daily p.o (Group 1) and 50 mg once daily p.o (Group 2) in a blinded fashion. Those participants who were randomized to receive alpelisib, will continue their treatment at the same dose level. No information regarding the treatment received during the first 16 weeks will be shared at the time of the switch to ensure maintaining the blinding until the primary analysis is conducted.

Dose escalation is NOT allowed during Core period.

Dose reductions because of safety/tolerability issues will be allowed in both groups at any time (as described in Section 6.5.1). Participants who at Week 16 are taking a dose lower than the initial one at randomization due to safety-tolerability issues should continue on the same (reduced) dose until the end of Core period and for at least 4 weeks of Extension 1 (by the end of Week 28).

Participants having a BIRC-confirmed progression at any time of Core Period may remain in the study at the discretion of the Investigator if the participant may derive clinical benefit from treatment continuation and has no safety/tolerability concerns. The participants will continue receiving active treatment with alpelisib. Alternatively, the participant with a BIRC-confirmed progression may be withdrawn from the study at the discretion of the Investigator. If progression, suspected by the Investigator at any time of Core period, is not confirmed by BIRC, the participant should remain on study treatment if not clinically contraindicated until BIRC confirms the progression at next radiological assessment. For more details, refer to Section 6.1.5.1.

The primary analysis will be performed after all participants (Group 1 and 2) have completed 48 weeks of study treatment or have discontinued earlier. The randomized treatment assignment

will remain blinded to participants, Investigators and the study team until the time of the primary analysis, when the last participant completes Week 48 or discontinues earlier.

[redacted]

Study period 2 - Extension 1: treatment with alpelisib (Week 25 up to the end of Week 48) – Groups 1 and 2

Participants (Group 1 and Group 2) will continue their treatment at the assigned dose if this dose was not reduced due to safety-tolerability reasons. Participants, who after completion of the first 24 weeks of study treatment are taking a dose lower than the initial one at randomization due to safety-tolerability issues, should continue on the same (reduced) dose.

Treatment will be continued until at least Week 29 when dose escalation is allowed. Dose escalation is NOT allowed during first 4 weeks of Extension 1 period (Weeks 25-28) to ensure that participants who were randomized to placebo have received at least 12 weeks of alpelisib at initially assigned dose, when dose escalation can be considered. Once a participant (Group 1 and 2) has completed initial 24 weeks of study treatment and reached Week 29, dose escalation will be allowed:

- For those who did not achieve ≥ 20% reduction in the sum of target lesion volume(s) (1 to 3 lesions) based on local radiological assessment.
- For those who did not derive sufficient clinical benefit although achieving ≥20% reduction in the sum of target lesion volume(s) (at Investigator's discretion based on local assessment, as described below).

Decision on dose escalation will be taken by the Investigator based on local assessment of PROS lesions response, overall clinical response, and safety/tolerability concerns which may preclude from treatment continuation at higher dose level. Further dose escalation is allowed at a minimum of 12-week intervals until the end of the study. In both age groups dose level escalations during extension periods are possible: 2 times in Group 1 and 3 times in Group 2 as described below:

- Group 1: from the dose 125 mg once daily p.o. to 200 mg once daily p.o., from the dose 200 mg daily p.o to 250 mg once daily p.o.
- Group 2: from the dose 50 mg once daily p.o to 125 mg once daily p.o, from the dose 125 mg daily p.o to 200 mg once daily p.o, from the dose 200 mg daily p.o to 250 mg once daily p.o.

The participant who received a dose lower than the initial one at randomization due to safety-tolerability issues, may be considered for dose re-escalation if the Investigator assess the clinical benefit/ safety risk of a dose re-escalation favorable. The Investigator should consult the Sponsor (Novartis) to make a decision to re-escalate the dose; re-escalation may be permitted after reaching Week 29 according to the dose modification guidance. For more details, refer to Section 6.5.1.

Participants having a BIRC- confirmed progression after completion of the Core Period may at the discretion of the Investigator remain in the study and undergo dose escalation (as described in Section 6.1.5.1) or, alternatively, may be withdrawn from the study at any time point.

Study period 3 - Extension 2: long-term treatment with alpelisib (Week 49 up to 5 years) – Groups 1 and 2

Groups 1 and 2 participants who continue the study treatment until Week 48 and continue deriving clinical benefit, will enter a long-term extension period. Dose escalation for response optimization as described above and treatment beyond progression are allowed in both Group 1 and Group 2. Additional safety and efficacy data will be collected during the extension period. This period will last up to 5 years from randomization.

Exploratory study part:

Group 3, open-label treatment with the alpelisib granules formulation

Group 3 participants will receive alpelisib granules in an open-label setting as follows:

- 0-<1 month of age: 20 mg alpelisib granules every other day;
- 1 month-<6 months of age: 20 mg alpelisib granules once daily;
- 6 months-<24 months of age: 40 mg alpelisib granules once daily;
- 2 years- < 6 years of age: 50 mg alpelisib granules once daily;

Dose adjustments as participants age to account for metabolic enzyme maturation are allowed (see Table 6-4).

Dose escalation is allowed for those participants who did not derive sufficient clinical benefit at the Investigator's discretion, once a participant has reached the age of 6 years old and has reached at least Week 25.

Decisions on dose escalation will be taken by the Investigator based on their local assessment of PROS lesions response, overall clinical response, and safety/tolerability concerns which may preclude from treatment continuation at a higher dose level. Further dose escalation is allowed at a minimum of 12-week intervals until the end of the study, according to the dose modification guidance. Refer to Section 6.5 for details on alpelisib dose escalation and dose modification.

Dose reductions because of safety/tolerability issues will be allowed at any time (as described in Section 6.5.1). The participant who received a dose lower than the initial one at enrollment due to safety-tolerability issues, may be considered for dose re-escalation if the Investigator assess the clinical benefit/ safety risk of a dose re-escalation is favorable. Re-escalation may be permitted after reaching Week 25 according to the dose modification guidance. Refer to Section 6.5 for details on alpelisib dose escalation and dose modification.

Participants having a BIRC- confirmed progression may at the discretion of the Investigator remain in the study and undergo dose escalation (as described in Section 6.1.5.1) or, alternatively, may be withdrawn from the study at any time point.

Treatment beyond progression is allowed in Group 3. Exploratory efficacy, safety and PK data will be collected during the whole study period. This period will last up to 5 years from treatment start.

- **Group 4, open-label treatment with the alpelisib FCT formulation:**

Participants of Group 4 will be enrolled immediately after implementation of Global Protocol Amendment 01 and will receive 50 mg alpelisib FCT formulation once daily in an open-label setting.

Dose escalation is allowed for those who did not derive sufficient clinical benefit at the Investigator's discretion, once participant has reached the age of 6 years old and has reached at least Week 25.

Decision on dose escalation will be taken by the Investigator based on their local assessment of PROS lesions response, overall clinical response, and safety/tolerability concerns which may preclude from treatment continuation at a higher dose level. Further dose escalation is allowed at a minimum of 12-week intervals until the end of the study, according to the dose modification guidance. Refer to Section 6.5 for details on alpelisib dose escalation and dose modification.

Dose reductions because of safety/tolerability issues will be allowed at any time (as described in Section 6.5.1). The participant who received a dose lower than the initial one at enrollment due to safety-tolerability issues, may be considered for dose re-escalation if the Investigator assess the clinical benefit/ safety risk of a dose re-escalation is favorable. Re-escalation may be permitted after reaching Week 25 according to the dose modification guidance. Refer to Section 6.5 for details on alpelisib dose escalation and dose modification.

Participants having a BIRC- confirmed progression may at the discretion of the Investigator remain in the study and undergo dose escalation (as described in Section 6.1.5.1) or, alternatively, may be withdrawn from the study at any time point.

Treatment beyond progression is allowed in Group 4. Exploratory efficacy, safety and PK data will be collected during the whole study period. This period will last up to 5 years from treatment start.

- **Group 5, open-label treatment with the alpelisib FCT formulation:**

Participants of Group 5 will be enrolled immediately after implementation of Global Protocol Amendment 02 and enrollment of Group 2 has been completed and will receive a starting dose of 125 mg alpelisib FCT formulation once daily in an open-label setting.

Dose escalation is allowed for those who did not derive sufficient clinical benefit at the Investigator's discretion and once participant has reached at least Week 25.

A decision on dose escalation will be taken by the Investigator based on their local assessment of PROS lesions response, overall clinical response, and safety/tolerability concerns which may preclude from treatment continuation at a higher dose level. Further dose escalation is allowed at a minimum of 12-week intervals until the end of the study, according to the dose modification guidance or details on alpelisib dose escalation and dose modification.

Dose reductions because of safety/tolerability issues will be allowed at any time (as described in Section 6.5.1). The participant who received a dose lower than the initial one at enrollment due to safety-tolerability issues, may be considered for dose re-escalation if the Investigator assesses that the clinical benefit/ safety risk of a dose re-escalation is favorable. Re-escalation may be permitted after reaching Week 25 according to the dose modification guidance. Refer to Section 6.5 for details on alpelisib dose escalation and dose modification.

Participants having a BIRC-confirmed progression may, at the discretion of the Investigator, remain in the study and undergo dose escalation (as described in Section 6.1.5.1) or, alternatively, may be withdrawn from the study at any time point.

Treatment beyond progression is allowed in Group 5. Exploratory efficacy, safety and PK data will be collected during the whole study period. Trial participation will last up to 5 years from treatment start.

- **Discontinuation of study treatment and End of Study (EoS) for all Groups:**

Discontinuation of study treatment for a participant occurs when study treatment is stopped permanently and the End of Treatment assessments are performed (End of Study Treatment visit/ Week 264). For the participants who discontinue treatment for reasons other than death, lost to follow-up, or withdrawal of consent, safety follow-up assessments must continue after study treatment discontinuation (30 days post-treatment safety follow-up visit).

End of Study (EoS) will occur when all participants have completed 5 years of treatment, unless the participant discontinues earlier. The end of the study for a given participant is defined as when the participant permanently discontinues study treatment and all the end of study procedures are completed (Refer to Section 9.2 for more details).

4 Rationale

4.1 Rationale for study design

This study is designed to demonstrate the efficacy and assess safety and tolerability of oral daily alpelisib in participants with PROS. Both pediatric and adult participants will be enrolled, as the disease may be diagnosed at different time points during a patient's life (Keppler-Noreuil et al 2014).

There is no approved pharmacological treatment for PROS outside the US. In the US, data from EPIK-P1 were submitted to the FDA and resulted in the FDA granting approval on 05-Apr-2022 for Vijoice (alpelisib) tablets for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s) (Vijoice® US Prescribing Information, 2022).

Venot et al 2018 described a postnatal mouse model of PROS/CLOVES and demonstrated the efficacy of alpelisib in preventing and improving organ dysfunction related to the disease. Preclinical results were promising and confirm the hypothesis of activity of alpelisib in PROS-related overgrowth. The promising and encouraging results were observed in the participants with diagnosis of PROS treated with alpelisib through a compassionate use program: previously intractable vascular lesions became smaller, congestive heart failure was improved, hemihypertrophy was reduced, and scoliosis was attenuated. The treatment was not associated with any substantial side effects (for the details, efficacy and safety results please refer to Section 1.1).

A very limited number of clinical studies have been conducted with medical treatments in PROS; encouraging results were observed with alpelisib (Venot et al 2018) which demonstrated in some cases efficacy as early as at 3 months and showed further improvement in participants with follow up beyond 6 months. Due to the paucity of data with medical therapy in PROS, there is no consensus on the treatment of choice at any stage of the disease in children and adults. Hence, there is no suitable active comparator that could be used in a randomized, controlled study design.

Based on published data from a few studies (Lindhurst et al 2012, Parker et al 2019, Venot et al 2018) volume measurement as a method of response evaluation will be implemented for the purpose of this study. Compared to photographs and linear measurements, MRI allows to assess volumetric changes in PROS-related domains. In the study, MRI assessment will be used to evaluate the primary endpoint, both MRI and other methods (including digital photography, measurements with caliper/ruler) will be used to evaluate the disease burden and secondary endpoints. Assessment of response of PROS lesions will be done by a BIRC, to ensure consistency in review.

Local overgrowth or hemi hypertrophy, mostly progressive, is the most frequently observed manifestation of the disease, often causing functional and/or mobility impairment and reduction in HR-QoL. Since the overgrowth is measurable in an objective way, the changes in the volume of the lesions will be considered the main efficacy measure in the study. This is in line with the clinical endpoints which have been used in clinical studies in participants with PROS and similar syndromes for efficacy assessments [Recently completed or ongoing studies with Sirolimus, miransertib and taselisib (Parker et al 2019, Adams et al 2016, NCT03290092, NCT03094832)]. Functional impairment and HR-QoL will also be assessed as secondary objectives.

Response rate (based on pre-defined volumetric reduction of target lesions) has been selected as a primary endpoint in pivotal studies to demonstrate treatment efficacy and has been used as the basis for regulatory approval of agents in different indications in a number of therapeutic areas such as oncology and neurology. The primary endpoint of this study is the proportion of participants randomized to alpelisib with a confirmed objective response. The 20% threshold is widely used in oncology and other indications for assessment of changes of tumor/other lesion size, based on intra-/inter- observer agreement (Solomon J. et al. 2004, Caron et al 2014). It is also expected that volumetric decrease in ≥20% of lesion(s) will be associated with clinical benefit such as improvement in pain, use of upper/low limbs, HRQoL, etc. (Venot et al 2018).

The clinical relevance of the volumetric reduction of the lesions and the hypothesis to be tested in the current study are based on data published for other compounds (two studies with Sirolimus). In Adams et al 2016 study, 35% (95% CI: 20 to 51%) of participants with complicated vascular anomalies had ≥20% reduction in size (max diameter) of the target lesion(s) at 24 weeks of treatment with Sirolimus. In the Parker et al 2019 study of 39 participants with PROS and progressive overgrowth, a significant reduction of 7.2% (SD 16.0) was observed in the volume change of affected tissues at the end of 26-week sirolimus treatment by dual energy X-ray absorptiometry (DXA) technique.

4.2 Rationale for dose/regimen and duration of treatment

Alpelisib was initially administered under compassionate use programs to 19 participants with severe/life threatening clinical manifestations of PROS and all participants showed substantial clinical improvement on alpelisib with acceptable tolerability. Film-coated tablets (FCT) containing 50 mg alpelisib once daily (taken without food) were used in all the pediatric participants regardless of age and body weight (15 out of 19 participants in total, there were 4 participants of 4-5 years old, 5 participants 6-12 years old, 6 participants of 13-16 years old), while 250 mg alpelisib FCT once daily (taken without food) were used in the 4 adult participants. No formal justification for the dose was provided in the Venot et al 2018 publication and no PK data of alpelisib in PROS participants are available.

Alpelisib is classified as a Biopharmaceutics Classification System Class II compound, with high permeability and low solubility, according to the criteria in the FDA Guidance for Industry (Waiver of in vivo Bioavailability and Bioequivalence Studies, FDA 2017). Bioavailability in vivo under fasted conditions is limited by solubility. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is considered to be the driver of the food effects that have been observed in earlier studies at high doses. Under fasted conditions, the fraction absorbed decreases at higher doses due to limited solubility (e.g., approximately 70% absorbed after a 300 mg dose and 50-60% absorbed after a 400 mg single dose in healthy volunteers). Under fed conditions, the absorption is nearly complete (>99%) irrespective of the dose. In addition, the PK of alpelisib under fed condition showed moderate inter-subject variability (Geo-mean CV% ~20-40%), while in fasted conditions, the inter-subject variability was higher (Geo-mean CV% ~40-70%). Thus, it is favorable to administer alpelisib with food to reduce the inter-subject variability, to use a lower dose to reach similar exposure as a high dose in a fasted state, as well as for the convenience for administration in children.

Novartis Study CBYL719F12101 demonstrated bioequivalence between 50 mg alpelisib granules and 50 mg alpelisib FCT in adults, both administered in the fed state. Geometric mean ratio (granules:FCT) point estimates and corresponding 90% CIs of the PK exposure parameters AUCinf, AUClast, and Cmax were 0.984 (90% CI: 0.952, 1.02), 0.980 (90% CI: 0.946, 1.02), and 0.947 (90% CI: 0.891, 1.01), respectively. The 50 mg alpelisib granule and FCT dosages are interchangeable when administered with food.

The proposed Phase II study will be conducted in five groups: Group 1 is 18 years and above, Group 2 and 5 are 6 to 17 years of age, Group 3 is 0 to 5 years of age and Group 4 is 2 to 5 years of age.

For Group 1: alpelisib 125 mg FCT once daily (taken with food) for adult participants age 18 and above. Alpelisib at 250 mg once daily taken without food was shown to be effective in all 4 adult participants with no significant safety concerns (Venot et al 2018). Since alpelisib has a positive food effect (50-80% exposure increases at 200-300 mg doses once daily), the current study proposes to use 125 mg once daily taken with food, in order to provide similar but slightly lower exposure than that following 250 mg once daily in fasting state. This is proposed for safety and tolerability reasons (e.g., diarrhea and hyperglycemia) in PROS participants as a long-term, possibly a life-long treatment will be required. Also, the lower inter- subject variability in fed state is a key consideration.

For Group 2: alpelisib 50 mg FCT once daily (taken with food) for pediatric participants from age 6 to 17 years. Alpelisib 50 mg FCT once daily was shown to be effective in all 15 pediatric participants (regardless of age and body weight) with no significant safety concerns identified (Venot et al 2018). Physiologically based Pharmacokinetic (PBPK) modelling and simulation suggest no food effect at 50 mg once daily: therefore, 50 mg FCT once daily taken with food is considered for participant 6 to 17 years of age for the convenience of administration in this age group. In case the tablets cannot be swallowed by young children, they could be crushed and taken as a suspension in 150 ml of water (or a smaller volume, provided that no visible solid residues remain in the glass) for convenience of administration in this age group.

For Group 4: alpelisib 50 mg FCT once daily (taken with food) for pediatric participants from age 2 to 5 years. In EPIK-P1 study, 11 patients at age 2-5 years (out of total 57 patients) had taken alpelisib 50 mg FCTs. Efficacy and safety results observed from these patients support the use of 50 mg alpelisib FCTs in this age group. Thus, the same starting dose of 50 mg is recommended for all pediatric patients (2-17 years of age). Of note, in EPIK-P1, all the pediatric patients who had dose escalation were ≥ 6 years of age. Ten of them (35.7%) had at least one dose increase of alpelisib during the study. As such, dose escalation can be considered in pediatric patients included in Group 4, but only when they reach 6 years of age, for response optimization (clinical/radiological) based on physician discretion after at least 24 weeks of treatment with alpelisib. In pediatric patients ≥ 6 years, alpelisib dose can be gradually increased from 50 mg up to 250 mg.

For Group 5: alpelisib 125 mg FCT once daily (taken with food) for pediatric participants from age 6 to 17 years. In the EPIK-P1 study, 28 of 57 participants were 6 to 17 years of age; 12 participants were 6 to 11 years of age, and 16 participants were 12 to 17 years of age. Per [CBYL719F12002 (EPIK-P1) CSR], the median duration of exposure was 13.6 months for the participants 6 to 11 years of age and 19 months for those 12 to 17 years of age, with a median relative dose intensity (RDI) of 100% and 112.6%, respectively, providing a long period of observation for safety. No life-threatening treatment related events or adverse events (AEs) leading to discontinuations or deaths were observed. There were no unique toxicities noted in these age groups. Additionally, one participant in the 6 to 11 years of age group started alpelisib at 100 mg, two participants in the 12 to 17 years of age group started alpelisib at 150 mg, and one participant in the 12 to 17 years of age group started alpelisib at 250 mg. Lastly, ten out of 28 (35.7%) pediatric participants had at least one dose increase of alpelisib during the study, without safety concerns, of which five participants were in the 6 to 11 years of age group and the other five in the 12 to 17 years of age group. Therefore, a starting dose of 125 mg can be considered to further explore the optimal dose for this pediatric group.

In case the tablets cannot be swallowed by young children, they could be crushed in water and taken as a suspension in 150 ml of water (or a smaller volume, provided that no visible solid residues remain in the glass) for convenience of administration in this age group. In CBYL719X2104 study (in head and neck cancer patients), similar alpelisib PK profiles were observed between film-coated tablets swallowed whole vs crushed tablets administered as oral suspension. Refer to preparation details in Table 6-23.

For Group 3: alpelisib granules mixed with food for pediatric participants from age 0 to 5 years. [redacted]

[redacted]

During the long-term extension periods, dose escalation will be allowed to optimize the dose for all participants for long-term efficacy and safety. Dose escalation will be allowed after completion of the initial 28 weeks of treatment in Groups 1 and 2 or 24 weeks of treatment for pediatric participants above the age of 6 years old in Group 3, 4 and 5. For Groups 1 and 5, dose escalation is possible from 125 mg to 200 mg once daily and from 200 mg to 250 mg once daily. For Groups 2, 3 and 4, dose escalation is possible from 50 mg to 125 mg once daily, from 125 mg to 200 mg once daily, and from 200 mg to 250 mg once daily. A minimum of 12-week intervals is needed for each dose adjustment, based on clinical signs and symptoms. Thus, participants without sufficient clinical improvement or not achieving the primary endpoint during the first 24-28 weeks of treatment, will have the chance to increase the dose. In the event of a dose increase for response optimization, an MRI has to be performed after at least 3 months to assess the benefit from the increased dose if further dose optimization is considered. This time interval would provide enough time for clinical improvement to be observed at a given dose level, based on the disease clinical course and the relatively fast response to alpelisib (Venot et al 2018). Dose reduction and interruption are allowed at any time for safety reasons (dose reduction, from 50 mg once daily, will use reduced dose administration frequency). See Section 6.5.1 for further details on dose modification.

4.3 Rationale for choice of control drugs (comparator/placebo)

A very limited number of clinical studies have been conducted with medical treatments in PROS; encouraging results were observed with alpelisib (Venot et al 2018) which demonstrated in some cases efficacy already at 3 months of treatment with alpelisib with further improvement beyond 6 months of treatment.

Due to this paucity of data with medical therapy in PROS, there is no consensus on the treatment of choice at any stage of the disease in children and adults. Neither taselisib nor miransertib are approved agents, and while sirolimus is commercially available for other indications, emerging data from Parker et al 2019 question the overall benefit/risk for use in PROS. Hence, there is no suitable active comparator that could be used in a randomized, controlled study design.

Only for Groups 1 and 2:

An upfront placebo/Best Standard of Care controlled period limited to 16 weeks duration is considered for the participants in the placebo group. Participants receiving placebo will be then subsequently treated with alpelisib from Week 17 onwards. A period of 16 weeks placebo is acceptable for the target participant population.

In order to further reduce exposure to placebo, participants will be randomized 2:1 (104 participants in the active arms and 52 participants in the placebo arms).

A period of 16 weeks would allow identifying early signs of efficacy and safety. The comparison of the proportion of participants with response at Week 16 is a key secondary objective of this study.

4.4 Purpose and timing of interim analyses/design adaptations

There is no planned interim efficacy analysis before the conduct of the primary analysis.

The DMC (Data Monitoring Committee) will conduct periodic safety data reviews (refer to Section 10.2.2 and Section 12.7).

4.5 Risks and benefits

Potential benefits to clinical study participants

PROS is a serious condition with no approved pharmacological treatment targeting the underlying cause of the disease outside the US. Current therapy includes debulking surgery, amputation, and/or endovascular occlusive procedures and mainly addresses symptoms and complications of the disease. There is a high unmet medical need for an effective systemic treatment. Alpelisib is considered to be a promising treatment option for pediatric and adult participants with PROS and confirmed PIK3CA mutation. Treatment with alpelisib in overgrowth related to mutation in PI3K gene may provide a clinical benefit compared to available treatment options (See Section 1.1). The participants enrolled in this study are planned to receive alpelisib as active treatment for their disease as per treatment assignment plan (see Section 6.1). Based on published clinical data (Venot et al 2018) and recent results from EPIK-P1 study, treatment with alpelisib is expected to be tolerated with a manageable safety profile.

For further details on clinical safety, please refer to Section 1.1 and the latest version of [Alpelisib (BYL719) Investigator's Brochure].

Potential risks to clinical study participants

Participants in this study will be carefully monitored using periodic laboratory, renal and liver function parameters, Electrocardiogram (ECG), bone development, teeth development, growth, sexual maturity, and other safety evaluations for key toxicities that have been already observed with alpelisib or may be observed in PROS pediatric and adult participants (see Section 8.4).

Risks will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.2.2), close safety monitoring (see Section 10), adherence to dose adjustment guidelines (see Section 6.5.1), and training of site personnel. An independent Data Monitoring Committee (DMC) will monitor safety data as outlined in the protocol. A Steering Committee (SC) comprising of Investigators, a patient advocate, and Novartis personnel participating in the study will ensure transparent management of the study according to the protocol. A Novartis Safety Management Team (SMT) will periodically review and evaluate all emerging data across the alpelisib program for potential safety signal assessment in a timely manner.

Females of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the

study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any concern that the participant will not reliably comply to study requirements, they should not be entered or continue in the study.

4.6 Public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

4.7 Rationale for planned off-site procedures (for Netherlands only)

Off-site procedures (e.g. fasting glucose plasma) are planned in this study to minimize burden on participants if unable to travel to the site, offering them increased flexibility to participate in the study from an off-site location (as described in Section 6.5 and defined in Section 10.1.6). The hybrid approach will allow participants to maintain contact with the investigator, both in person, during clinic visits at site, and during off-site participation.

5 Study Population

It is planned to enroll approximately 192 participants in total, 78 adults and 114 children and adolescents. The study will first start enrolling adult and pediatric participants ≥6 years old treated with alpelisib/matching placebo FCT and following the implementation of Global Protocol Amendment 01, participants ≥2 years old treated with alpelisib FCT. Following the implementation of Global Protocol Amendment 05, participants 0-5 years old in Group 3 will be treated with alpelisib granules.

First, a total of approximately 162 participants with PROS will be enrolled in three groups - N=78 participants for Groups 1 and 2 each, and N=6 for exploratory Group 4:

- Group 1: ≥18 years old
- Group 2: 6-17 years old
- Group 4: ≥ 2-5 years old

Following the implementation of Global Protocol Amendment 02 and enrollment of Group 2 is completed, exploratory Group 5 will be opened to enroll approximately 15 additional pediatric participants with PROS who will be treated with alpelisib FCT at a higher starting dose:

- Group 5: 6-17 years old

After completion of the primary analysis, approximately 15 additional pediatric participants with PROS, treated with the alpelisib granules formulation, will be enrolled in an exploratory Group 3:

- Group 3: 0 to 5 years old

The same inclusion/exclusion criteria will apply for all groups, except for the below which are adjusted based on Group:

- inclusion criterion on tissue sample collection and performance status assessment
- exclusion criterion concerning pneumonitis, interstitial lung disease as well as comprehension and compliance with study instructions.

The phenotypic variability of PROS is broad in terms of overgrowth localization, number of lesions, disease progression, and severity of the impact on the participants' everyday life, mobility, organ function and quality of life. In order to assess the efficacy of alpelisib in PROS in an objective manner and consistently with the recent literature (Kuentz et al 2017), Keppler-Noreuil et al 2014, participants with syndromic disease and participants with isolated disease will be included. Criteria for inclusion will be bearing clinically relevant and measurable lesion(s) and confirmed mutation in the PIK3CA gene. Participants with isolated features like macrodactyly, megalencephaly and epidermal nevus will not be considered for inclusion, because these features are not considered sufficiently severe to require specific treatment and are unlikely to qualify for a measurable lesion.

Participants with functional /mobility impairment can be included in the study and the changes will be assessed as indicated in Section 8 study visit schedule and assessments.

The Investigator or his/her designee must ensure that all participants who meet the inclusion and none of the exclusion criteria during screening are offered enrollment in the study. No additional exclusions can be applied by the Investigator, in order to ensure that the study population will be representative of all eligible participants.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent and assent (when applicable) from the patient, parent, legal authorized representative or guardian must be obtained prior to any study related screening procedures are performed.
2. Male or female patients who, at the time of informed consent, were of the below age:
   - Group 1: ≥18 years old
   - Group 2: 6-17 years old
   - Group 3: 0-5 years old
   - Group 4: ≥ 2-5 years old
   - Group 5: 6-17 years old
3. Patients with diagnosis of PROS [according to Clinical Diagnostic Criteria for PIK3CA-related Overgrowth Spectrum (PROS) proposed by Keppler-Noreuil et al 2014 (Section 16.1 - Appendix 1)] with symptomatic and /or progressive overgrowth and at least one measurable PROS-related lesion confirmed by BIRC assessment, who have syndromic disease or isolated features (with the exception of isolated macrodactyly, macrocephaly or epidermal nevus) at the time of informed consent. Patients, who previously have been receiving systemic treatment for PROS (e.g., mTOR inhibitors, AKT inhibitors, anti angiogenic agents), may enter the study.

4. Documented evidence of a somatic mutation(s) in the PIK3CA gene performed in local laboratories (certified, if applicable per local practices) using a DNA based test validated according to the local regulations at the time of informed consent.
5. A tissue sample (fresh or archival) is to be sent to a Novartis-designated central laboratory. If archival tissue is not available, collection of a fresh tissue biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated. For participants in Groups 3 and 4, a fresh tissue biopsy is not mandatory.

   [redacted]

   For Germany only: If archival tissue is available, it must be sent to a Novartis-designated central laboratory. If no archival tissue is available, obtaining a fresh tissue biopsy is recommended, if it is not clinically contraindicated, but is not mandatory.
6. Karnofsky (in patients > 16 years old at study entry)/Lansky (≤16 yrs of age at study entry) performance status index ≥50.
7. Adequate bone marrow and organ function (as assessed by central laboratory for eligibility:
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - Platelets ≥ 100×10^9/L
   - Hemoglobin ≥ 9.0 g/dL (transfusions are allowed)
   - Calcium (corrected for serum albumin) and magnesium within normal limits or ≤Grade 1 according to NCI-CTCAE version 4.03 if judged clinically not significant by the Investigator
   - Potassium within normal limits, or corrected with supplements
   - INR ≤1.5 unless anticoagulant therapy (related to PROS) is ongoing at the time of screening

     Note: Participants receiving anticoagulants for PROS related coagulopathy, primary or secondary prophylaxis of thrombosis may be included in the study.
   - Creatinine Clearance ≥ 30 mL/min using Modification of Diet in Renal Disease (MDRD) (≥18 years old) or creatinine-based Bedside Schwartz (<18 years old) Glomerular filtration rate (GFR) equation
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.
   - Total bilirubin< ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
   - Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L)* and Glycosylated hemoglobin (HbA1c) ≤ 6.5% (both criteria have to be met)
   - Fasting Serum amylase ≤ 2 × ULN
   - Fasting Serum lipase ≤ ULN

*For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥5.7% (i.e., threshold for pre-diabetes) at screening, recommend lifestyle changes according to the American Diabetes Association (ADA) or European Association for the Study of Diabetes (EASD) guidelines, i.e., dietary advice (e.g., small frequent meals, low carbohydrate content, high fiber, balancing carbohydrate intake over the course of the day, three small meals and 2 small snacks rather than one large meal) and exercise. A consultation with a diabetologist is highly recommended.

8. Presence of at least one PROS-related measurable lesion defined as a lesion with longest diameter ≥2 cm, when the volume can be accurately and reproducibly assessed by MRI, and associated with complaints, clinical symptoms or functional limitations affecting the patient's everyday life. Measurability must be confirmed by BIRC before randomization.
9. Able to swallow study drug (as assessed within 7 days before study treatment start):
    - Group 1, Group 2, Group 4 and Group 5: FCT, or as drinkable suspension when applicable (refer to Section 6.7.2)
    - Group 3: granules. Drug administration via feeding tube is allowed.

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are not eligible for inclusion in this study.

1. Participant with only isolated macrodactyly, epidermal nevus/nevi and macroencephaly (the only clinical feature or a combination of any of three of them), in absence of other PROS-related lesions at the time of informed consent.
2. Previous treatment with alpelisib and/or any other PI3K inhibitor(s) (except treatment attempt, defined as the attempt to treat PROS with any of PI3K inhibitors, with treatment duration less than 2 weeks and stopped at least 4 weeks prior to the first dose of study medication with alpelisib)

Notes:

- patients treated with small molecules (such as mTOR inhibitors, AKT inhibitors) and/or anti angiogenic agents for PROS must discontinue from these specific treatments before any of study related assessments and for at least 4 weeks before the start of study treatment
- those patients who previously received systemic treatment for PROS other than PI3K inhibitor(s), should recover from all toxicities related to prior therapies to Grade ≤1 according to NCI CTCAE version 4.03, with exception for any grade of alopecia, where the patients are allowed to enter the study
- in pretreated patients, all screening assessments should be performed after discontinuation from previous specific systemic therapy for PROS.

3. Radiation exposure for PROS treatment purpose within the previous 12 months on those PROS areas which are expected to qualify for target lesions (except lesion(s) progressing after completion of radiotherapy) at time of informed consent.
4. Debulking or other major surgery performed within 3 months at time of informed consent.
5. Clinically meaningful bleeding related to PROS: Grade 2 within 14 days or Grade 3 and more within 28 days before study treatment start as per CTCAE v. 4.03.
6. Clinically meaningful PROS-related thrombotic event (Grade 2 and more as per CTCAE v.4.03) within 30 days before informed consent, and/or sclerotherapy/embolization for vascular complications performed within 6 weeks before informed consent. Note: Participants receiving anticoagulants for PROS-related coagulopathy, primary or secondary prophylaxis of thrombosis may be included in the study.
7. History of prior and or ongoing malignancy (within 5 years before informed consent except radically treated Carcinoma in situ of radically treated basal-cell carcinoma of skin or

thyroid gland well differentiated microcarcinoma or Stage 1 Wilms' tumor of a histology other than anaplastic), or ongoing investigations or treatment for malignancy at time of informed consent.

8. Clinically significant heart disease at time of informed consent, including:
   - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
   - Clinically significant uncontrolled cardiac arrhythmias
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
   - Corrected QT (QTcF) at screening: >470 ms for Group 1 / >450 ms for Groups 2, 3, 4 and 5.
9. For participants in Groups 1, 2 and 5 (i.e., those ≥ 6 years of age): Participants with documented pneumonitis or interstitial lung disease at the time of informed consent and with impaired lung function (e.g., FEV1 (Forced expiratory volume) or DLCO (Diffusing Capacity of the Lung for Carbon Monoxide) ≤ 70% of predicted) that is not related to PROS.

   For participants in Groups 3 and 4 (i.e., those who are less than 6 years of age): Participants with documented or suspicious pneumonitis or interstitial lung disease based on MRI images at time of informed consent.

Note: When lung function impairment is, in the opinion of the Investigator, related to PROS, the patient may be included but caution must be exercised.

10. History of acute pancreatitis within 1 year before informed consent or past medical history of chronic pancreatitis at time of informed consent.
11. Participants with an established diagnosis of type I diabetes mellitus or uncontrolled type II diabetes mellitus at time of informed consent.
12. Known impairment of gastrointestinal (GI) function due to concomitant GI disease that may significantly alter the absorption of the study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) at time of informed consent.
13. History of hypersensitivity to any drugs or metabolites of PI3K inhibitor or any of the excipients of alpelisib at time of informed consent.
14. Known history of Steven Johnson's syndrome, erythema multiforme or toxic epidermal necrolysis at time of informed consent.
15. Known history of seizure, or epilepsy, regardless of relatedness to PROS spectrum at time of informed consent, when epilepsy is not controlled and/or the patient may not be switched to non-enzyme inducing antiepileptic drug(s) at time of informed consent.
16. Participant with other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate administration of alpelisib (e.g., Active and/or uncontrolled severe infection, chronic active hepatitis, hepatic impairment Child-Pugh-Score C, immuno-compromised, etc.) at time of informed consent. Participant with an active documented COVID-19 infection (any grade of disease severity) at time of informed consent may be included only when completely recovered (in accordance with

local guidance) and had no symptoms for at least 28 days before first dose of study medication.

17. Pregnant or breastfeeding female participants at time of informed consent.
18. Female participants of childbearing potential (see Section 8.4.3) who do not consent to use a highly effective method of contraception and male participants who do not consent to use a condom and/or a highly effective method of contraception for the duration of the study and for one week following discontinuation of alpelisib. Highly effective contraception is one of the following:
    - Total abstinence: when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization: have has surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking alpelisib. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone assessment.
    - Male sterilization at least six months prior to screening. The vasectomized male partner should be the sole partner for the female study participant.
    - Use of oral, injected or implanted hormonal methods of contraception, or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

20. Participant is currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment:
    - Strong inducers of CYP3A4
    - Inhibitors of Breast Cancer Resistance Protein (BCRP).
21. Not able to understand and to comply with study instructions and requirements (in patients, legal authorized representative or guardian as applicable) at time of informed consent.
22. Participation in a prior investigational study within 4 weeks prior to study treatment start or within 5 half-lives of the investigational product, whichever is longer.
23. Participants with clinically significant worsening of PROS-related laboratory anomalies, physical signs and symptoms (such as, but not limited to increase of D-dimers, worsening of underlying pain, newly occurring swelling or redness) indicating an uncontrolled condition during the screening phase, particularly if systemic treatment with any other inhibitor of the PI3K/AKT/mTOR pathway was stopped prior to the start of study treatment. This includes but is not limited to hypercoagulability state in participants not receiving prophylactic treatment.

6 Treatment

6.1 Study treatment

In this study, the “study treatment” refers to alpelisib or placebo, as no other treatment beyond investigational drug is included in this study. The "participant" refers to the patient diagnosed with PROS who will be consented to the trial prior to any study procedures being performed. The term “investigational drug” refers to the Novartis study drug, alpelisib/BYL719 or placebo.

Novartis Global Clinical Supply (GCS) will provide alpelisib or placebo as global clinical double-blind labeled supplies (alpelisib and placebo FCT as 50 mg or 125 mg, as individual participant supply packed in bottle) during study period 1 (Core period Week 1 to Week 16: Double-Blind Phase). Study drug for study period 1 (Core period Week 17 to Week 24), study period 2 (Extension 1) and study period 3 (Extension 2) will be provided as global clinical open-label supplies (alpelisib as 20 mg, 50 mg, 125 mg or 200 mg, as individual participant supply packed in bottle).

The FCT will be differentiated through different FCT sizes and/or shades of the color. Granules (Group 3 only) will be provided in 20 mg or 50 mg sachets. Alpelisib will be dosed on a flat scale of mg/day, based on age, and will not be adjusted to body weight or body surface area. Alpelisib FCT or granules will be administered orally with food on a continuous basis (see Section 6.7). The storage conditions will be described on the medication label.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the appropriate Case Report Form (CRF).

6.1.1 Investigational and control drugs

Administration of study treatment

This study will include:

Core period, Extension 1 and Extension 2 periods applicable to the participants ≥6 years old (Group 1 – ≥ 18 years, Group 2 – participants 6 to 17 years old). The participants of less than 6 years old (Groups 3 and 4) and additional participants of 6 to 17 years old (Group 5) will be included in exploratory study parts. Enrollment in Group 4 will start with implementation of Global Protocol Amendment 01. Enrollment in Group 5 will start after implementation of Global Protocol Amendment 02 and enrollment in Group 2 is completed, whereas enrollment in Group 3 will start later (as described in Section 3).

Study treatment in Group 1 and Group 2

In the double-blind, randomized, placebo-controlled part, alpelisib/matching placebo will be administered at the assigned starting doses based on the groups. Eligible participants will enter the study and start treatment with alpelisib/matching placebo at 125 mg once daily p.o. in Group 1 or 50 mg alpelisib/matching placebo once daily p.o. in Group 2. Both groups will be enrolled in the study in parallel. In the Core Period 1, participants will receive treatment in blinded fashion, with an upfront 16-week placebo-controlled period. After Week 16 those participants who were randomized to receive placebo will be switched to active treatment with alpelisib and

will receive 125 mg once daily p.o (Group 1) or 50 mg once daily p.o (Group 2). Those participants who were randomized to receive alpelisib will continue their treatment at the same dose level. When the dose of alpelisib/matching placebo was reduced during initial 16 weeks of treatment because of safety/tolerability concerns, the participants will continue their treatment at the reduced dose.

During the initial 16 weeks of the Core period, study treatment will be given in a blinded fashion, starting from Week 17 of the Core period - in open-label fashion. The randomized treatment assignment to the treatment arms will remain blinded to participants, Investigators and the study team until the time of the primary analysis, when the last participant reaches Week 48 from randomization or discontinues earlier.

Study treatment in Group 4

The participants in Group 4 will receive alpelisib FCT 50 mg once daily in an open-label setting.

Study treatment in Group 5

The participants in Group 5 will receive alpelisib FCT 125 mg once daily in an open-label setting.

Study treatment in Group 3

The participants in Group 3 will receive alpelisib granules with an age-dependent starting dose and maximum dose levels for participants < 2 years of age in an open-label setting. Group 3 will be an exploratory group (for more details, please refer to Section 3 Study Design).

Details are presented in Table 6-1, Table 6-2, Table 6-3, Table 6-4, Table 6-5 and Table 6-6.

Table 6-1 Investigational and control drug - Core period Week 1 - Day 1 to Week 16

Group (Age range)	Investigational / control drug (name and strength)	Pharmaceutical dosage form/ Route of administration	Frequency	Supply type
Group 1 (≥ 18 years)	(DB=Double Blind) DB_Alpelisib 125 mg	FCT/ Oral	Once daily	Double-Blind, label participant packs, bottles
Group 1 (≥ 18 years)	DB_ Placebo 125 mg	FCT/ Oral	Once daily	Double-Blind, label participant packs, bottles
Group 2 (6-17 years)	DB Alpelisib 50 mg	FCT/ Oral	Once daily	Double-Blind, label participant packs, bottles
Group 2 (6-17 years)	DB placebo 50 mg	FCT/ Oral	Once daily	Double-Blind, label participant packs, bottles

Table 6-2 Investigational drug - Core period Week 17 to Week 24

Group (Age range)	Investigational drug (name and strength)	Pharmaceutical dosage form/ Route of administration	Frequency	Supply type
Group 1 (≥ 18 years)	(OL=Open-Label) OL alpelisib 125 mg	FCT/ Oral	Once daily	Open- label participant packs, bottles
Group 2 (6-17 years)	OL alpelisib 50 mg	FCT/ Oral	Once daily	Open- label participant packs, bottles

Table 6-3 Investigational drug - Extension 1 and Extension 2

Group (Age range)	Investigational Drug	Pharmaceutical Dosage Form/ Route of administration	Frequency	Strength	Dose escalation	Dose decrease[a]	Supply type
Group 1 (≥ 18 years)	OL Alpelisib	FCT/ Oral	Once daily	50 mg; 125 mg; 200 mg	200 mg or 250 mg	50 mg or 125 mg or 200 mg	Open-label participant packs, bottles[b]
Group 2 (6-17 years)	OL Alpelisib	FCT/ Oral	Once daily	50 mg; 125 mg; 200 mg	125 mg or 200 mg or 250 mg	Frequency changed (i.e.,50 mg QOD) or 50 mg or 125 mg or 200 mg	Open-label participant packs, bottles[b]

a: The dose used upon decrease will depend on the previous dose administered
b: The randomized treatment assignment to the treatment arms will remain blinded to participants, Investigators and the study team until the time of the primary analysis, when the last participant completes Week 48 or discontinues earlier

Table 6-4 Investigational drug - Exploratory Group 3

Group (Age range)[a]	Investigational Drug	Pharmaceutical Dosage Form	Route of administration	Frequency	Strength	Supply type
Group 3 (<1 month)	OL Alpelisib	Granules	Oral use	Every other day	20 mg; 50 mg;	Open-label participant packs
Group 3 (1 to <6 months)	OL Alpelisib	Granules	Oral use	Once daily	20 mg 50 mg;	Open-label participant packs
Group 3 (6 to < 24 months)	OL Alpelisib	Granules / FCT[b]	Oral use	Once daily	20 mg 50 mg 125 mg[b] 200 mg[b]	Open-label participant packs, bottles
Group 3	OL Alpelisib	Granules /	Oral use	Once daily	50 mg	Open-label participant

(2-5 years)		FCT[b]			125 mg[b] 200 mg[b]	packs, bottles
a: dose adjustments as participants age to account for enzyme maturation are allowed (see Table 6-7) b: FCT used for strength > 50 mg						

Table 6-5 Investigational drug - Exploratory Group 4

Group (Age range)	Investigational Drug	Pharmaceutical Dosage Form	Route of administration	Strength	Supply type
Group 4 (2-5 years)	OL Alpelisib	FCT	Oral use	50 mg 125 mg; 200 mg	Open-label participant packs, bottles

Table 6-6 Investigational drug - Exploratory Group 5

Group (Age range)	Investigational Drug	Pharmaceutical Dosage Form	Route of administration	Strength	Supply type
Group 5 (6-17 years)	OL Alpelisib	FCT	Oral use	50 mg; 125 mg; 200 mg	Open-label participant packs, bottles

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this study.

6.1.3 Treatment arms/group

During double-blind, randomized study Period 1 "Core period Week 1 Day 1 to Week 16", eligible participants aged ≥6 years old will be assigned to one of the following treatment arms in a 2:1 ratio:

- Group 1: Alpelisib or matching placebo arms (125 mg QD)
- Group 2: Alpelisib or matching placebo arms (50 mg QD)

Both participant and Investigator will remain blinded.

During double-blind study Period 1 "Core period Week 17 to Week 24":

Those participants who were randomized to receive alpelisib will continue their treatment at the same dose level. Those participants who were randomized to receive placebo will be switched to active treatment with alpelisib in a blinded fashion at the dose level received at the end of the placebo period. Study treatment will be given in an open-label fashion.

- Group 1: Alpelisib (125 mg QD)
- Group 2: Alpelisib (50 mg QD)

The randomized treatment assignment will remain blinded for both participant and Investigator until last participant reaches the 48-week treatment period.

During the open-label study period 2 - Extension 1 and 2 (Week 25 up to 5 years after randomization):

Participants (Group 1 and Group 2) will continue their treatment at the randomized dose if this dose was not reduced due to safety-tolerability reasons. Once a participant (Groups 1 and 2) has reached Week 29 then dose escalation will be allowed (Refer to Section 6.5.1)

- Group 1: Alpelisib (50 mg, or 125 mg, or 200 mg, or 250 mg QD)
- Group 2: Alpelisib (50 mg, or 125 mg, or 200 mg, or 250 mg QD)

During the open-label exploratory study parts:

- Group 3: Participants from this group will receive alpelisib granules in an open-label setting in doses ranging from 20 mg every other day to 50 mg daily depending on the age. Please refer to Table 6-7 for details on starting doses dependent on the age. Age related dosing adjustments up to 50 mg alpelisib p.o. daily will be allowed for participants with a starting dose below 50 mg p.o. daily, once they reach the age range for a higher maximum dose as per Table 6-7. Once a participant has reached the age of 6 years old and has reached at least Week 25, dose escalation will be allowed.

Table 6-7 Group 3 starting dose and maximum age-related dose

Age range	< 1 month	≥1 month to < 6 months	≥6 months to < 2 years	≥2 years to < 6 years
Starting dose / maximum dose	20 mg every other day	20 mg once daily	40 mg once daily	50 mg once daily

- Group 4: Participants from this group will receive 50 mg alpelisib FCT formulation once daily in an open-label setting. Once a participant has reached the age of 6 years old and has reached at least Week 25, dose escalation will be allowed.
- Group 5: Participants from this group will receive 125 mg alpelisib FCT formulation once daily in an open-label setting. Once a participant has reached at least Week 25, dose escalation will be allowed.

6.1.4 Guidelines for continuation of treatment

Refer to guidelines for management of toxicities and doses modifications instruction (Section 6.5.1 and Section 6.5.2).

6.1.5 Treatment duration

The planned duration of alpelisib treatment in the study will be up to 5 years after study treatment start for all groups.

The Treatment Period for each participant will begin on study Day 1. Participant may be discontinued from treatment with alpelisib earlier due to unacceptable toxicity (refer to Section 6.5.1 and Section 6.5.2), BIRC-confirmed disease progression (refer to Section 6.1.5.1 and Section 8.3.1 for more details), death, and/or any other reason at the discretion of the Investigator or the participant.

For all participants, the Core Period, Extension 1 and Extension 2 are considered. Those participants, who continue in the study until Week 24 and have clinical benefit from the study treatment at the end of Core Period, will enter Extension 1 (Week 25-48) and Extension 2 (Week

49 – up to 5 years) periods with no interruption in alpelisib therapy (except interruptions for safety reasons). Participants who did not derive sufficient clinical benefit or have progressed, may remain on study therapy if there are no safety concerns and the Investigators feel that they may benefit, from continuation.

Participants who complete 5 years of treatment in the study and are still deriving clinical benefit from alpelisib based on the Investigator's evaluation, may receive post-trial access. Post Trial Access (PTA) means the provision of treatment to study participants following their completion of study participation. Every effort will be made to continue provision of study treatment after 5 years of total duration of study treatment. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, Investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the study participant's country, or the clinical program is discontinued for any other reason. Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, provision of the Novartis investigational product in a non-study setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

6.1.5.1 Treatment beyond disease progression

During Core period, progression of lesions must be confirmed by BIRC to make a decision on treatment beyond progression. Starting from Week 25 the Investigator will review the results of PROS lesions response assessment based on local assessments and other assessments to conclude, if the participant has progression of the disease, and to make treatment decision (refer to Section 8.3.1). The Investigator must perform an unscheduled MRI in case of suspected disease progression as soon as feasible and within the coming 3 months maximum in participants of all groups at any time point in the study. Unscheduled MRI must be submitted to BIRC as other lesions assessment. Any treatment that is considered necessary for the treatment of progression is allowed in addition to treatment with alpelisib beyond progression except prohibited medication (refer to Section 6.2.2).

Participants of Group 1, Group 2 and Group 5 who have BIRC-confirmed disease progression by Week 16, may remain on study therapy at the same dose level if there is no safety/tolerability concerns, and the participant may benefit from continuation at the discretion of the Investigator, or discontinue. When progression is suspected on a local assessment but not confirmed by BIRC, the participant should remain in the study at the same dose level and undergo all required assessments according to evaluation schedule until progression is confirmed by BIRC at subsequent assessment. Participant may be discontinued if continuation of study drug until confirmation of progression by BIRC is not clinically acceptable or at the discretion of the Investigator.

Participants of Group 1, Group 2 and Group 5 with BIRC- confirmed disease progression by Week 24 and later, who do not have safety/tolerability issues, may remain on study therapy at the discretion of the Investigator; they will also have the option to undergo dose escalation after 28 weeks for Groups 1 and 2 and after 24 weeks for Group 5 of study treatment. The participant with BIRC-confirmed progression may remain on study therapy at the same or the next dose level, or discontinue.

Participants of Group 1, Group 2 and Group 5 will have a possibility to undergo dose escalation for response optimization purpose and continue treatment beyond progression of the disease (twice from 125 mg to 200 mg and from 200 to 250 mg in Groups 1 and 5, and 3 times from 50 mg to 125 mg, from 125 to 200 mg, from 200 to 250 mg in Group 2).

In the event of a dose increase for response optimization, an MRI has to be performed after at least 3 months to assess the benefit from the increased dose if further dose optimization is considered.

Participants of Group 1, Group 2 and Group 5 receiving alpelisib beyond disease progression should undergo all required assessments according to evaluation schedule (See Table 8-2).

Group 4 participants with disease progression by Week 24 and later, who do not have safety/tolerability issues, may remain on study therapy at the discretion of the Investigator; they will also have the option to undergo dose escalation once they have reached the age of 6 years old and have reached at least Week 25. The participant with progression may remain on study therapy at the same or the next dose level, or discontinue.

Group 3 of 0 to 5 years old participants will be enrolled after implementation of Global Protocol Amendment 05. Group 3 participants with disease progression by Week 24 and later, who do not have safety/tolerability issues, may remain on study therapy at the discretion of the Investigator; they will also have the option to undergo dose escalation once they have reached the age of 6 years old and have reached at least Week 25. The participant with progression may remain on study therapy at the same or the next dose level or discontinue.

6.2 Other treatment(s)

All participants will be allowed to receive concomitant medication and/or other non-medication treatment (e.g., rescue surgery) when clinically indicated to control comorbidities and/or complications of PROS. Rescue surgery is defined as a salvage intervention, and includes e.g. debulking surgery, orthopedic surgery, invasive vascular surgeries/procedures. As much as possible, surgery targeting PROS-related lesion volume reduction should be avoided. Systemic therapy targeting PI3K/AKT/mTOR pathway other than alpelisib and/or any investigational/not approved medication for PROS are not allowed during the conduct of the study.

During the course of the study, the participant must also not receive anti angiogenic agents for the purpose to treat PROS.

The participant must discontinue from specific treatment with small molecules (such as mTOR inhibitors, AKT inhibitors) for PROS before any of study related assessments and at least 4 weeks before study treatment start.

It is not allowed to receive any other investigational drugs.

6.2.1 Concomitant therapy

All medications (other than alpelisib) and significant non-drug therapies (e.g., physical therapy, vitamins) administered during treatment should be noted in the participant's record. In addition, any known prior medications, procedures, or significant non-drug therapies administered for the treatment of PROS should be recorded on the appropriate Case Report Forms (see also Section 8.2 for details).

The Investigator must instruct the participant to notify the site about any new medication he/she takes after the start of the study.

During the course of the study, the participant may receive the following concomitant therapies:

- Transfusions of blood and blood components
- Pain relief medication
- Anti-infective medications (see prohibited and cautioned medications in the Section 6.2.1.1 and Section 6.2.2 below). Investigators should discuss prescription of anti-fungal, anti-viral agents with Novartis
- Treatment for concomitant medical conditions, adverse events (see prohibited and cautioned medications in the Section 6.2.1.1 and Section 6.2 below)
- Supplemental nutrition (enteral, parenteral)
- Routine vaccinations

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution are described below and listed in the Appendix in Table 16-1. This list is not comprehensive and is only meant to be used as a guide. Please contact Novartis with any questions.

These medications should be excluded from participant use if possible. If they must be given based on the Investigator's judgment, then use with caution and consider an alpelisib interruption, as appropriate, if the concomitant medication is only needed for a short time.

Medications to be used with caution:

- **CYP2C9 substrates with narrow therapeutic index (NTI) (e.g., anticoagulants):** *In vitro* evaluations indicated that pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. In the absence of clinical data, caution is recommended with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may reduce the clinical activity of such drugs. Alternatively, therapeutic anticoagulation may be accomplished using low- molecular weight heparin or Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors.
- **CYP2B6 sensitive substrates or CYP2B6 substrates with NTI:** Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In the absence of clinical data, sensitive CYP2B6 substrates (e.g., bupropion, evafirenz) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such drugs.
- **Selected CYP3A4 substrates:** Alpelisib can be co-administered with sensitive CYP3A4 substrates (e.g., midazolam) and CYP3A4 substrates with narrow therapeutic window (e.g., fentanyl). Caution is recommended when alpelisib is used in combination with CYP3A4

substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (refer to Table 16-2). Systemic exposures of such CYP3A4 auto-inhibitors and auto-inducers may be either decreased or increased depending on the drug and nature of auto-perpetrator potential, respectively, when alpelisib is co-administered, based on PBPK simulations.

- Co-administration of alpelisib with bis-phosphonates and/or denosumab should be avoided since the risk of osteonecrosis increases with the combination.
- Please refer to the latest version of [Alpelisib (BYL719) Investigator's Brochure] for additional information pertaining to alpelisib.

6.2.1.2 Oral anti diabetic therapy

Participants who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association)/EASD (European Association for the Study of Diabetes) guidance. It is recommended to start treatment with metformin. Metformin is not recommended in participants below the age of 10 years, metformin extended release (XR) is not recommended in pediatric participants below the age of 18 years. Consultation with a diabetologist is needed to find the optimal individualized treatment for hyperglycemia, especially in pediatric participants under 10 years old (where international or local guidelines may apply). Participants receiving oral anti-diabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored with respect to their effectiveness as alpelisib was found to be an inducer of CYP2C9 in vitro.

6.2.1.3 Corticosteroids

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes). Hyperglycemia is a common adverse drug reaction for PI3K inhibitors like alpelisib; corticosteroids should therefore be used with caution and participants should be closely monitored.

6.2.1.4 Gastric protection agents

Alpelisib is characterized by a pH-dependent solubility. Therefore, acid reducing agents (ARAs, e.g., proton-pump inhibitors, H2-antagonists and antacids) may alter the solubility of alpelisib and hence its bioavailability. A drug-drug interaction study in human healthy volunteers confirmed that co-administration of alpelisib with the H2-antagonist ranitidine after a meal lead to a decrease in exposure by only ~20%, considered not to be clinically relevant. Alpelisib can be co-administered with any ARAs.

6.2.2 Prohibited medication

The following medications are prohibited during treatment with alpelisib:

This list is not comprehensive and is only meant to be used as a guide.

- **Strong inducers of CYP3A4:**

Coadministration of alpelisib with a strong CYP3A4 inducer may decrease alpelisib concentration, which may decrease alpelisib activity. Avoid coadministration of alpelisib with strong CYP3A4 inducers.

- **Inhibitors of BCRP:**
  Coadministration of alpelisib with a BCRP inhibitor may increase alpelisib concentration, which may increase the risk of toxicities. Avoid the use of BCRP inhibitors in participants treated with alpelisib.
- **Herbal Medications:**
  The use of herbal preparations/medications and dietary supplements (except for vitamins) are prohibited throughout the study, as a potential drug-drug interaction is possible. Herbal medication include, but are not limited to St. John's Wort (Hypericum perforatum), and Avasimibe (see Table 16-2) or BCRP inhibitors such as Curcumin (see Table 16-3). Medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential for complex interactions. Participants must stop using all herbal medications (refer to Table 16-2 and Table 16-3) and dietary supplements at least 7 days prior to first dose of study treatment.

Other investigational and antineoplastic therapies

In addition, the participant should discontinue from specific treatment with small molecules (such as mTOR inhibitors, AKT inhibitors) and/or anti angiogenic agents for PROS before any of study related assessments and for at least 4 weeks before the start of study treatment whichever comes first.

Please refer to the latest version of [Alpelisib (BYL719) Investigator's Brochure] for additional information.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by Subject Number (Subject No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the study. The Subject No. consists of the Site Number (Site No.) (as assigned by Novartis Rave EDC to the investigative site) with a sequential Subject number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Subject No. available. A new Informed Consent Form (ICF) will need to be signed if the Investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Subject number.

6.3.2 Treatment assignment, randomization

The assignment of a participant to alpelisib or matching placebo at the appropriate starting dose will be based on age using an Interactive Response Technology (IRT). Prior to dosing, all participants who fulfill all inclusion/exclusion criteria will be enrolled via IRT. The IRT must

be used for all study drug allocations as the system will specify the unique medication numbers for participant dispensation.

Groups 1 and 2 (Core Period- Double blind phase)

A total of approximately 156 eligible participants aged over 6 years old will be randomized in a 2:1 ratio to alpelisib or matching placebo; the starting dose will be 125 mg once daily p.o. in Group 1, and 50 mg once daily p.o. in Group 2.

The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

Groups 3, 4 and 5 (Exploratory study parts – Open-label phase)

In this exploratory study part, the participants of Groups 3, 4 and 5 will receive alpelisib in an open-label setting; no randomization will be performed. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system. Approximately 15, 6 and 15 eligible participants will be enrolled via IRT for treatment with alpelisib into Groups 3, 4, and 5, respectively.

6.4 Treatment blinding

Groups 1 (≥18 years old) and 2 (6 to 17 years old)

The clinical study team (CTT) at Novartis will remain blinded to the identity of the treatment assigned randomly to the treatment arms in Groups 1 and 2, from the time of randomization until analysis of the primary endpoint. Participants, Investigator staff, and persons performing the assessments including BIRC will remain blinded to the identity of the treatment from the time of randomization until database lock for primary analysis (when the last participant completes Week 48 from randomization or discontinues earlier), using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: Independent biostatistician and programmer who will perform DMC analysis and the Bioanalysts. The

randomization codes associated with participants from whom PK samples are to be analyzed will be disclosed to Bioanalysts upon request who will keep PK results confidential until the point when the database is locked for primary endpoint analysis.

(2) The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of participants. Unblinding will only occur in the case of participant emergencies (see Section 6.6.2).

In rare cases when unblinding occurs because of emergency participant management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the study. Unblinding a single participant at a site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant must be discontinued from the study treatment. After primary analysis, the participants, Investigators, Novartis employees involved in running of the study will be unblinded, BIRC will be kept blinded.

At the time of safety review, the DMC will review unblinded interim reports created by an (independent) analysis team. More details will be provided in the DMC charter.

Exploratory study parts: Groups 3 and 4 (less than 6 years old) and Group 5 (6 to 17 years old)

Treatment will be open to participants, Investigator staff, persons performing the assessments, and the clinical trial team (CTT) at Novartis.

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

Dose escalation

Dose escalation for response optimization purpose is considered in this study (Table 6-8 and Table 6-9).

Dose escalation is not allowed for Group 1 and Group 2:

- During Core period (Week 1 – Week 24).
- First 4 weeks of Extension 1 period (Week 25 – Week 28)

Dose escalation is allowed for Group 1 and Group 2:

- During Extension 1 period starting from Week 29
- During Extension 2 period, decision to escalate the dose for response optimization purpose will be done by the Investigator based on local assessment of lesion response and overall clinical response. Escalation will be allowed, when:
- The participant does not meet criteria for lesion response based on local assessment and there are no safety/tolerability concerns which may preclude from treatment continuation at a higher dose level.

- The participant, in the opinion of the Investigator, did not derive sufficient clinical benefit (based on overall clinical response assessed by the Investigator) from previous treatment regardless of meeting criteria for lesion response and there are no safety/tolerability concerns which may preclude from treatment continuation at higher dose level.
- The participant has BIRC-confirmed disease progression, but, in the opinion of the Investigator, may remain in the study and benefit from dose escalation, and there are no safety/tolerability concerns which may preclude from treatment continuation at higher dose level.

Dose escalation is allowed for Group 4 once the participant has reached the age of 6 years old and has completed 24 weeks of treatment and has reached at least Week 25. Dose escalation is allowed for Group 5 once the participant has reached at least Week 25. Decision on dose escalation will be taken by the Investigator based on local assessment of PROS lesions response, overall clinical response, and safety/tolerability concerns which may preclude from treatment continuation at higher dose level. Dose escalation is allowed at a minimum of 12-week intervals.

In Group 1 and Group 2, dose escalations are possible from Week 29 visit onwards as following:

- Group 1: from 125 mg to 200 mg, from 200 mg to 250 mg once daily p.o. (Refer to Table 6-8).
- Group 2: from 50 mg to 125 mg, from 125 mg to 200 mg, and from 200 mg to 250 mg once daily p.o. (Refer to Table 6-9).

In Group 3 and 4, dose escalations are allowed for participants who reached 6 years of age and are possible from Week 25 onward as follows:

- from 50 mg to 125 mg, from 125 mg to 200 mg, and from 200 mg to 250 mg once daily p.o. (Refer to Table 6-9).
- For participants in Group 3, dose adjustments are allowed (please refer to Section 6.1.3 and Table 6-7 for details), and adjustment up to 50 mg once daily must be performed prior to starting with any further dose escalations.

In Group 5, dose escalations are possible from Week 25 onwards as follows:

- from 125 mg to 200 mg, from 200 mg to 250 mg once daily p.o. (Refer to Table 6-8).

Table 6-8 Dose escalation for alpelisib in Group 1 and Group 5

Alpelisib dose level	Adult dose	Number of tablets & strength
Starting dose	125 mg/day	1 x 125 mg FCT
Dose level 1	200 mg/day	1 x 200mg FCT
Dose level 2	250 mg/day	1 x 200 mg + 1 x 50 mg FCT

Table 6-9 Dose escalation for alpelisib in Groups 2, 3 and 4

Alpelisib dose level	Pediatric dose starting at 6 years old	Number of tablets/ granules sachet & strength
Starting dose or dose after age related dose adjustments	50 mg/day	1 x 50 mg FCT or granules[a]
Dose level 1	125 mg/day	1 x 125 mg FCT
Dose level 2	200 mg/day	1 x 200 mg FCT
Dose level 3	250 mg/day	1 x 200 mg + 1 x 50 mg FCT
a: 50 mg granules are to be used in Group 3 only.		

For those participants from Groups 1 and 2, who receive the lower dose because of safety/tolerability concerns, re-escalation of the dose after a dose reduction is possible starting from Week 29 in certain conditions as defined in the dose modification guidance below. The Investigator should consult Novartis to make a decision to re-escalate the dose.

For those participants from Group 3 and 4, who receive the lower dose because of safety/tolerability concerns, re-escalation of the dose is possible starting from Week 25, provided that the participant has reached the age of 6 years old and certain conditions, as defined in the dose modification guidance provided below, are met. The Investigator should consult Novartis to make a decision to re-escalate the dose.

For those participants from Group 5, who receive the lower dose because of safety/tolerability concerns, re-escalation of the dose is possible starting from Week 25 in certain conditions as defined in the dose modification guidance below. The Investigator should consult Novartis to make a decision to re-escalate the dose.

In the event of a dose increase for response optimization, an MRI has to be performed after at least 3 months to assess the benefit of the increased dose and if further dose optimization is considered.

Monitor fasting plasma glucose (FPG) 8 and 15 days after each dose escalation, and HbA1c 3 months after each dose escalation. Additional monitoring of FPG and HbA1c may be undertaken at the discretion of the Investigator, particularly for participants with at least one risk factor for development of severe hyperglycemia, including prediabetes/diabetes (elevated FPG and/or HbA1c at the upper limit of normal or above), use of concomitant systemic corticosteroids, and/or obesity (BMI $\geq$ 30). Hematology and clinical chemistry can be repeated, if clinically indicated, at that timeframe. Home nursing is allowed for monitoring of FPG in the Netherlands only.

For the Netherlands only and at the Investigator's discretion based on benefit-risk considerations of the participant's clinical condition, participants who are unable to travel to the site may be offered the option to have certain clinical trial procedures (e.g., monitoring of FPG) performed at an off-site location as described in Section 10.1.6. A qualified Off-site Health Provider (OHP) will perform fasting glucose plasma (under the direction of the Investigator) if allowed by national and local/site regulations and if participant provides consent (See Section 4.7).

Dose reduction

Dose reduction and/or interruption is allowed in all groups at any time for reasons of tolerability and safety.

Generally, when dose reduction is permitted as per toxicity management guidance, maximum 2 consequent dose reductions are possible. When the participant experiences safety concerns at starting dose level, only one dose reduction is permitted. Depending on the dose of alpelisib, the Investigator should follow the general guidance for alpelisib dose reductions sequential steps as described in Table 6-10, Table 6-11, Table 6-12 and Table 6-13.

Investigators should exercise caution and consider dose interruption for safety reasons, especially in participants who experience adverse events of grade 3 and higher, regardless of their apparent relatedness to study medication, and in participants experiencing recurrent or prolonged adverse events. This is particularly important for pediatric participants. A combined approach of drug interruption with subsequent re-initiation of study medication at a reduced dose may be pursued.

Dose interruption because of safety and/or other medically relevant reason may last up to 60 days, afterward the participant may restart study therapy. When the Investigator plans to restart alpelisib after more than 60 days of interruption, he/she should consult the Novartis.

The sections below provide specific guidance for management and study drug modification in the event of: QTcF prolongation, skin toxicity, hyperglycemia, pneumonitis, diarrhea and stomatitis/oral mucositis.

When minor or major surgical invasive procedure is planned, the Investigator may make a decision to interrupt study medication based on clinical condition of the participant.

Dose reduction sequential steps are described in the Table 6-10, Table 6-11, Table 6-12 and Table 6-13; guidelines and criteria for dose reduction/interruption/re-initiation are provided in the following Section 6.5.1.

Table 6-10 Dose reduction sequential steps for alpelisib in Group 1

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
125 mg daily p.o	50 mg daily p.o	Not allowed
200 mg daily p.o	125 mg daily p.o	50 mg daily p.o
250 mg daily p.o	200 mg daily p.o	125 mg daily p.o

Table 6-11 Dose reduction sequential steps for alpelisib in Group 2 and 4

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
50 mg daily p.o	50 mg every other day p.o	Not allowed
125 mg daily p.o	50 mg daily p.o	50 mg every other day
200 mg daily p.o	125 mg daily p.o	50 mg daily p.o
250 mg daily p.o	200 mg daily p.o	125 mg daily p.o

Table 6-12 Dose reduction sequential steps for alpelisib in Group 5

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
125 mg daily p.o	50 mg daily p.o	50 mg every other day

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
200 mg daily p.o	125 mg daily p.o	50 mg daily p.o
250 mg daily p.o	200 mg daily p.o	125 mg daily p.o

Table 6-13 Dose reduction sequential steps for alpelisib in Group 3

Alpelisib dose	Reduced dose / Level -1	Reduced dose / Level -2
20 mg every other day p.o	Not allowed	Not allowed
20 mg daily p.o	20 mg every other day p.o	Not allowed
40 mg daily p.o	20 mg daily p.o	20 mg every other day p.o
50 mg daily p.o	50 mg every other day p.o	Not allowed
125 mg daily p.o	50 mg daily p.o	50 mg every other day
200 mg daily p.o	125 mg daily p.o	50 mg daily p.o
250 mg daily p.o	200 mg daily p.o	125 mg daily p.o

6.5.1.1 Dose adjustments for QTcF prolongation

The Fridericia QT correction formula (QTcF) should be used for clinical decisions. When QTcF > 500 ms or > 60 ms change from baseline (≥ Grade 3) is detected on at least two separate ECGs, the Investigator should follow criteria for interruption and re-initiation of study treatment as per Table 6-14 below.

Table 6-14 Criteria for interruption and re-initiation of alpelisib/placebo treatment due to QTcF prolongation

If QTcF > 500 ms or > 60 ms change from baseline (≥ Grade 3) is identified:

- Assess the quality of the ECG recording and the QT value and repeat if needed
- If deemed necessary, consult with a cardiologist (or qualified specialist) to confirm ECG diagnosis

If QTcF prolongation is confirmed:

- Interrupt study treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
- Review concomitant medication use for other causes for QT prolongation (refer to crediblemeds.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check study drug dosing schedule and treatment compliance
- Consider collecting a time-matched PK sample and record time and date of last study drug intake
- Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 ms or < 60 ms change from baseline

After resolution to ≤ 480 ms / 60 ms change from baseline, re-introduce treatment at a reduced dose (if possible), and increase ECG monitoring

- If QTcF prolongation recurs (> 500 ms / 60 ms change from baseline, i.e., ≥ Grade 3) after treatment re-introduction, discontinue participant from study.

6.5.1.2 Guidelines for the treatment of alpelisib induced skin toxicity

Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. Dermatologist consult is mandated for serious cutaneous reactions (i.e., fulfilling seriousness criteria for AE Reporting) and for severe

cutaneous reactions like Stevens-Johnson-Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or Erythema Multiforme (EM). Dose modification guidelines are described in Table 6-15.

Table 6-15 Criteria for interruption and re-initiation of alpelisib/placebo treatment due to skin toxicity

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Skin and subcutaneous tissue disorders	
Grade 1 (<10% body surface area (BSA) with active skin toxicity*)	**Maintain dose level** • Initiate topical corticosteroids 3-4 times daily, preferred compounds to use are triamcinolone, betamethasone as long as skin toxicity is active, for a duration of maximum 28 days For participants with symptoms like burning and/or pruritus, add a non-sedating anti-histamine; consider adding a sedating anti-histamine at night If active rash is not resolved within 28 days of appropriate treatment, consider adding low dose systemic corticosteroid
Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level** • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone as long as skin toxicity is active, during max. 28 days • Consider adding systemic corticosteroids in adult participants. The optimal doses of systemic steroids in pediatric participants should be defined individually after a consultation with a dermatologist according to the local label. If rash resolves to ≤ G1 within 10 days, the systemic corticosteroid may be discontinued. For participants with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine; consider adding a sedating anti-histamine at night
Grade 3 (>30% BSA with active skin toxicity*)	**Omit alpelisib/placebo** dose until rash /skin toxicity is no longer active but fading (G1), skin biopsy may be considered if part of local practice • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days • Add systemic corticosteroids If rash resolves to ≤ G1 within 10 days, systemic corticosteroid may be discontinued For participants with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine during day time; consider adding a sedating anti-histamine at night Re-start alpelisib/placebo dose once rash/skin toxicity is no longer active but fading (G1): • at same dose in case of first occurrence, at reduced dose level in case of second occurrence • If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Skin and subcutaneous tissue disorders	
	corticosteroid for at least 48 hours upon re-challenge with alpelisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued For participants with symptoms like burning, stinging and/or pruritus an antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue participant from alpelisib/placebo • Mandated to consult a dermatologist. Photographs and skin biopsy** may be considered if part of local practice. Treatment may follow guidelines for Grade 3 above with the exception of rechallenge. Additional measures may be taken as per local treatment guidance
Any Grade of Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis or other SJS/TEN-like severe skin reactions	• Permanently discontinue participant from alpelisib/placebo treatment • Consult dermatologist, ensure documentation by imaging like photographs and consider skin biopsy** if part of local practice. • Follow local treatment guidelines for SJS/TEN
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy. ** Skin biopsy: skin biopsy can be performed as clinically indicated and assessed locally; no skin samples will be sent for central assessment.	

6.5.1.3 Guidelines for the treatment of alpelisib induced hyperglycemia

Always consider consultation with a diabetologist, particularly for pediatric participants, and recommend/reinforce lifestyle changes as per American Diabetes Association (ADA) or European Association for the Study of Diabetes (EASD), i.e., exercise and dietary advice (e.g., small frequent meals, low carb, high fiber, balancing carbs over the course of the day. Three small meals and two small snacks rather than one large meal).

The table below provides dose management recommendations. The preferred option for treating alpelisib-induced hyperglycemia, in participants over 10 years old, is metformin, given its wide availability and well characterized safety profile. For pediatric participants under 10 years of age (where international or local guidelines may apply), or in case of intolerance, unavailability or unsuitability of metformin, it is needed to consult a diabetologist to find the optimal individualized treatment for hyperglycemia. Other insulin sensitizers such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors may be used for the treatment of alpelisib-induced hyperglycemia in adult participants. Dose modification guidelines are described in Table 6-16.

Table 6-16 Criteria for interruption and re-initiation of alpelisib/placebo treatment due to hyperglycemia

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For participants with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this applies only for findings > 140 mg/dL (7.7 mmol/L)	**Maintain dose level** and remind participant on lifestyle changes. • If FPG < 140 mg/dl, consider adding metformin as per guidance below or in cooperation with diabetologist (for children<10 years old, a consultation with diabetologist to individualize treatment is required). • If FPG 140-160 mg/dl, start/intensify metformin as per guidance below or in cooperation with diabetologist (for children<10 years old, a consultation with diabetologist to individualize treatment is required). Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until FPG is within baseline values.
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	**Maintain dose level** and remind participant of lifestyle changes, exclude confounding factors like e.g., urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. If FPG is still rising on maximum tolerated dose of metformin or persistently >160mg/dl (>8.9 mmol/L), add an insulin-sensitizer, e.g., pioglitazone 30 mg (max. dose). Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	**Omit alpelisib/placebo** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g., urinary tract infection and consider consultation with a diabetologist.

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
	Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. • If FPG resolves to ≤ Grade1 within 3-5 days, while off program treatment and on metformin, re-start alpelisib/placebo and reduce by 1 dose level, continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl • If FPG does not resolve to Grade1 within 3-5 days while off program treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g., urinary tract infection, permanently discontinue participant from alpelisib/placebo treatment.
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	**Omit alpelisib/placebo**, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors (e.g., urinary tract infection). Should consult with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. • If grade improves then follow specific grade recommendations • If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue participant from alpelisib/placebo.
A diabetologist consultation should always be considered. In cases where there is rapidly increasing serum glucose suspicious of severe clinical presentation and/or diabetic ketoacidosis without obvious confounding factors, a diabetologist should be consulted with consideration of potential hospitalization and close monitoring.	

6.5.1.4 Guidelines for treatment of alpelisib induced pneumonitis

An early consultation with a pulmonologist is recommended at any suspicion of pneumonitis for an appropriate evaluation and management**.** Dose modification guidelines are described in Table 6-17.

Table 6-17 Management of pneumonitis related to alpelisib/placebo with or without other agents in combination

Pneumonitis	Recommended Investigations	Management of Pneumonitis	Program Treatment Modification
Any Grade	Obtain appropriate imaging (e.g., high resolution CT scan) Consider broncho-alveolar lavage (BAL) and biopsy, if clinically appropriate Infectious causes of interstitial lung disease should be ruled out	Follow institutional practice for management of pneumonitis (e.g., Treatment with high dose corticosteroids; concurrent antibiotic therapy if infectious causes are suspected). Consultation with a pulmonologist is highly recommended	Immediately interrupt alpelisib/placebo for any case of suspected pneumonitis. For all participants with confirmed pneumonitis alpelisib/placebo should be permanently discontinued

6.5.1.5 Guidelines for the treatment of alpelisib induced diarrhea

Mild to moderate diarrhea has been reported in studies of single-agent alpelisib. Severe diarrhea and its clinical consequences including dehydration and acute kidney injury, as well as colitis, have been reported in participants treated with alpelisib. Based on the severity of diarrhea, alpelisib may require dose interruption, reduction, or discontinuation.

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, participant education as well as proper management of alpelisib-induced diarrhea is mandatory. For pediatric participants, early detection and treatment of diarrhea is particularly important to avoid dehydration, and consultation with a gastroenterologist is recommended. The Investigators and care givers should ensure appropriate hydration and nutrition of the participants experiencing diarrhea; standards of local practice to be applied. In pediatric participants the Investigator may consider immediate dose interruption and initiation of anti-diarrhea treatment at occurrence of the first episode of diarrhea, and should ensure, that participants and care givers are guided how to control diarrhea in timely manner. Dose modification guidelines are described in Table 6-18.

The following algorithm for treatment and management of diarrhea is based on Wadler et al 1998, Kornblau et al 2000.

Table 6-18 Criteria for interruption and re-initiation of alpelisib treatment due to diarrhea

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at same dose
Grade 3	Omit dose until resolved to ≤ Grade 1, then reduce 1 dose level
Grade 4	Permanently discontinue treatment

Participant history of diarrhea:

- At baseline, the participant's history of diarrhea should be reviewed and the participant (and care-giver) should be appropriately informed of potential alpelisib-induced diarrhea and its management
- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions
- Stop all diarrheogenic agents, otherwise exclude from program
- Instruct participants regarding risk of developing diarrhea
- Perform baseline clinical/laboratory studies (e.g., one could rule out carrier state of *Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium* which can lead to opportunistic infections in immunosuppressed participants)
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 6-19)

First report of diarrhea:

- Obtain history of onset and duration of diarrhea
- Description of number of stools and stool composition (e.g., watery, blood, mucus in stool)
- Assess participant for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)
- Proactively look for occurrence of diarrhea. If no problems occur, instruct the participant and care-giver to call when a problem does arise

Management of diarrhea:

General Recommendation

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g., Metamucil®) and stool softeners (e.g., docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g., bananas, rice, apple sauce, toast)

It is recommended that participants are treated with loperamide (refer to the local label). Participants and care-givers should be instructed on the use of loperamide in order to manage signs or symptoms of diarrhea at home. Participants should be instructed to start oral loperamide at the first sign of loose stool or symptoms of abdominal pain (initial administration for adults: 4 mg, then 2 mg every 4 hrs to a maximum of 16 mg/day; for children below 12 years, depending on age: 1-2 mg up to 4 times a day). These instructions should be provided at each visit and the treating physician should ensure that the participant understands the instruction. At each visit, participants should be specifically questioned regarding any experience of

diarrhea or diarrhea related symptoms. If symptoms were experienced, then the treating physician should question the participant regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea.

Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide, however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the participant's response to treatment should be observed and appropriately documented.

For colitis consider additional treatment, such as steroids.

Treatment of diarrhea CTCAE Grade 1 or 2

Diarrhea CTCAE Grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool) (Table 6-19). Dosage and dosage schedule for pediatric participants should be individualized according to the local loperamide label.

12-24 hours later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hours diarrhea-free interval

Diarrhea unresolved

- Persisting diarrhea CTCAE Grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of participants condition to rule out dehydration, sepsis, ileus, medical check and selected workup if participant does not need hospitalization (see section Diarrhea workup below). Observe participant for response to antidiarrheal treatment.
- Persisting diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of participants condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe participant for response.

After 12-24 hours:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (CTCAE Grades 1 and 2) after 48 hrs with high dose loperamide and opiates, then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.
- If diarrhea still persisting and progressed to CTCAE Grades 3 and 4, employ measures described below.

Treatment of diarrhea CTCAE Grade 3 or 4

Severe diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of participants condition (to rule out dehydration, sepsis, ileus) medical check and workup (Table 6-19) (see Diarrhea workup section below).

Observe participant for response.

After 12-24 hours:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 µg tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE Grade 3 or 4 still persists participants should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE Grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolves.

Diarrhea workup

Perform appropriate tests (Fine and Schiller 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed participants), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water).

Endoscopic examinations

Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures:

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

Table 6-19 NCI CTCAE version 4.03 grading of diarrhea for participants without Colostomy

Toxicity	1	2	3	4
Diarrhea	Increase of < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care Activity of Daily Living (ADL)	Life-threatening consequences; urgent intervention indicated
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements.				

6.5.1.6 Guidelines for the treatment of alpelisib induced stomatitis/oral mucositis

For pediatric participants, early consultation with a stomatologist is recommended on suspicion of alpelisib-induced stomatitis for appropriate evaluation and management. Dose modification guidelines are described in Table 6-20.

Table 6-20 Criteria for interruption and re-initiation of alpelisib treatment due to stomatitis

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Grade 1/Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash.
Intolerable Grade 2 or Grade 3	First occurrence: hold until ≤ Grade 1 and reduce 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the Investigator). Second occurrence: hold until ≤ Grade 1 and reduce 1 dose level.
Grade 4	Permanently discontinue participant from alpelisib/placebo.

6.5.1.7 Guideline for treatment of alpelisib induced pancreatitis

If acute pancreatitis is diagnosed, initiate appropriate treatment and follow dose modification guidelines described in the Table 6-21.

Table 6-21 Criteria for interruption and re-initiation of alpelisib treatment due to pancreatitis.

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Grade 2 (enzymatic elevation or radiologic findings only)	Maintain dose level. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3	Omit dose until resolved to Grade ≤ 1, then resume treatment at decrease 1 dose level. Only 1 dose reduction is allowed. If toxicity recurs, permanently discontinue participant from alpelisib/alpelisib matching-placebo.
Grade 4	Permanently discontinue participant from alpelisib/alpelisib matching-placebo.

6.5.1.8 Investigations: alpelisib dose modifications

Recommendations for dose reduction or dose interruption of alpelisib in the management of changes in the investigations when they are considered adverse events are summarized in the Table 6-22 and Table 6-23.

Clinical judgment of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each participant based on individual benefit/risk assessment.

- One dose reduction will be allowed after which treatment must be discontinued as indicated in the Table 6-22 and Table 6-23.

- After treatment is resumed at a lower dose:
- If the same toxicity reoccurs with the same severity, treatment must be discontinued.
- Once the AE has resolved and alpelisib dose has been reduced, the Investigator may consider a dose re-escalation only if it may be needed to provide optimal clinical benefit (based on overall response assessment) and if there are no safety/tolerability concerns which may preclude from treatment continuation at higher dose level.

Table 6-22 Criteria for interruption and re-initiation of alpelisib treatment: Investigations (hematologic)

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	• Maintain dose level. • Maintain dose level and monitor as clinically indicated.
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level.
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level. Discontinue from study in the event of recurrence.
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until resolved, then decrease 1 dose level. Discontinue from study in the event of recurrence.
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level. Maintain dose level and monitor as clinically indicated.
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level.
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level. Discontinue from study in the event of recurrence.

Table 6-23 Criteria for interruption and re-initiation of alpelisib treatment: Investigations (other)

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level.
2 – 3 x ULN	• Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level. • If resolved in > 7 days, then decrease 1 dose level.
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue participant from study drug.
Grade 4 (> 6.0 x ULN)	Permanently discontinue participant from study drug.
Investigations (Hepatic)	
Isolated total Bilirubin elevation (for participants with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Grade 1 (>ULN - 1.5 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.
Grade 3 (>3.0 - 10.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (>10.0 x ULN)	Permanently discontinue.
Isolated AST or ALT elevation	
Grade 1 (>ULN - 3.0 x ULN) Grade 2 (>3.0 - 5.0 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (>5.0 - 20.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (>20.0 x ULN)	Permanently discontinue.
Combined ALT/AST and TBIL elevation	Please see specific instructions in Section 6.5.2.1
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level.
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level.
Grade ≥ 3 (> 2.0 x ULN)	• Omit dose until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level. • If resolved in > 14 days, then decrease 1 dose level. Note: • In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase).
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	Maintain dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.
Grade 4	Permanently discontinue participant from alpelisib/alpelisib matching-placebo.

For additional details on the safety profile of alpelisib, please refer to the [alpelisib (BYL719) Investigator's Brochure].

6.5.2 Follow-up for toxicities

All participants must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment (alpelisib).

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or a clinically significant laboratory value must be followed until resolution or stabilization of the event, whichever comes first. Further guidelines and recommendations for the management of specific study treatment induced toxicities are provided below.

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with an increase of total bilirubin (TBIL) may be indicative of potential DILI, these cases should be considered as clinically important events.

In general, any increase of serum aminotransferases to > 3 x ULN should be followed by repeat testing within 48 to 72 hours.

If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and TBIL value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN (For participants with Gilbert syndrome: doubling of direct bilirubin)
- For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in participants without bone pathology, or elevation of ALP liver fraction in participants with bone pathology.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or alkaline phosphatase (ALP) elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these participants should be immediately discontinued from study treatment, and repeat Liver function test (LFT) testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

Upon presentation

- Obtain PK sample to determine exposure to study drug and metabolites.
- Perform comprehensive medical history including cardiac disease, blood transfusions, i.v. drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc.

- History of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.
- Exclude other causes of liver disease.

Participant monitoring:

- Repeat liver chemistry tests within 48-72 hours.
- Retest frequency can decrease to weekly or less if abnormalities stabilize, drug has been discontinued, and the participant is asymptomatic.

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed (see Table 6-24). Liver biopsy has limited value in the diagnosis of DILI as histopathological findings in DILI can resemble many other liver conditions. However, biopsy can be useful to establish an alternative diagnosis especially if other tests are inconclusive.

Table 6-24 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	Immunoglobulin M (IgM) anti-HAV; Hepatitis B virus surface antigen (HBsAg), IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, gammaGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, Endoscopic Retrograde Cholangiopancreatography (ERCP) as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as “probable” i.e., > 50% likely, if it appears greater than all other causes combined.

All cases confirmed on repeat testing that meet the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as “medically significant” and thus, meet the definition of SAE and should be reported as a SAE using the term “potential treatment-induced liver injury.” All events should be followed up with the outcome clearly documented.

6.5.2.2 Management of pneumonitis

Alpelisib is associated with pneumonitis/interstitial lung disease.

Closely monitor all participants for signs and symptoms of pneumonitis.

All participants will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities).

Participants who are suspected to have developed pneumonitis should interrupt study treatment immediately and undergo appropriate imaging (high resolution CT scan); broncho-alveolar lavage (BAL) and biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which generally includes treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment.

After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with alpelisib/placebo and promptly initiate appropriate treatment and supportive measures.

6.5.2.3 Guidelines for the treatment of alpelisib induced skin toxicity

Skin toxicity is a class-effect observed with PI3K inhibitors.

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of starting treatment and is reversible with adequate concomitant medications and alpelisib treatment interruption/reduction, if needed. Skin reactions may improve over several weeks. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity at any grade, and mandated if a severe cutaneous reaction like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis or Erythema multiforme is suspected.

Workup for skin toxicities includes skin photography, a complete blood count with differential, and a full chemistry panel. A paired skin biopsy may be obtained as clinically indicated (from both affected and an unaffected skin area) for local histopathology assessment to further assess the skin toxicity, especially to confirm suspected diagnosis of any severe cutaneous reactions. In case of Grade 3/4 skin toxicity or any grade of severe cutaneous reactions, Novartis recommends that photographs are taken and a skin biopsy is performed as clinically indicated and assessed locally.

At the Investigator's discretion, non-sedating antihistamines (e.g., cetirizine (Zyrtec©), fexofenadine (Allegra), loratadine (Claritin) may be used as prophylactic treatment to reduce severity of rash, especially for participants with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis or drug allergies.

Recommended therapies for skin toxicity events include:

- Topical steroids Triamcinolone or Betamethasone 3-4 times daily for at least 28 days. Consider spray, lotion, or cream preparation for ease of application on trunk. For scalp involvement, consider a foam preparation. Ensure that at least 240 g are dispensed.
- GABA analogs: Gabapentin 300mg every 8 hours, Pregabalin 50-75 mg every 8 hours (adjust as tolerated). Please refer to the local labels and apply local standards of care as

needed to optimize treatment for skin toxicity. Depending on participant's clinical condition be aware of potential and common adverse effects observed with GABA agonists such as: somnolence, dizziness and peripheral edema among others adverse events.

For grade 4 skin events, alpelisib/placebo treatment must be permanently discontinued without any re-challenge.

Dry skin has been reported. It is recommended that participants with dry skin use mild and fragrance free soaps and detergents.

Although preclinical experiments demonstrated that alpelisib has no potential phototoxic effect, it is recommended to caution participants to avoid sun exposure during treatment with alpelisib, especially when they already have experienced rash or other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Participants should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

6.5.2.4 Guidelines for the treatment of alpelisib-induced hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy et al 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Participants with pre-diabetes (i.e., FPG ≥100 mg/dl or ≥5.6 mmol/L; HbA1c ≥ 5.7%) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in FPG while on alpelisib/placebo treatment. However, even participants with FPG within normal limits at screening may develop alpelisib-induced hyperglycemia. Participants should always be instructed to follow dietary guidelines provided by the American Diabetes Association (ADA) or European Association for the Study of Diabetes (EASD), e.g., small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal and exercise, as appropriate.

Detailed guidelines for the management of alpelisib induced hyperglycemia are provided in Table 6-16.

This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID. Local standard clinical practice may be followed. Fasting plasma glucose may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. Special attention should be paid to the risk of hypoglycemia in participants interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas. Due to the short half-life of alpelisib, all glucose lowering medications should be discontinued when alpelisib is stopped. Consultation with a diabetologist is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

6.5.2.5 Follow-up on amylase or lipase elevation (CTCAE Grade 3)

Participants with amylase or lipase elevation ≥ CTCAE Grade 3 must be tested weekly (or more frequently if clinically indicated) until values return to ≤ Grade 1. After resumption of dosing,

continue to test weekly for one additional cycle. If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle.

An exception to these follow-up guidelines will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. In such cases, total amylase and fractionated amylase should be monitored weekly (or more frequently if clinically indicated) for 4 weeks. If pancreatic amylase remains ≤ Grade 1, subsequent monitoring must be performed at least every 4 weeks (or more frequently if clinically indicated).

Participants who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold study treatment, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

Please also refer to Table 6-23: Criteria for interruption or re-initiation of alpelisib treatment.

6.5.2.6 Guidelines for hypersensitivity

Alpelisib is associated with hypersensitivity reactions, including anaphylaxis. These are manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever or tachycardia. Alpelisib/placebo should be permanently discontinued and should not be re-introduced in participants with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The Investigator must promote compliance for alpelisib/placebo by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or study personnel using pill counts and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

PK parameters (measures of treatment exposure) will be determined in participants treated with alpelisib, as detailed in Section 8.5.2.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is absolutely necessary to treat the participant safely. Most often, study treatment discontinuation without knowledge of the possible treatment assignments is generally sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she

must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The Investigator will provide:

- protocol number
- name (if available)
- participant number

In addition, the Investigator will inform the participant how to contact his/her backup in cases of emergency when he/she is unavailable.

Study treatment must be discontinued once emergency unblinding has occurred. If a participant is unblinded, he/she must be discontinued from the study.

6.7 Preparation and dispensation

Participants will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit (see Table 6-25). Participants will receive alpelisib/placebo on an outpatient basis.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of Investigational Medicinal Product (IMP) directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment without performing an on-site visit. The on-site visit would be replaced with a remote/virtual assessment. Implementation will need to be discussed with Novartis. The dispatch of IMP (alpelisib/placebo) from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 4 weeks supply for the first year of treatment or every 24 weeks during subsequent visits after Week 48. In this case, regular phone calls or virtual contacts (at the time of every scheduled visit or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

The Investigator or responsible site personnel must instruct the participant or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the participant by authorized site personnel only. All dosages prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to the dose. Responsible site personnel will identify the study treatment package(s) to dispense to the participant by using the IRT and obtaining the medication number(s). Site personnel will add the participant number on the label. Immediately

before dispensing the package to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that participant's unique participant number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the participant.

Table 6-25 Preparation and dispensation

Study treatment	Dispensing	Preparation
Alpelisib	For Groups 1, 2, 4 and 5 participants, the FCT in bottles (50 mg, 125 mg, 200 mg) are dispensed by study personnel on an outpatient basis and oral instruction on dose administration will be provided by the Investigator or responsible site personnel. Participants (or parents or caregivers) will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit. For Group 3, granules in sachets applicable for 20 mg and 50 mg dose are dispensed by study personnel on an outpatient basis and oral instruction on dose administration will be provided by the Investigator or responsible site personnel. Participants (or parents or caregivers) will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	In participants with swallowing dysfunction (including pediatric participants who are unable to swallow), alpelisib FCTs can be administered as drinkable suspension by crushing the tablets under water with a spoon. The drinkable suspension prepared from the film-coated crushed tablets must not be administered through feeding tubes. Procedure **for alpelisib oral suspension using FCT**: Place alpelisib tablets in a glass containing 50 -150 ml of still water and let the mixture stand for 5 minutes, then stir and crush the tablets with the help of a spoon until a suspension is obtained. Gently stir the suspension with the spoon and drink the full amount immediately after stirring. Discard the oral suspension if it is not administered within 60 minutes after preparation. If any solid residue remains visible, add approximately 20– 50 ml of still water to the same cup, stir with the same spoon to resuspend any remaining residue and administer the entire contents of the cup. Repeat the procedure if necessary. Beverages other than still water should not be used to make the suspension. Procedure for alpelisib oral granules: 20 mg, 2 x 20 mg and 50 mg sachets can be poured directly onto the tongue and swallowed with 60-120 mL of water, or mixed with 1 – 3 teaspoon of water, milk, apple juice, applesauce or yogurt followed by a 40 mL rinse. Infants can be dosed with an oral syringe, but not a bottle due to particulates in the suspension. Once mixed with a food vehicle, granules should be consumed within 2 hours. Administration of granules through feeding tubes (sizes 8 Fr (length 125 cm to 160 cm) to 12 Fr (length 125 cm) for nasogastric tubes consisting of silicone or polyurethane, and 12 Fr to 24 Fr for gastric tube consisting of silicone) is allowed.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the

instructions specified on the labels and in the latest version of [Alpelisib (BYL719) Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the study. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

Document destruction of unused study treatment, drug labels and packaging is allowed as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines.

Otherwise, at the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.7.1.2 Handling of additional treatment

No other treatment beyond investigational drug is included in this study (Section 6.1.2)

6.7.2 Instruction for prescribing and taking study treatment

Dosing and treatment schedule will be performed according to Section 6.1.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.7.2.1 Alpelisib/placebo administration

The Investigator or responsible site personnel should instruct the participant to take the study drugs as per protocol (promote compliance). Drug accountability must be performed on a regular basis. Participants will be instructed to return unused study drugs to the site monthly. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the participant with the correct amount of drugs for subsequent dosing.

Participant should be instructed to take the dose of alpelisib once daily at approximately the same time each day immediately after food (preferably in the morning after breakfast), except on the days blood collection is scheduled at the clinic, at which time the participants should take their doses at the clinic at any later point of time (please refer to Section 6.7.2.2).

Alpelisib/placebo must be taken immediately after a meal or snack, any type of food is acceptable. If, for any reason, a breakfast (or other meal) was not consumed, then the participant should take study treatment with a glass of still water immediately after a snack. If this happens on days of PK sampling, it should be documented in the eCRF.

Alpelisib granules can be poured directly onto the participant's tongue and swallowed with a glass of water or mixed with another vehicle (Table 6-25). Please refer to Appendix 7 for details on administration of study drug granules.

Alpelisib/placebo FCT should be taken with a glass of an appropriate 150 ml volume of still water. Refer to preparation details in Table 6-25. Alpelisib/placebo FCT should be swallowed whole (tablets should not be chewed, or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested. In participants with swallowing dysfunction (including pediatric participants who are unable to swallow), alpelisib/placebo FCT can be administered as drinkable suspension by crushing the tablets under water with a spoon. Administration of FCT or granules by mouth or through feeding tubes (sizes 8 Fr (length 125 cm to 160 cm) to 12 Fr (length 125 cm) for nasogastric tubes consisting of silicone or polyurethane, and 12 Fr to 24 Fr for gastric tube consisting of silicone) is allowed for Group 3 only. A minimum dispersion volume of 40 mL should be used. When using feeding tubes, co-administration with medium caloric food is recommended to reduce the risk for hyperglycemia.

If a dose of alpelisib/placebo is missed, it can be taken immediately after food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, alpelisib should be taken at its usual time. If the participant vomits after taking the alpelisib/placebo dose, the participant should not take an additional dose on that day and should resume the usual dosing schedule the next day, at the usual time. Vomiting during a treatment must be reported in the adverse events section of the eCRF.

During the treatment phase, the participant or caregiver/legal guardian should record if the dose was taken or not in the alpelisib/placebo participant dosing diary.

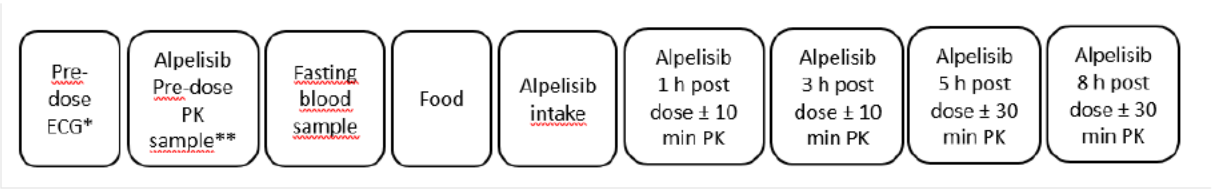
6.7.2.2 Additional dosing guidelines for scheduled visit days

On days when pre-dose fasting safety samples are collected as described in Table 8-2 and Table 8-3 and Section 8.5, participants should be instructed to arrive at the site in fasted state. The following additional guidelines should be followed:

- On scheduled visit days, participants must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days participants will take alpelisib at home
- The participants must take alpelisib immediately after food
- ECG measurement should always occur before dosing of alpelisib
- If a pre-dose PK sample should be obtained, then the sample should be collected after the ECG and before dosing of alpelisib
- Pre-dose PK samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the eCRF. Furthermore, the date and time of alpelisib dose on the day before the PK assessment must be precisely recorded in the eCRF
- Post-dose PK samples should be collected after dosing of alpelisib
- ECG and PK sample collection will be performed according to Section 8.4.2 and Section 8.5.2

Please refer to Figure 6-1 for the study drug administration on scheduled visit days.

Figure 6-1 Study drug administration on scheduled visit days



*Please refer to local ECG collection plan in Section 8.4.2
**Please refer to PK Blood collection logs in Section 8.5.2.1

7 Informed consent procedures

Eligible participants may only be included in the study after participant, parents or caregivers provide written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)-approved informed consent/assent.

If possible, in cases where the participant's representative gives consent, the participant should be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study -specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to Investigators, in a separate document, a proposed informed consent form (ICF) and assent form that is considered appropriate for this study and complies with the ICH E6 GCP guideline and regulatory requirements. Any changes to this ICF or the assent form as suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC/REB.

Information about common adverse effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) and/or prescribing information for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Female of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information and agree that in order to participate in the study, they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval. Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

A participant can be re-screened, for more details please refer to Section 6.3.1.

As per Section 4.6, during a public health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant or their legally authorized representative and person obtaining informed consent, etc).

In case Home Nursing is implemented during the COVID-19 pandemic or for monitoring of FPG (in the Netherlands only), a separate Home Nursing consent document must be implemented in addition to the main ICF.

8 Visit schedule and assessments

Assessment schedule Table 8-2 and Table 8-3 lists all of the assessments when they are performed. An "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. An "S", the assessments that are in the participant's source documentation only and do not need to be recorded in the clinical database.

All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2 and Table 8-3) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue from study treatment are requested to return for the end of treatment visit as soon as possible, and attend the Safety follow-up visit as indicated in the Assessment Schedule. Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree as soon as possible, at which time all of the assessments listed for the end of treatment visit will be performed. At this visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. Phone calls, virtual contacts (e.g. teleconsultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home if allowable by a local health authority and depending on operational capabilities, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are

qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

During the course of the study, test procedures should occur on schedule whenever possible as per allowable visit windows specified in Table 8-1 below.

Table 8-1 Allowable visit windows

All assessments during treatment (other than MRI and digital photos for disease and response evaluation)	+/- 7 days (during Year 1 until visit Week 48 included/ Core Period and Extension 1); +/- 14 days (Starting from visit Week 48 excluded/Extension period 2)
PK sampling	Please refer to Table 8-11, Table 8-12, Table 8-13 and Table 8-14 in Section 8.5.2.1
Disease assessment	MRI/digital photos Screening: -42 to -1 days; Weeks 16, 24, 40: +/- 7 days; Week 48: -7/+30 days; Weeks 72, 96 (+/-30 days); Starting from visit Week 48 excluded/Extension period 2): -/+ 30 days
End of treatment	< 14 days after permanent discontinuation of study treatment
End of Study (30 days post-treatment safety follow-up visit)	+/- 3 days

Table 8-2 Assessment Schedule (≥ 2 years of age)

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Informed consent	X																								
IRT registration	S																								
IRT randomization (except Groups 3, 4 and 5)			X																						
Demography	X																								
Inclusion / Exclusion criteria		X																							
Eligibility Checklist (within IRT)			S																						
Prior PROS disease history; Prior PROS therapies; Prior PROS surgeries	X																								
Medical history/current	X																								

Period	**Screening**		**Core / Exploratory (Treatment)**										**Extension 1 / Exploratory (Treatment)**						**Extension 2 / Exploratory (Treatment)**						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
medical conditions																									
Prior medications	X																								
Non-drug therapies / Surgical and medical procedures	X		Continuous up to 30 days after the last dose of study treatment																						
Concomitant medications	X		Continuous up to 30 days after the last dose of study treatment																						
Subject disposition	X		X																						
Performance Status (Karnofsky (in patients > 16 years old / Lansky ≤ 16 years old)		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Height		X	X[1]					X[1]		X[1]		X[1]			X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Body Weight		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		S[11]	S					S[11]				S[11]			S[11]			S[11]	S[11]	S[11]	S[11]	S[11]	S[11]	S[11]	S[11]

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Hematology		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Plasma Glucose (central)		X	X	X	X[10]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1C		X						X				X			X			X	X	X	X	X	X	X	X
Coagulation Panel (INR, PTT, APTT)		X						X[2]				X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
[redacted]																									
Hepatitis Screen		X	as clinically indicated																						
Urine pregnancy test (local)						S	S	S		S	S	S	S	S	S	S	S	S	Monthly[15] (S)						
Serum pregnancy test (central)		X	S[12]																						
Whole-body MRI, Digital photography of PROS related	X								X			X				X		X	X	X		X		X	

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
lesions for Groups 1 and 2																									
Overall clinical response assessment for Groups 1 and 2									X			X				X		X	X	X		X		X	
Whole-body MRI, Digital photography of PROS related lesions for Group 4	X											X						X	X	X		X		X	
Overall clinical response assessment for Group 4												X						X	X	X		X		X	
Whole-body MRI, Digital photography of PROS related lesions for Group 5	X								X			X						X	X	X		X		X	
Overall clinical response assessment for Group 5									X			X						X	X	X		X		X	

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Electrocardiogram (ECG)		X	X			X	X	X	X			X			X	X		X	X	X	X	X	X	X	X
Echocardiography		X							X[2]			X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Spirometry[4] for Groups 1, 2 and 5		X							X[2]			X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Walking distance test[13] (except Groups 3 and 4)		X				X[2]	X[2]		X[2]			X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Archival tissue for central PIK3CA mutation testing or fresh biopsy [5]	X																								
PROMIS profile			X			X			X		X	X	X	X		X		X	X	X	X	X	X	X	X
Patient Global Impression of Symptom Severity			X	X		X	X		X		X	X	X	X		X		X	X	X	X	X	X	X	X

Period	**Screening**		**Core / Exploratory (Treatment)**										**Extension 1 / Exploratory (Treatment)**						**Extension 2 / Exploratory (Treatment)**						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Patient Reported Outcome Diary		Start at screening and continuous daily until week 16[6]									Daily					X		X	X	X	X	X	X	X	X
[redacted]																									
Trial Feedback Questionnaire			S															S							
Adverse Events	X		Continuous up to 30 days after the last dose of study treatment																						
Dental assessment (<18 years old)	X											X						X	X	X	X	X	X	X	X
Hospitalizations for PROS-related reasons	X		Continuous up to 30 days after the last dose of study treatment																						
Bone development assessment (<18 years old)[7]	X[8]											X[9]						X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Assessment of sexual	X											X						X	X	X	X	X	X	X	X

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	**Screening**		**Week 1 - Day 1**	**Week 2 - Day 1**	**Week 3 - Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 17- Day 1**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 72**	**Week 96**	**Week 120**	**Week 144**	**Week 168**	**Week 192**	**Week 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
maturation (Tanner staging 6 to <18 years old)																									
IRT Study Drug Dispensation			S			S	S	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Participant Dosing Diary			Start at D1 and continues until last dose (S)																						
Meal record			See Section 8.5.2 for time points of blood collection for alpelisib PK assessment and Section 6.7.2.1 for more details on meal record																						
Blood sample for Alpelisib PK sampling			See Section 8.5.2 for time points of blood collection for alpelisib PK assessment applicable for Groups 1&2 (Table 8-11), Group 3 (Table 8-12), Group 4 (Table 8-13) and Group 5 (Table 8-14).																						
Alpelisib/Placebo			Daily																						

Period	Extension 2 / Exploratory (Treatment)	End of Study Treatment (Non-Treatment)	Safety Follow up / End of Study
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
Informed consent			
IRT registration			

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
IRT randomization (except Groups 3, 4 and 5)			
Demography			
Inclusion / Exclusion criteria			
Eligibility Checklist (within IRT)			
Prior PROS disease history; Prior PROS therapies; Prior PROS surgeries			
Medical history/current medical conditions			
Prior medications			
Non-drug therapies / Surgical and medical procedures	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Concomitant medications	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Subject disposition	X	X	X
Performance Status (Karnofsky (in patients > 16	X	X	X

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
years old / Lansky ≤ 16 years old)			
Body Height	X[1]	X[1]	X[1]
Body Weight	X	X	X
Vital Signs	X	X	X
Physical Examination	S[11]	S[11]	S[11]
Hematology	X	X	X
Clinical Chemistry	X	X	X
Fasting Plasma Glucose (central)	X	X	X
HbA1C	X	X	X
Coagulation Panel (INR, PTT, APTT)	X[2]	X[2]	
[redacted]			
Hepatitis Screen	as clinically indicated		
Urine pregnancy test (local)	Monthly[15] (S)		
Serum pregnancy test (central)		X[12]	X[12]
Whole-body MRI, Digital photography of PROS related lesions for Groups 1 and 2	X	X	
Overall clinical response	X	X	

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
assessment for Groups 1 and 2			
Whole-body MRI, Digital photography of PROS related lesions for Group 4	X	X	
Overall clinical response assessment for Group 4	X	X	
Whole-body MRI, Digital photography of PROS related lesions for Group 5	X	X	
Overall clinical response assessment for Group 5	X	X	
Electrocardiogram (ECG)	X	X	X
Echocardiography	X[2]	X[2]	
Spirometry[4] for Groups 1, 2 and 5	X[2]	X[2]	
Walking distance test (except Groups 3 and 4)	X[2]	X[2]	
Archival tissue for central PIK3CA			

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
mutation testing or fresh biopsy [5]			
[redacted]			
PROMIS profile	X	X	
Patient Global Impression of Symptom Severity	X	X	
Patient Reported Outcome Diary	X	X	
[redacted]			
Trial Feedback Questionnaire		S	
Adverse Events	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Dental assessment (<18 years old)	X	X	
Hospitalizations for PROS-related reasons	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Bone development assessment (<18 years old) [7]	X[9]	X[9]	
Assessment of sexual maturation (Tanner staging 6 to <18 years old)	X	X	

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
IRT Study Drug Dispensation	S		
Participant Dosing Diary	Start at D1 and continues until last dose (S)		
Meal record	See Section 8.5.2 for time points of blood collection for alpelisib PK assessment and Section 6.7.2.1 for more details on meal record		
Blood sample for Alpelisib PK sampling	See Section 8.5.2 for time points of blood collection for alpelisib PK assessment applicable for Groups 1&2 (Table 8-11), Groups 3 & 4 (Table 8-12 and Table 8-13) and Group 5 (Table 8-14)		
Alpelisib/Placebo	Daily		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor.
[1] <18 yrs only.
[2] Only if impairment associated with PROS identified at screening.
[3] Only if PROS-related clinically meaningful alteration at screening.
[4] Pulmonary Function Test; Spirometry will not be performed in Groups 3 and 4.
[5] If archival block or slides is not available, a fresh biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated. For participants in Groups 3 and 4, a fresh tissue biopsy is not mandatory.

[redacted]

For Germany only: If archival tissue is available, it must be sent to a Novartis-designated central laboratory. If no archival tissue is available, obtaining a fresh tissue biopsy is recommended, if it is not clinically contraindicated, but is not mandatory.

[6] Starting 7 days prior to the first dose of study treatment.
[7] Includes assessment of growth plate abnormalities (knee) and skeletal bone age (wrist, hand).
[8] Either X-rays or MRIs of knee, wrist, hand should be performed at screening.
[9] Bone development assessments are required per scheduled protocol timepoints. If there is evidence of thickening or changes in the growth plate at screening, then further assessment of bone development should be based on x-rays, as clinically indicated. X-rays can be replaced by MRIs according to institutional standard or if there is any clinical contraindication for further assessment of bone development after screening.
[10] Test may be done locally and results of the local laboratory are to be recorded in the eCRF.

Period	Extension 2 / Exploratory (Treatment)	End of Study Treatment (Non-Treatment)	Safety Follow up / End of Study
Visit Name	Week 240	Week 264/End of Study Treatment	Safety Follow up
Days	1680	1848	Last dose +30

[11] Physical Examination findings for extremities examined are to be recorded in the eCRF.

[12] May be replaced by urine test done locally if participants cannot have a serum pregnancy test done during a public health emergency as declared by Local or Regional authorities.

[13] Walking distance test will not be performed in Groups 3 and 4.

[redacted]

[15] Monthly home pregnancy test are allowed

Table 8-3 Assessment schedule (less than 2 years of age)

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	Screening		Wk 1 - Day 1	Wk 2 - Day 1	Wk 3 - Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 17- Day 1	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 72	Wk 96	Wk 120	Wk 144	Wk 168	Wk 192	Wk 216
Days	-42 to -1	-28 to -1	1	8	15	28	56	84	112	113	140	168	196	224	252	280	308	336	504	672	840	1008	1176	1344	1512
Informed consent	X																								
IRT registration	S																								
Demography	X																								
Inclusion / Exclusion criteria		X																							
Eligibility Checklist (within IRT)			S																						
Prior PROS disease history;	X																								

Period	**Screening**		**Core / Exploratory (Treatment)**										**Extension 1 / Exploratory (Treatment)**						**Extension 2 / Exploratory (Treatment)**						
Visit Name	**Screening**		**Wk 1 - Day 1**	**Wk 2 - Day 1**	**Wk 3 - Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 17- Day 1**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 72**	**Wk 96**	**Wk 120**	**Wk 144**	**Wk 168**	**Wk 192**	**Wk 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Prior PROS therapies; Prior PROS surgeries																									
Medical history/current medical conditions	X																								
Prior medications	X																								
Non-drug therapies / Surgical and medical procedures	X		Continuous up to 30 days after the last dose of study treatment																						
Concomitant medications	X		Continuous up to 30 days after the last dose of study treatment																						
Subject disposition	X		X																						
Performance Status (Lansky ≤ 16 years old)		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Length and head circumference		X	X					X		X		X			X			X	X	X	X	X	X	X	X
Body Weight		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		S[9]	S					S[9]				S[9]			S[9]			S[9]	S[9]	S[9]	S[9]	S[9]	S[9]	S[9]	S[9]
Hematology		X				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening**		**Core / Exploratory (Treatment)**										**Extension 1 / Exploratory (Treatment)**						**Extension 2 / Exploratory (Treatment)**						
Visit Name	**Screening**		**Wk 1 - Day 1**	**Wk 2 - Day 1**	**Wk 3 - Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 17- Day 1**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 72**	**Wk 96**	**Wk 120**	**Wk 144**	**Wk 168**	**Wk 192**	**Wk 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Clinical Chemistry		X				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Plasma Glucose (central)		X		X	X[8]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1C								X				X			X			X	X	X	X	X	X	X	X
Coagulation Panel (INR, PTT, APTT)		X[1]						X[2]				X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Whole-body MRI, Digital photography of PROS related lesions	X											X						X	X	X		X		X	
Overall clinical response assessment												X						X	X	X		X		X	
Electrocardiogram (ECG)		X	X			X	X	X	X			X			X	X		X	X	X	X	X	X	X	X
Echocardiography		X							X[2]			X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Archival tissue for central PIK3CA mutation testing or fresh biopsy [4]	X																								
PROMIS profile			X			X			X		X	X	X	X		X		X	X	X	X	X	X	X	X

Period	**Screening**		**Core / Exploratory (Treatment)**										**Extension 1 / Exploratory (Treatment)**						**Extension 2 / Exploratory (Treatment)**						
Visit Name	**Screening**		**Wk 1 - Day 1**	**Wk 2 - Day 1**	**Wk 3 - Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 17- Day 1**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 72**	**Wk 96**	**Wk 120**	**Wk 144**	**Wk 168**	**Wk 192**	**Wk 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Patient Global Impression of Symptom Severity			X	X		X	X		X		X	X	X	X		X		X	X	X	X	X	X	X	X
[redacted]																									
Trial Feedback Questionnaire			S																	S					
Adverse Events	X		Continuous up to 30 days after the last dose of study treatment																						
Dental assessment (<18 years old)	X											X						X	X	X	X	X	X	X	X
Hospitalizations for PROS-related reasons	X		Continuous up to 30 days after the last dose of study treatment																						
Bone development assessment (<18 years old) [5]	X[6]											X[7]						X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
IRT Study Drug Dispensation			S			S	S	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Participant Dosing Diary			Start at D1 and continues until last dose (S)																						
Meal record			See Section 8.5.2 for time points of blood collection for alpelisib PK assessment and Section 6.7.2.1 for more details on meal record																						

Period	Screening		Core / Exploratory (Treatment)										Extension 1 / Exploratory (Treatment)						Extension 2 / Exploratory (Treatment)						
Visit Name	**Screening**		**Wk 1 - Day 1**	**Wk 2 - Day 1**	**Wk 3 - Day 1**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 17- Day 1**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 72**	**Wk 96**	**Wk 120**	**Wk 144**	**Wk 168**	**Wk 192**	**Wk 216**
Days	**-42 to -1**	**-28 to -1**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**113**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**504**	**672**	**840**	**1008**	**1176**	**1344**	**1512**
Blood sample for Alpelisib PK sampling			See Section 8.5.2 for time points of blood collection for alpelisib PK assessment applicable for Group 3 (Table 8-12)																						
Alpelisib			Every other day or Daily																						

Period	Extension 2 / Exploratory (Treatment)	End of Study Treatment (Non-Treatment)	Safety Follow up / End of Study
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
Informed consent			
IRT registration			
Demography			
Inclusion / Exclusion criteria			
Eligibility Checklist (within IRT)			
Prior PROS disease history; Prior PROS therapies; Prior PROS surgeries			
Medical history/current medical conditions			
Prior medications			
Non-drug therapies / Surgical and medical procedures	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
Concomitant medications	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Subject disposition	X	X	X
Performance Status (Lansky ≤ 16 years old)	X	X	X
Body Length and head circumference	X	X	X
Body Weight	X	X	X
Vital Signs	X	X	X
Physical Examination	S[9]	S[9]	S[9]
Hematology	X	X	X
Clinical Chemistry[1]	X	X	X
Fasting Plasma Glucose (central)[1]	X	X	X
HbA1C	X	X	X
Coagulation Panel (INR, PTT, APTT)	X[2]	X[2]	
D-dimer and fibrinogen[1]	X[3]	X[3]	
Whole-body MRI, Digital photography of PROS related lesions	X	X	
Overall clinical response assessment	X	X	
Electrocardiogram (ECG)	X	X	X
Echocardiography	X[2]	X[2]	
Archival tissue for central PIK3CA			

Period	**Extension 2 / Exploratory (Treatment)**	**End of Study Treatment (Non-Treatment)**	**Safety Follow up / End of Study**
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
mutation testing or fresh biopsy [4]			
[redacted]			
PROMIS profile	X	X	
Patient Global Impression of Symptom Severity	X	X	
[redacted]			
Trial Feedback Questionnaire		S	
Adverse Events	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Dental assessment (<18 years old)	X	X	
Hospitalizations for PROS-related reasons	Continuous up to 30 days after the last dose of study treatment	X	Continuous up to 30 days after the last dose of study treatment
Bone development assessment (<18 years old) [5]	X[7]	X[7]	
IRT Study Drug Dispensation	S		
Participant Dosing Diary	Start at D1 and continues until last dose (S)		
Meal record	See Section 8.5.2 for time points of blood collection for alpelisib PK assessment and Section 6.7.2.1 for more details on meal record		

Period	Extension 2 / Exploratory (Treatment)	End of Study Treatment (Non-Treatment)	Safety Follow up / End of Study
Visit Name	**Week 240**	**Week 264/End of Study Treatment**	**Safety Follow up**
Days	**1680**	**1848**	**Last dose +30**
Blood sample for Alpelisib PK sampling	See Section 8.5.2 for time points of blood collection for alpelisib PK assessment applicable for Group 3 (Table 8-12)		
Alpelisib	Every other day or Daily		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor.

[1] Coagulation assessment are ONLY required at screening in case of history of coagulopathy.

[2] Only if impairment associated with PROS identified at screening. Coagulation panel should not be assessed on the same day as hematology (including HbA1C) and chemistry panels.

[3] Only if PROS-related clinically meaningful alteration at screening. [redacted]

[4] Fresh tissue biopsy not mandatory for participants in Groups 3.

[redacted]

For Germany only: If archival tissue is available, it must be sent to a Novartis-designated central laboratory. If no archival tissue is available, obtaining a fresh tissue biopsy is recommended, if it is not clinically contraindicated, but is not mandatory.

[5] Includes assessment of growth plate abnormalities (knee) and skeletal bone age (wrist, hand).

[6] Either X-rays or MRIs of knee, wrist, hand should be performed at screening.

[7] Bone development assessments are required per scheduled protocol timepoints. If there is evidence of thickening or changes in the growth plate at screening, then further assessment of bone development should be based on x-rays, as clinically indicated. X-rays can be replaced by MRIs according to institutional standard or if there is any clinical contraindication for further assessment of bone development after screening.

[8] Test may be done locally and results of the local laboratory are to be recorded in the eCRF.

[9] Physical Examination findings for extremities examined are to be recorded in the eCRF.

8.1 Screening

Participants diagnosed with PROS will be consented to the study prior to any study procedures being performed. If the participant has been previously treated with systemic PROS-targeting therapy, the participant should be discontinued from this treatment before study-related disease evaluations at screening (see Section 6.2.2).

Screening period will begin once the participant has signed the study Informed Consent and will be a maximum of 42 days (Day -42 to Day -1).

Whole-body MRI and other images (e.g., digital photography) will be collected and sent to BIRC for review. The Investigators should put all efforts to perform images as early as possible during screening. Transfer of images and submission of supplemental clinical information should occur as early as Day -42 and no later than Day -15.

Technical aspects on imaging are provided in the Vendor Site Manual.

For participants who may have had procedures previously performed as part of the participant's routine disease care (prior to signing study informed consent), the following procedures can be used providing that the procedure fulfill the protocol mandated requirements and a proper documentation in participant's file is available:

- Any imaging assessments within 42 days of start of treatment
- For eligibility purpose,
  - local laboratory report confirming PIK3CA mutation(s) will be used. The Investigator should ensure, that the report from the local laboratory is available and maintained in the participant's source documents. PIK3CA mutation(s) confirmation is required at time of inform consent. The participant will be randomized based on local laboratory results, a confirmation of PIK3CA mutation(s) by the central laboratory is not required.
  - Archival tissue (refer to Table 8-15 in Section 8.5.3.1 for the number of slides required) must be provided to be sent to the central laboratory for testing of PIK3CA mutations. It is strongly recommended to provide a tissue sample and/or slides in which the initial PIK3CA determination was made by the local laboratory, when an archival tissue sample is not available, a fresh biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated, and tissue to be sent to the central laboratory. For participants in Groups 3 and 4, if no archival tissue is available, a fresh tissue biopsy is not mandatory.

    [redacted]

    For Germany only: If no archival tissue is available, obtaining a fresh tissue biopsy is recommended, if it is not clinically contraindicated, but is not mandatory.

    Details are provided in the Laboratory Manual.

The written informed consent must be obtained prior to the performance of any screening evaluations. Screening procedures are outlined in the visit evaluation schedule (Table 8-2 and Table 8-3) including blood samples tested as needed, and assessment of inclusion and exclusion criteria.

The Investigator or his/her designee must review the results of all screening evaluations, to ensure that all inclusion and exclusion criteria have been satisfied prior to enrollment of the participant into the study.

All study procedures should be performed within 42 days (or within 28 days) before treatment initiation on Day 1. Screening laboratory assessments may be performed within 28 days of treatment initiation, Central Laboratory will be used. When screening laboratory assessments are performed within 7 days of treatment initiation, they will not be repeated at Week 1 Day 1.

A participant who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These tests may be repeated as soon as the Investigator believes the retest result is likely to be within the acceptable range to satisfy the entrance criteria, and can be completed within the 28 days screening period. In this case, the participant will not be required to sign another ICF, and the original participant ID assigned by the Investigator will be used.

All baseline assessments should be performed on Day 1 as per Table 8-2 and Table 8-3. Laboratory assessments performed within 7 days of Day 1 are not required to be repeated at Week 1 Day 1.

A participant is considered a screen failure in the event that the laboratory test(s) cannot be available within the screening period, or the retest(s) do not meet the entry criteria or the participant's medical condition has changed significantly during the screening period so that the inclusion/exclusion criteria are no longer met (more details are outlined in Section 5).

Laboratory results from the central laboratory are the only one to be used to determine participant's eligibility to the study with the exception of local PIK3CA results.

A new study ICF will need to be signed if the Investigator chooses to re-screen the participant after a participant has screen failed and a new participant ID will be assigned. All required screening activities must be performed when the participant is rescreened for participation in the study. An individual participant may only be rescreened once for the study.

Participants from Groups 1 and 2 meeting all inclusion and none of exclusion criteria will be randomized to receive either alpelisib or placebo. Participants from Groups 3, 4, and 5 meeting all inclusion and none of exclusion criteria will be enrolled to receive alpelisib treatment in an open-label fashion.

8.1.1 Eligibility screening

Following IRT registration at screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. The eligibility checklist form must be completed in IRT by the Investigator or designee on Day 1 prior to starting the treatment phase and receiving the first dose of study drug. Verification of all eligibility criteria must be done prior to contacting IRT. After the eligibility has been checked in IRT and confirmed that the participant is eligible for the study, then the participant can be assigned to a dose based on age and enrolled/randomized into the treatment phase of the study.

Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign the informed consent form and subsequently are found to be ineligible will be considered a screen failure.

The reason for screen failure should be recorded on the Disposition CRF page. The demographic information, informed consent, and inclusion/exclusion and Disposition pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 8.4).

If the participant fails to be randomized/start treatment, the IRT must be notified within 2 days of the screen fail, that the participant was not randomized/enrolled in the treatment phase. Data and samples collected from participants prior to screen failure may still be analyzed. Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristics data will be collected on all enrolled participants:

- Demography (gender, age, race and ethnicity as allowed by local regulations, height [or length and head circumference for 0-2 years of age] and weight). Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.
- Disease baseline characteristics including diagnosis, anatomic and functional extent of disease, prior PROS history (including clinical manifestation of PROS, disease extent and PROS related functional impairment), prior PROS therapies and previous/ foreseen surgical and/or other interventions.
- Medical History other than PROS; Current medical conditions present before signing the informed consent. Investigators will have the discretion to record clinically significant laboratory abnormalities on the appropriate eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.
- Prior/concomitant therapy.
- Availability of archival tissue for central testing of PIK3CA mutations. When archival tissue sample is not available, a fresh biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated. For participants in Groups 3 and 4, a fresh tissue biopsy is not mandatory (See details in Section 8.5.3).
- Clinical Outcome Assessments including participant-reported outcome questionnaires (see Section 8.5.1).

Furthermore, the following assessments will be performed to assess the eligibility of the participant:

- Vital signs including body temperature, blood pressure and pulse
- Karnofsky or Lansky performance status

- ECG (12 lead, in triplicate)
- Cardiac imaging (echocardiography)
- Lung function test (spirometry) (not applicable for Groups 3 and 4 and replaced by chest MRI images)
- Disease evaluation (anatomic and functional extent of the disease)
- Laboratory evaluations
- Complete physical examination (including neurologic assessment of central and peripheral nervous systems as per local standards, as well as assessment of functioning of extremities)

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

The phenotypic variability of PROS is broad in terms of the overgrowth localization, number of lesions and affected limb/trunkal sites, disease progression, and severity of the impact on the participant everyday life, mobility, organ function and quality of life. Standard criteria for response assessment are not yet established. Primary efficacy in the study will be determined based on radiological response of PROS lesions assessed by BIRC.

Definition of target and non-target lesions

Target lesion is defined as anatomically reproducibly defined tissue(s) masses, which may be composed of one or several tissue types, and can be accurately measured by imaging technique MRI. Target lesion(s) (up to 3) should be identified at screening, be at least 2 cm in the longest diameter at baseline (for each selected lesion) and may be further reproducibly assessed by MRI. All selected target lesions must be associated with at least one of the following: participant's complaints, clinical symptoms, impaired organ function, functional limitations affecting participant's everyday life. Clinically meaningful PROS-related vascular anomalies (for instance, vascular malformations) may qualify for target lesion when they may be accurately measured (by volumetric technique). Macrocephaly must not qualify for target lesion. The volume of these lesions will be measured at each MRI assessment during the study. The same imaging modality must be used throughout the study.

All lesions which do not qualify for target, measurable or not, will be considered non-target, to demonstrate response for anatomic PROS lesions and/or anatomic areas affected by the disease. In addition to MRI, the Investigator may select the other additional appropriate, accurate and informative method(s) to evaluate the response objectively: imaging technique and/or digital photography accompanied with measuring with caliper/ruler when applicable.

Non-target lesions are all other PROS-related anatomic changes (lesions, affected limb/trunkal areas, organomegaly) and may include the following:

MRI-measurable non-target lesions

All anatomic lesions other than selected as target and may be measured at radiologic assessment (at least 2 cm in the longest diameter at baseline, the volume may be further reproducibly assessed by MRI).

Other non-target lesions

Anatomic lesions, limb/trunkal areas affected by PROS, organomegaly when they may be measured only by caliper/ruler (e.g., circumference of changed limb or body part)

Truly non-measurable lesions (e.g., small lesions less than 2 cm on MRI, superficial visual lesions, masses, organomegaly, PROS-related enlargement of anatomic area identified by physical exam that is not measurable by reproducible imaging technique)

Selection of target and non-target lesions at screening:

Whole-body MRI without contrast is mandated at baseline. In addition, focused MRI imaging may be required to adequately assess small anatomic areas with PROS lesions. All images (MRI, digital photography) will be submitted to BIRC and reviewed centrally. Review of the screening MRI will assess and confirm the presence of at least one lesion qualifying for target and this will be communicated to the site before randomization. When the Investigator disagrees on the presence or absence of target lesion, an adjudication process will apply. The adjudicator will make a final decision. (Additional details will be described in the BIRC Charter).

8.3.1 Evaluation of response of PROS lesions

Definitions of response and progression of PROS lesions:

Response of PROS lesions will be determined based on response of target lesion(s) (changes in volume will be assessed by MRI) and non-target lesions (assessed by MRI, digital photography, manual measurements with caliper/ruler, clinical examination of superficial visual lesions including size, thickness, circumference, coloration, other applicable parameters based at the discretion of the Investigator). The same modality must be used throughout the study.

For primary efficacy, the response of PROS lesions will be evaluated by BIRC. It is defined as achieving ≥ 20% reduction from baseline in the sum of target lesion volumes (1 to 3 target lesions, via BIRC) confirmed by a subsequent imaging assessment performed at least 4 weeks after the onset of the response, provided that none of the individual target and/or MRI-measurable non-target lesions has ≥ 20% increase from baseline and in absence of progression of other non-target lesions and without new lesions.

For secondary efficacy in Groups 1 and 2, the response of PROS lesions will be evaluated by BIRC in similar way at Weeks 16, 24, 40, 48, 72, 96 and then every 48 weeks during the study.

For exploratory Group 3, the response of PROS lesions will be evaluated by BIRC in similar way at Weeks 24, 48, 72, 96 and then every 48 weeks during the study.

For exploratory Group 4, the response of PROS lesions will be evaluated by BIRC in similar way at Weeks 24, 48, 72, 96 and then every 48 weeks during the study.

For exploratory Group 5, the response of PROS lesions will be evaluated by BIRC in similar way at Weeks 16, 24, 48, 72, 96 and then every 48 weeks during the study.

If disease progression is suspected for any patients, an MRI must be taken as soon as feasible and within the coming 3 months maximum.

Progression of PROS lesions will be recorded when at least one of the following criteria are met:

- Increase of ≥ 20 % of the volume of target and/or MRI-measurable non-target PROS lesions relative to baseline at any timepoint of efficacy evaluation, otherwise to nadir (defined as best achieved response)
- Progression of other non-target PROS lesions
- Appearance of a new PROS lesion(s) (when the new lesion is at least 1 cm long and clearly attributed to PROS)

Relative to other non-target lesions, response of each of non-target lesion identified at screening will be assessed individually during BIRC review, then the reviewer will make a conclusion if overall level of non-target disease burden decreased or increased meaningfully and evaluate the status of all non-target lesions as improvement, stable, progression.

Evaluation of PROS lesions for response by BIRC:

The Investigators will send all MRI and other images (including but not limited to digital photographs), as well as information about clinical relevance of PROS lesions to BIRC performing central imaging review for the study. Two radiologists at BIRC (each will be a qualified different independent reader from the designated vendor) will perform their own review of images (e.g., MRI, digital photographs) to assess response of PROS lesions (both target and non-target, occurrence of new lesion(s)) throughout the study. In case of disagreement between the two readers, an adjudication will be performed. An adjudicator will review the assessment of both readers and will make a final decision about the evaluation of PROS lesion response. These evaluations will be independent and will be used for the purpose of primary and secondary endpoints.

BIRC evaluations will not be communicated to the Investigator (unless the Investigator suspects progression and specifically request BIRC to confirm the fact of radiologic progression). A process of keeping independence of reviewers will be applied and defined in the BIRC charter.

Evaluation of overall clinical response (by Investigators):

The Investigators will review the MRI and other images (including but not limited to digital photographs), assess the PROS lesion radiological response applying the above response criteria, will review the results from other assessments performed at response evaluation time point, and make their clinical judgement on overall clinical response: if the condition of the participant, in general, has been improved, remained stable, or worsened compared to Baseline assessment. Clinical management of the patients will be based on the Investigator assessment of the radiological response combined with assessment of the participants' general condition.

Improvement will be registered when ALL of the following criteria are met:

- Reduction in PROS lesions (by local review)
- Clinical improvement (by Investigator, clinically relevant improvement in at least one of the following: participant's complains, clinical symptoms, impaired organ function, functional limitations affecting patient's everyday life
- Absence of PROS-related severe or life-threatening complications

Worsening will be registered when at least ONE of the following criteria are met:

- Growth in PROS lesions qualifying for progression (by local review)
- Clinical deterioration (assessed by the Investigator, clinically relevant worsening in at least one of the following: patient's complains, clinical symptoms, impaired organ function, functional limitations affecting participant's everyday life
- PROS-related severe or life-threatening complications (assessed by the Investigator; including but not limited to rescue surgery, bleeding Grade ≥2, thromboembolic event Grade ≥2, uncontrolled severe or life threatening organ dysfunction, other severe medical event, which is, in opinion of the Investigator, certainly caused by progressing PROS)

The overall clinical response will be assessed as stable disease when none of the above are met.

Clinical management of the participants will be based on the Investigator assessment of overall clinical response combining the radiological response as assessed locally and assessment of the participant's general condition. If Investigator suspect a radiological progression of the PROS lesions as defined above at any timepoint of efficacy evaluation, Investigator must require BIRC to confirm the radiological progression in an expedited fashion. If radiological progression is not confirmed by BIRC, the patient should continue study treatment until next PROS lesion assessment if not clinically contra-indicated. If radiological progression is confirmed by BIRC, Investigator will assess the clinical condition of the patient. Progression of the disease corresponds to the worsened condition of the participant per Investigator's assessment of overall clinical response. For more information on treatment beyond progression, please refer to Section 6.1.5.1

Methods of evaluation for PROS lesions

Magnetic Resonance Imaging (MRI):

Whole-body MRI without contrast is proposed to be the primary method for the assessment of the changes in the volumes of the lesions and is mandatory at baseline. Whole-body MRI is also recommended to be performed at all scheduled imaging time points. If this is not feasible, at least the lesions identified at baseline by the Investigator should be captured. Additionally, focused MRI imaging may be required to adequately assess small anatomic areas with PROS lesions. MRI is a precise and sensitive imaging method to detect volumetric changes in different types of tissues, which may be affected by the disease (fibro-fatty, muscular, and/or bony overgrowth). MRI is also the preferable imaging in pediatric participants, as it does not expose to radiation. MRI may also apply to assessment of non-target lesions when the Investigator considers it the most appropriate, informative and accurate method. For small and truly non-measurable PROS lesions, MRI will still be a preferred method of assessment.

Technical aspects on imaging are provided in the Vendor Site Manual.

For Groups 1 and 2, MRI of the whole-body will be performed at screening, at Week 16, 24, 40, 48, 72, 96 and then at other time points of response assessment. For Group 3 and 4, MRI of the whole-body will be performed at screening, at Week 24, 48, 72, 96 and then at other time points of response assessment. For Group 5, MRI of the whole-body will be performed at screening, at Week 16, 24, 48, 72, 96 and then at other time points of response assessment. At the End of treatment, an MRI will also be performed for all participants if not performed within last 8 weeks during Year 1 (until visit Week 48 included), and within last 3 months during Year 2 - Year 5.

At any time during the study, if disease progression is suspected for any participants, an MRI must be taken as soon as feasible and within the coming 3 months maximum.

In addition, in the event of a dose increase for response optimization, an MRI has to be performed after 3 months to assess the benefit of the increased dose and to potentially guide for further optimization.

In the event of a surgery due to PROS lesions, an MRI must be performed, prior to the procedure. No additional MRI is required if an existing MRI was already performed within 4 weeks of the surgical procedure.

PROS lesions, which are defined as non-target (e.g., non-measurable vascular anomalies, skin lesions, superficial visual lesions, enlargement of anatomic area related to PROS spectrum) and may not be assessed by MRI, should be evaluated with the use of digital photography accompanied with measurements by caliper/ruler when applicable.

Digital photography:

Digital photographs will include:

- Images of the whole-body (front, both sides, back)
- Images of the body parts changed due to PROS when applicable
- Images of PROS-related skin/superficial visual lesions and/or other lesions which may not be assessed by MRI

Photographs should be taken by a high resolution digital camera (≥3 megapixels), a caliper or ruler should be included in the photo whenever possible. The photographs will be performed at screening and repeated further at response evaluation time points and at the End of treatment. These digital photographs will be used solely to document the response to study treatment of PROS-related target non-measurable and non-target anatomic lesions changing the body parts as well as response of skin/superficial visual anatomic lesions. These digital photographs should be sent to the central review facility for review and archiving.

The imaging assessment collection plan is presented in Table 8-4.

Table 8-4 Imaging Assessment Collection Plan

Assessment	Screening/Baseline	Treatment
• Whole-body MRI • Digital photography	Mandated within 42 days prior to randomization	For Groups 1 and 2: Mandated, at Week 16, 24, 40 (+/- 7 days);

Assessment	Screening/Baseline	Treatment
• Linear measurement with scale/ruler when applicable		at Week 48 (- 7/+30 days); at Week 72, 96 (+/-30 days);and every 48 weeks (+/- 30 days) thereafter until Week 264 (End of Treatment). For Group 3 and 4: Mandated, at Week 24 (+/- 7 days); at Week 48 (- 7/+30 days); at Week 72, 96 (+/-30 days); and every 48 weeks (+/- 30 days) thereafter until Week 264 (End of Treatment). For Group 5: Mandated, at Week 16, 24 (+/- 7 days); at Week 48 (- 7/+30 days); at Week 72, 96 (+/-30 days); and every 48 weeks (+/- 30 days) thereafter until Week 264 (End of Treatment).

8.3.2 Other assessments for PROS

Assessment of changes in symptoms and complications/comorbidities associated with PROS over time.

Information on complaints, PROS-related symptoms, PROS-related complications (including taken treatment measures) and comorbidities will be collected at baseline and then at every time point for response assessment. In participants with cardiac function, pulmonary function impaired because of PROS, echocardiography (see Section 8.4.2.1) and spirometry (see Section 8.5.5) will be performed as a part of efficacy assessment(s), to demonstrate changes from baseline.

Assessment of the frequency of hospitalizations/surgeries

Information about the frequency of healthcare visits/hospitalizations, surgeries, invasive procedures, interventions due to PROS, surgeries (including type and intent, e.g., rescue surgery, radical surgery) and/or actions other than study treatment required to manage PROS (including avoidance/delay in planned disease-related surgery) will be collected at baseline and then at every time point for response assessment. The Investigators may in addition collect all other information about PROS-related treatment considered medically relevant.

Assessment of mobility and a need to use additional tools to enable mobility

Assessment of mobility will be performed at screening and then for those participants who have PROS-related impairment of mobility after 4 and 8 weeks of initial treatment, and then at efficacy assessment time points. In addition to 2 Min Walking Distance Test, information on the participant need to use additional supporting tools to enable mobility (for instance, walking

stick, moving chair), will be collected when applicable. Walking Distance Test will not be performed in participants in Groups 3 and 4 (less than 6 years old).

8.3.3 Blinded Independent Review Committee (BIRC) assessment

BIRC is set up for this study with the mission to evaluate efficacy data related to PROS lesions response in the study. The central review of the images will be carried out in a blinded fashion. The decision regarding participant management will remain with the Investigators. Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. This CRO has been contracted to provide an independent selection of target and non-target PROS lesions at screening and evaluation of PROS lesions for response in each participant enrolled in this study. The assessment of the presence or absence of a measurable lesion qualifying for target by BIRC will be provided to Investigator during the screening period to confirm PROS lesion-specific eligibility of the patient. The BIRC assessment of PROS lesion response during the study treatment will not be communicated to the Investigator. The only exception will be when the Investigator will require BIRC to confirm a disease progression suspected on the local assessment of the MRI. A process of keeping independence of reviewers will be applied and defined in the charter. The clinical management of the patient will be based on the PROS lesions radiological response assessed by the Investigator (except Core period of the study where progression of the lesions must be confirmed by BIRC for making treatment decision) and the associated clinical manifestations.

Details on the independent central imaging review process will be described in BIRC Charter.

8.3.4 Appropriateness of efficacy assessments

Substantial efforts over the past 20 years were invested in the clinical delineation of mosaic or segmental overgrowth disorders; in particular, preliminary recommendations for a uniform approach to a clinical evaluation of PROS were determined as an outcome of the workshop in Bethesda, Maryland, in September 2013. The clinical diagnostic criteria for PROS will be utilized to assess all spectrum of findings related to the disease at screening in our study (Keppler-Noreuil et al 2016).

The uniformed protocols on PROS disease evaluation, definitions for clinical severity of disease, as well as criteria defining key characteristics of PROS lesions for further evaluation of response, and criteria for response assessment are not established. Disease assessments in routine clinical practice vary depending on participant characteristics, site experience and local practices. Because of these reasons and taking into consideration the high variability of the disease phenotype, methods of efficacy assessments selected for this study are expected to cover all clinically relevant characteristics of the disease.

The primary/key secondary objectives are to demonstrate the efficacy of alpelisib as measured by the proportion of participants with confirmed objective response (primary) and response at Week 16 (key secondary) by BIRC for Group 2 (6 - 17 yr-old) and for Group 1 (≥ 18 yr-old). For details, please refer to Section 2, Table 2-1, Section 8.3, Section 12.

Evaluation of PROS lesions for response will be done by BIRC with the use of MRI and digital photography. MRI will be the primary and preferred method of response evaluation. This highly informative method allows performing volumetric measurements in an accurate, reproducible

and consistent manner. It is acknowledged that it might be difficult to collect the volumes for all existing PROS lesions/areas, digital photographs will be also performed with the purpose to collect information on changes in existing visual PROS lesions and get supporting information about changes in disease burden. When possible, linear measurements will accompany digital photos. All images will be reviewed centrally by a BIRC. Methods of PROS lesions evaluation for response in this study are consistent with published case series and evaluations utilized in other studies in PROS indication.

Overall clinical response will be assessed by the Investigators. They will make the conclusion based on response of PROS anatomic lesions/affected areas assessed locally and their assessment of other clinical parameters in the individual participants as following:

- Changes in PROS-related symptoms and complications/comorbidities based on clinical evaluation, supported by other examinations (e.g., echocardiography to be used in those participants who have at screening LVEF clinically meaningful decreased due to PROS, spirometry to be used when lung function is affected due to PROS)

[redacted]

- Information about type and outcome of hospitalizations for PROS when happens
- Information about type and outcome of surgery to manage PROS when happens

[redacted]

In addition, patient reported outcomes will be assessed with usage of PRO measures with evidence to support their content validity in PROS [Worst Pain Intensity (adapted from BPI and Wong-Baker Faces Scale) as collected with the PRO Diary, PROMIS profile (Patient Reported Outcome Measurement Information System), participant Global Impression of Symptom Severity] [redacted].

The study considers a possibility to individualize the plan of assessments in the individual participants based on existing signs of the disease, after evaluation of disease burden during screening and making a conclusion on clinical relevance of the certain findings. For additional information, and the details please refer to Section 4.1, Section 8.3, Section 8.5.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

Safety will be monitored by assessing physical examination, vital signs, performance status (refer to Table 8-5), ECG,5 cardiac function evaluation by echocardiography/ECHO, laboratory testing (hematology, coagulation, serum chemistry, and urinalysis6) as well as routine safety monitoring of AEs and SAEs. For details on adverse event collection and reporting, refer to Section 10.

CTCAE version 4.03 will be used throughout the study to allow pooling of safety data at the alpelisib program level.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Regular phone or virtual calls will occur (at the time of every scheduled visit or more frequently if needed) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

Table 8-5 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Physical examination will include information on clinical manifestations of PROS. Complications of PROS depend on the anatomical site and extent of overgrowth, and may include functional impairment amongst other manifestations all of which may be debilitating, and cause early mortality. A short physical exam will be done at all visits as indicated in Table 8-2, Table 8-3 and Table 8-1, starting during treatment except where a complete physical examination is required. It will include at least the examination of general appearance and vital signs (blood pressure [Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature. During the COVID-19 pandemic that limits or prevents on-site study visits or if visits by site staff to a participant's home are not feasible, the measurements of vital signs may be modified by Novartis and will be communicated to the Investigator (e.g., local vital sign measurements).
Height and weight	Height in centimeters (cm) [or length and head circumference for 0-2 years of age] and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-2, Table 8-3 and Table 8-1.

Performance status

Performance status will be assessed at baseline and then at every efficacy assessment time points, to document changes in performance status measured with use of Karnofsky/Lansky scores as described in Table 8-2 and Table 8-3.

8.4.1 Laboratory evaluations

Clinical laboratory analyses (hematology, biochemistry, coagulation, fasting lipid panel/glucose, HbA1C and pregnancy test) are to be performed by the central laboratory designated by Novartis as outlined in Table 8-6 and as per assessment schedule in Table 8-2 and Table 8-3. In case of urgent safety management of hyperglycemia, fasting plasma glucose assessment may be allowed locally according to the schedule of assessments and collection plan

outlined in Table 8-2 and Table 8-3. For routine monitoring of hyperglycemia, the fasting plasma glucose results of the local laboratory at Week 3 Day 1 will be recorded in the eCRF.

Per the EMA recommendations for trial related blood loss (including any losses in the maneuver) in pediatric populations. no more than 3% of total blood volume should be taken during a four-week period and not more than 1% of total blood volume at a single time-point. At a total blood volume estimated at 80 to 90 mL per kilogram (kg) body weight, this equates to 2.4 mL to 2.7 mL blood per kilo body weight during a four-week period, or 0.8 to 0.9 mL blood per kg body weight at any one time.

For participants below 2 years of age (Table 8-3), if required as per protocol, coagulation panel may be performed on a different day than hematology (including HbA1c) and chemistry panels (please refer to allowed visit windows as per Table 8-1) to follow EMA recommendations for trial related blood loss in pediatric populations.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site scheduled study visits, or if visits by site staff to participants' home are not feasible. If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

[redacted]

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Unscheduled local laboratory assessments may also be performed if medically indicated to assess a (potential or ongoing) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g., dose modifications or AE management). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

- A treatment decision was made based on the local results, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event severity is worse than the one reported by the central lab, or
- There are no concomitant central results available

For assessment of participants' eligibility to the study, only laboratory results from the central laboratory will be used

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the eCRF page. Additional analyses are left to the discretion of the Investigator.

Visit windows as per Table 8-1 are allowed. Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a participant has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The Investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

Table 8-6 Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, (absolute value preferred, %s are acceptable)
Fasting Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose
Fasting Lipid panel	Total Cholesterol, Low density lipoprotein (LDL), High density lipoprotein (HDL), Triglycerides
Coagulation	International normalized ratio [INR]), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT), [redacted]
Additional tests	Hepatitis at screening (except for participants < 2 years of age), HbA1c
Pregnancy Test for women of child-bearing potential	Serum human chorionic gonadotropin (hCG) (central laboratory at screening, EOT and 30 days safety follow up), serum (local laboratory at Week 1 Day 1), urine (at other visits)

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. ECGs are to be performed in triplicate with a minimal interval of 1 minute between the end of one trace and the start of another. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Triplicate 12 lead ECGs are collected at each time point (as specified in7 Table 8-7) with ECG machines available at the site. Pre-dose ECGs should be performed on the day of the visit; time window should allow to perform ECG in triplicate, review it and assess QTcF before dosing.

The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

For any single 12 Lead ECGs with participant safety concerns (additional ECG other than scheduled per protocol Table 8-2 and Table 8-3), two additional ECGs must be performed to confirm the safety finding. A local monitoring or review process should be in place for clinically significant ECG findings (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms, cardioversion) throughout the study and especially at baseline before administration of study treatment by an appropriately skilled physician.

Figure 8-1 Timing of study procedures

Any identifier details must be redacted e.g., participant initials, date of birth.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

A standard triplicate, 12 lead ECG will be performed as presented in Table 8-7:

Table 8-7 Local ECG collection plan

Visit	Day	Timing	ECG type
Screening	-28 to -1	Pre-dose (baseline ECG)	12 Lead, Triplicate
Week 1	1	Pre-dose	12 Lead, Triplicate
Week 4	28	Pre-dose	12 Lead, Triplicate
Week 8	56	Pre-dose	12 Lead, Triplicate
Week 12	84	Pre-dose	12 Lead, Triplicate
Week 16	112	Pre-dose	12 Lead, Triplicate
Week 24	168	Pre-dose	12 Lead, Triplicate
Week 36	252	Pre-dose	12 Lead, Triplicate
Week 40	280	Pre-dose	12 Lead, Triplicate
Week 48	336	Pre-dose	12 Lead, Triplicate
Week 72	504	Pre-dose	12 Lead, Triplicate
Week 96	672	Pre-dose	12 Lead, Triplicate
Week 120	840	Pre-dose	12 Lead, Triplicate
Week 144	1008	Pre-dose	12 Lead, Triplicate
Week 168	1176	Pre-dose	12 Lead, Triplicate
Week 192	1344	Pre-dose	12 Lead, Triplicate
Week 216	1512	Pre-dose	12 Lead, Triplicate
Week 240	1680	Pre-dose	12 Lead, Triplicate
Week 264 (EOT)	1848	Pre-dose	12 Lead, Triplicate

Visit	Day	Timing	ECG type
Safety Follow-up	Last dose + 30	Anytime	12 Lead, Triplicate
Unscheduled or Unplanned sample		Anytime	12 Lead, Triplicate

Interpretation of the tracing will be made locally by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings detected at screening must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the Investigator.

Paper ECGs should be appropriately labeled and the original kept in the source documents at the study site. If an unscheduled ECG is performed at an external medical facility, a copy of the ECG should be obtained and a copy kept in the source documents at the study site.

Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

8.4.2.1 Cardiac imaging: Echocardiography

An echocardiography is an ultrasound of the heart, which uses high-pitched sound waves to produce an image of the heart. It is used to evaluate cardiac chamber size, wall thickness, wall motion, valvular anatomy, valve motion, the proximal great vessels and the pericardium. A wide variety of cardiac diseases can be diagnosed echocardiographically, the severity of the disease ascertained and a prognosis for life derived. Echocardiography has increased the diagnostic accuracy of noninvasive cardiac evaluation and provides a tool for the monitoring of diagnostic and therapeutic procedures.

The left ventricular ejection fraction (LVEF) will be evaluated by echocardiography at Screening and at EOT. Additional cardiac imaging during treatment is to be performed if indicated by clinical signs or symptoms.

In those participants, who have PROS-related clinically relevant decrease of LVEF and are considered eligible after a consultation with Novartis, echocardiography will be used as a part of efficacy assessment for secondary endpoints (for more details, please refer to Section 8.3.2). The same imaging modality should be used.

8.4.3 Pregnancy and assessments of fertility

A condom and/or highly effective methods of contraception is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner from the date of receiving alpelisib until at least one week after the last dose received. In addition, male participants should not donate sperm during this time.

All pre-menopausal women of child-bearing potential who are not surgically sterile will be required to use highly effective contraception (see Section 5.2) and have pregnancy testing. When pregnancy testing is required, a serum pregnancy test (central laboratory) will be performed at screening, EOT and 30 days safety follow up, a serum (local laboratory) at Week 1 Day 1 and urine pregnancy test at other visits.

Any local positive serum test needs to be confirmed with a central serum test. If positive, the participant must be discontinued from study treatment.

Additional pregnancy testing might be performed if requested by local requirements. If a positive pregnancy test is obtained in between study visits, the participant must immediately notify the Investigator.

If participants cannot visit the site to have serum pregnancy tests during a public health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of Fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes pediatric participants who are menarchal or who become menarchal during the study. All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

Female participants of child-bearing potential who are or might become sexually active, must be informed of the potential teratogenic risk with alpelisib and the need for highly effective contraception to prevent pregnancy while on alpelisib therapy.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

For females in the pediatric groups, an assessment of fertility should be made at the discretion of the Investigator, but in all girls of the age of 16 years and above.

8.4.4 Other safety evaluations

Height/length and Body Mass Index (BMI) will be assessed in pediatric participants, using the standard deviation scores (SDS, also called z-score), growth velocity and velocity SDS. SDS will be calculated based on published referenced height/length and BMI information.

Sexual maturation assessment will be performed in all pediatric participants (6 to < 18 years old at time of informed consent); assessments of sexual maturation will be performed using the Tanner Staging scale. Additional Tanner Staging assessments will be based on the score at screening and subsequent scores:

- Stage 5 = no additional Tanner Staging assessments needed

Stage 4 or less = continue Tanner Staging assessments per Table 8-2 and Table 8-3

Dental development will be assessed in all pediatric participants (<18 years) by a qualified physician. If needed, further follow-up assessments should be performed by a qualified specialist, such as a dentist or a maxillofacial surgeon. For participants that turn 18 years of age while on trial, dental assessments may be discontinued at the discretion of the Investigator. A routine method of visual evaluation will be used. Panoramic radiographs are not mandated but may be performed as per local standards when clinically indicated. Management of any participant experiencing treatment-related dental effects will be handled at the Investigator's discretion.

Bone development will be assessed in all pediatric participants (<18 years) by a qualified specialist, such as a site radiologist. At screening, a baseline X-ray with anteroposterior/lateral views will be performed to assess growth plate abnormalities (knee/wrist) and skeletal bone age (wrist, hand, knee) according to Greulich-Pyle standards (Greulich and WW and Pyle 1959, Sasaki et al 2002, Tomei E. et al 2011 and Hojreh et al 2018). When the extremities of the participant are affected by PROS, it is recommended to use contralateral side for evaluations, when not affected - left side of the body. It is expected that MRI will be used for further assessments of bone development during the study; repeated X-rays of knee(s), wrist(s), hand should only be performed in case clinically significant changes are detected by MRI. The baseline X-rays should be used as reference images for comparison and assessment of the suspected changes. If there is evidence of thickening or changes in the growth plate, further assessment of bone development should be based on X-rays, as clinically indicated. When evaluations may not be performed with use of MRI scans, X-rays of appropriate anatomic areas should be considered.

X-rays can be replaced by MRIs according to institutional standard or if there is any clinical contraindication.

Assessments of growth, bone/dental development and sexual maturation will be performed locally in appropriate groups at screening, then every 6 months and at the End of Treatment visit (if not assessed during last 3 months). Bone development assessments may be stopped when participant reaches skeletal maturity or Tanner stage 5.

All findings should be recorded and assessed for clinical significance; clinically significant abnormalities should be reported as adverse events.

If clinically significant changes in growth, bone/dental development, and sexual maturation are observed, the Investigator should reassess the risk/benefit ratio of continued alpelisib treatment and discuss with the Sponsor on a case-by-case basis.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

The participant-perceived effects of treatment with alpelisib will be assessed though changes in patient-reported outcomes measures (PROMs), as the basis of a secondary endpoints in this study. These PROMs will assess concepts including pain intensity, physical functioning, mental health, social functioning, fatigue, sleep, and shortness of breath. The inclusion of such PROMs will enable a better understanding of how treatment with alpelisib impacts health and wellbeing, with reports coming directly from the participant (or, when the participant is unable to self-report, as recorded by the caregiver). Participant input should inform which domains should be measured in a clinical study protocol (Patrick et al 2011). Novartis conducted a targeted literature review and cognitive debriefing interviews with participants with PROS, to support the content validity of each measure, to demonstrate that they are comprehensive, relevant, and understandable to the specific ages and patient populations while also detecting the heterogeneity across the PROS patient populations.

The PROMs will be included on PRO Diaries implemented on electronic patient-reported outcomes (ePRO) devices given to each participant (or caregiver). Pain and dyspnea-related questions will be collected on a daily basis from home, starting in the screening period (starting 7 days prior the first dose of study treatment) through Week 16, and again starting at Week 20 though Week 24, as well as at other times as indicated in the VES. The other health-related quality of life (HRQoL) measures will also be implemented on the ePRO devices and will appear for completion at baseline and specified time points during the study.

The following PROMs are included in the PRO Diary on the ePRO device:

- In this study, the BPI item that assesses worst pain intensity in the past 24 hours will be used. Participants respond to the item on an 11-point response scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). An item pertaining to pain interference with general activity in the past 24 hours asks participants to respond to the item on an 11-point response scale ranging from 0 (does not interfere) to 10 (completely interferes). The participant will indicate the location of pain and where it hurts the most on a modified BPI diagram. A separate item will allow the participant to indicate the type of pain experienced. Additional questions on worst pain intensity, location and type of pain will also be asked, if the participant wishes to answer these questions for an additional area of pain experienced. Adult and pediatric participants 12 years of age and older will report pain with these questions (Cleeland 2009).
- For children 3-11 years old, the Wong-Baker FACES® Pain Rating Scale of pain interference will be asked in place of the BPI worst pain intensity question. This scale is a single-item that includes simple line drawings of 6 faces, each depicting an increasing

amount of pain. It has reliability and validity for use in children 3-18 years of age. Each face is associated with both a numeric rating and a descriptor (ranging from 0, "no hurt" to – 10 "hurts worst"). Children will be asked to choose the face that best describes their level of pain (Wong and Baker 1988).

- Two items on Dyspnea Severity will also be included to assess the degree to which participants felt short of breath while completing various physical activities. One item asks about shortness of breath when walking up 10 stairs and another asks about shortness of breath when talking while walking. Each has a recall period of the past 24 hours and includes 5 response options: no shortness of breath (0), mildly short of breath (1), moderately short of breath (2), severely short of breath (3), and I did not do this. Participants 12 years and older will be asked to respond to these items.

For the assessment of pain and dyspnea, participants (or their caregivers) will be asked to complete these items on the PRO Diary on the ePRO devices every evening starting in the screening period (starting 7 days prior the first dose of study treatment) through Week 16, and again starting at Week 20 through Week 24. Participant (or their caregivers) will be alerted for their completion prior to the time interval during which the assessment should be completed.

The following PROMs will be included at Baseline and other specified times during the study:

A Patient Global Impression of Symptom Severity item will be used to understand the overall severity of symptoms experienced and clinical meaningfulness of treatment effects experienced during this study. This item includes 5 response options: no symptoms, mild, moderate, severe, and very severe.

The PROMIS Profiles are a group of PROMIS short forms measuring different domains of HRQoL from the patient-Reported Outcomes Measurement Information System (PROMIS) system (Ader and Deborah 2007). The PROMIS-29 plus 2 Profile v2.1 is designed for adults ≥18 years of age, and includes 29 items across 7 domains (4 items per domain): depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participant in social roles and activities (corresponding to PROMIS Short Forms 6a/b); the 27th and 28th item[s] are the "plus 2" and assess cognitive function abilities and the 29th item assesses pain intensity. All items except those related to physical function are answered in reference to the past 7 days; the physical function items do not have a specific recall period. All items include 5 response options, except for the pain intensity item, which has 11 response options (Cella et al 2019).

The PROMIS Pediatric-25 Profile v2.0 is designed for self-report by children; The PROMIS Parent-Proxy-25 Profile v2.0 is designed for completion by a parent or caregiver observer on behalf of children unable to record for themselves. Four items are included for each of the following domains: depressive symptoms, anxiety, physical function-mobility, pain interference, fatigue, and peer relationships (corresponding to PROMIS pediatric Short Forms 6a/b); the 25th item assesses pain intensity. All items are answered in reference to the past 7 days and include 5 response options, except for the pain intensity item, which has 11 response options. The content of the child self-report and parent/caregiver versions are identical, except for minor modifications to account for differences in responders (e.g., "I felt worried" vs "My child felt worried"). The PROMIS Pediatric-25 Profile v2.0 will be completed by children 12

and older, and the PROMIS Parent-Proxy-25 Profile v2.0 will be completed by parents/caregiver for children under 12 years of age.

Unlike the adult PROMIS Profile, the pediatric and parent-proxy PROMIS profile does not include a sleep disturbance domain. In order to achieve similar content coverage across the COAs administered to adults, children, and parent versions, the PROMIS Pediatric and Parent-Proxy Sleep Disturbance Short Form 4a will also be included for pediatrics and parent-proxies. The short form includes 4 items that assess difficulty falling asleep, sleeping through the night, problems with sleep, and trouble sleeping. Each item is answered in reference to the past 7 days and includes 5 response options.

These health-related quality of life measures will be collected at baseline and specified time points during the study (refer to the Table 8-2 and Table 8-3). The participants (or their caregivers) should be asked to complete their PRO measure(s) on the ePRO device at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant, and participants should be given sufficient space and time to complete the PRO measure(s).

Table 8-8 and Table 8-9 below provide details on the PRO versions given by age range.

Table 8-8 Daily Diary: Starting at Screening period, then at specified time points in Table 8-2 and Table 8-3

Concept of interest	Adult Self-report (≥18 years old)	Child Self-report (≥12-17 years old)	Child report with Parent/Caregiver Assistance (3-11 years old)	Parent/Caregiver report (<12 years old)
Pain intensity	BPI Worst Pain Item	Brief Pain Inventory, Worst Pain Item	Wong Baker FACES Pain Scale	NA
Pain interference	Pain interference with activity	Pain interference with activity item	NA	NA
Pain location	BPI pain diagram (areas that hurt, and where hurts most)	BPI pain diagram (areas that hurt, and where hurts most)	NA	NA
Pain type	BPI pain type item	BPI pain type item	NA	NA
Dyspnea	Dyspnea Severity, 2 items	Dyspnea Severity, 2 items	NA	NA

Table 8-9 PRO measures on ePRO Device by age range: Starting at Week 1 Day 1 then at specified time points in Table 8-2 and Table 8-3

Concept of interest	Adult Self-report (≥18 years old)	Child Self-report (≥12-17 years old)	Child Report with Parent/Caregiver Assistance (3-11 years old)	Parent/Caregiver Reporter (<12 years old)
	PRO measure			
Global Impression of severity of symptoms	Single item on the overall severity of PROS[1]		NA	Single item on the overall severity of PROS[1]
Physical function	PROMIS-29+2 Profile v2.1	PROMIS Pediatric-25 Profile v2.0	NA	PROMIS-Parent-Proxy-25 Profile v2.0
Fatigue				
Ability to participate in social/peer relationships[2]				
Pain interference				
Pain severity				
Anxiety				
Depression				
Cognitive function		NA	NA	NA
Sleep disturbance[3]		PROMIS Pediatric Short Form v1.0 - Sleep Disturbance 4a	NA	PROMIS Parent Proxy Short Form v1.0 -Sleep Disturbance 4a

[redacted]

[1] While the overall content of these items will be identical across the adult, child, and parent-proxy measures, minor changes to item wording were made (and tested) to make it relevant for the intended group (e.g., modifying "how would you rate your overall symptoms" to "how would you rate your child's overall symptoms").
[2] Domain "ability to participate in social roles and activities" is assessed for adults, while "peer relationships" is assessed for children/parent-proxy.
[3] Sleep disturbance is assessed in the PROMIS-29 Profile v2.1 using the PROMIS Sleep Disturbance Short

Concept of interest	Adult Self-report (≥18 years old)	Child Self-report (≥12-17 years old)	Child Report with Parent/Caregiver Assistance (3-11 years old)	Parent/Caregiver Reporter (<12 years old)
Form 4a. Sleep disturbance is not assessed on the PROMIS pediatric or parent profile version, and thus a separate short form assessment is needed.				

Trial Feedback Questionnaire (TFQ)

This study will include an option for participants (or parent/caregiver) to complete an anonymized questionnaire, 'Trial Feedback Questionnaire'. The intention of this questionnaire is to collect participant feedback on their clinical study experience. Individual participant level responses will not be reviewed by Investigators. Responses would be used by Novartis to understand where improvements can be made in the clinical study process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or adverse events and is therefore considered as outside of the clinical trial data, therefore would not be study data. The TFQ data will be stored in the Vendor's database, separate from the clinical trial database, and will not be part of the clinical trial database and study Clinical study report (CSR) and is outside scope of Data Review and Cleaning/ Reconciliation by Data Management personnel. Should any spontaneous information be collected about AEs, this would be transferred to the safety database.

During the COVID-19 pandemic that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible, the Clinical Outcome Assessments may be collected remotely (through e.g., ePRO devices, web portal, or telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.5.2 Pharmacokinetics

Blood samples for PK evaluation will be collected from all participants who receive at least one dose of study treatment. PK blood sampling will be performed in each study period as indicated in the Visit Evaluation Schedule (Table 8-2 and Table 8-3), PK blood collection log for Groups 1 and 2 (Table 8-11), Groups 3 (Table 8-12), Group 4 (Table 8-13) and Group 5 (Table 8-14).

Complete dosing information, including the date and time of actual blood draw and time of the last study treatment dose prior to the sampling (24-h clock time), should be obtained on all sampling days and recorded on the PK CRF and/or Contract Research Organization (CRO) requisition form(s). Sampling problems will be noted in the relevant field in the eCRF and on appropriate source documentation.

An additional blood sample (unscheduled) should be collected in the event that a participant experiences an AE which requires premature termination from the study treatment. The unscheduled PK blood sample must be obtained whenever possible and as soon as possible after

the last dose of alpelisib. For samples collected in China only: Pharmacokinetic samples will be sent to a Novartis designated central laboratory and processed locally, both in China.

Complete instructions for sampling processing, handling and shipment will be provided in the [CBYL719F12201 Laboratory Manual].

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein, blood will be collected into tubes containing K2-EDTA and gently inverted several times to thoroughly mix the anticoagulant.

Tubes will be centrifuged to separate plasma and plasma will be immediately split and transferred into two separate tubes for primary and backup samples. The primary sample shall at minimum contain 0.5 mL of plasma (0.3 mL for participants in Group 3). Plasma samples will be stored frozen in an upright position until shipment is requested by Novartis.

[redacted]

During the COVID-19 pandemic that limits or prevents on-site study visits, the collection of samples may be modified by Novartis and will be communicated to the Investigator.

For standard pharmacokinetic abbreviations and definitions see the list of abbreviations.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher): Cmax, Tmax, AUClast, AUCinf, T1/2, Ctrough, Vz/F and CL/F from the plasma concentration time data.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf and CL/F.

8.5.2.1 Pharmacokinetic blood collection and handling

Table 8-11 Pharmacokinetic blood collection log for Groups 1 and 2

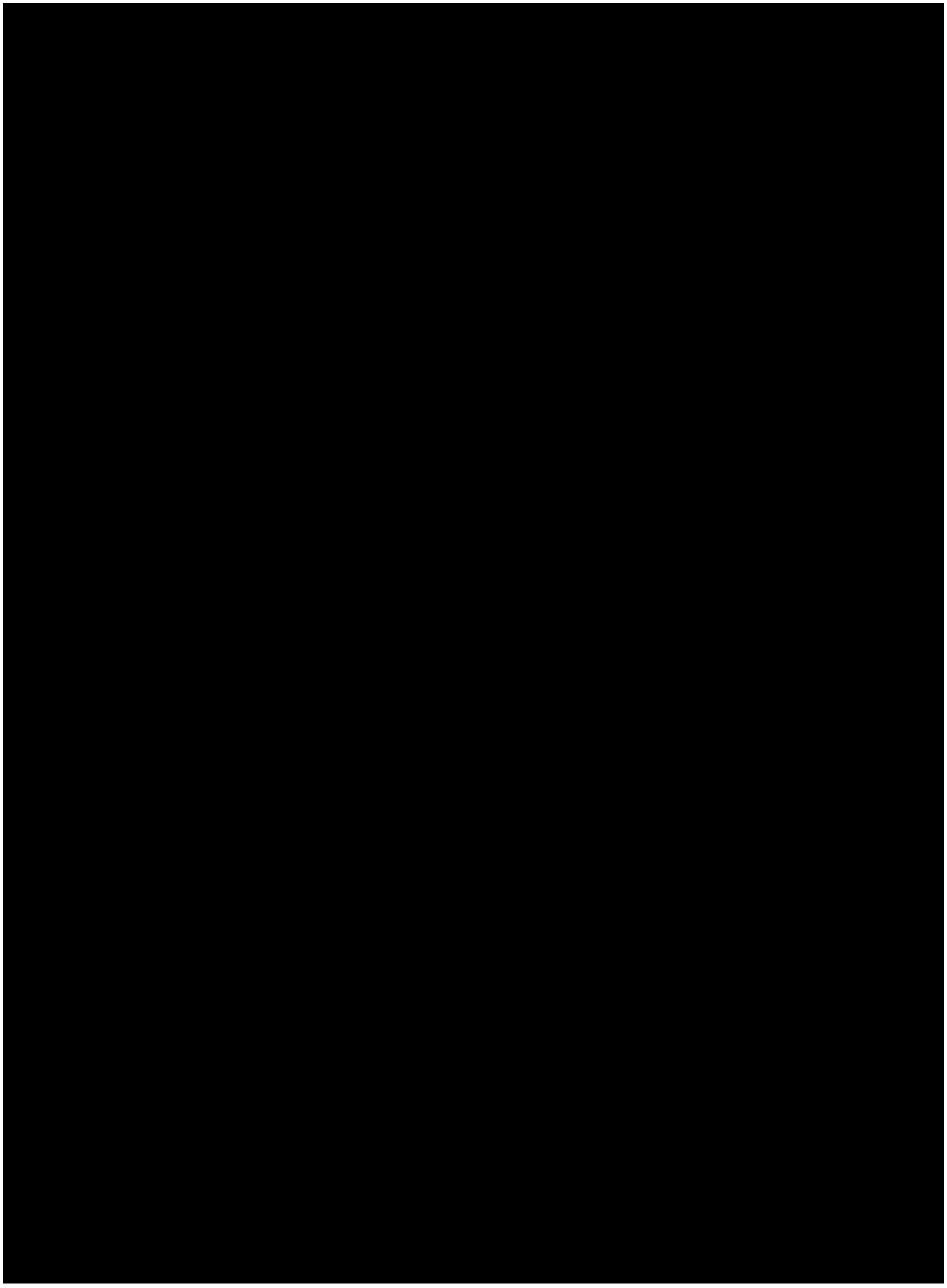
Week	Day	Scheduled Time Point	Dose Reference ID§		PK Sample No	Sample Volume (mL)
17	1	Pre-dose/0 h*	1	10	100	2
17	1	1 h post-dose ± 10 min	1	-	101	2
17	1	3 h post-dose ± 30 min	1	-	102	2
17	1	5 h post-dose ± 30 min	1	-	103	2
17	1	8 h post-dose ± 30 min	1	-	104	2
17	1 **	24 h post-dose ± 2 h/ Pre-dose of Day 2 **	1	20	105	2
20	1	Pre-dose/0 h*	2	11	106	2

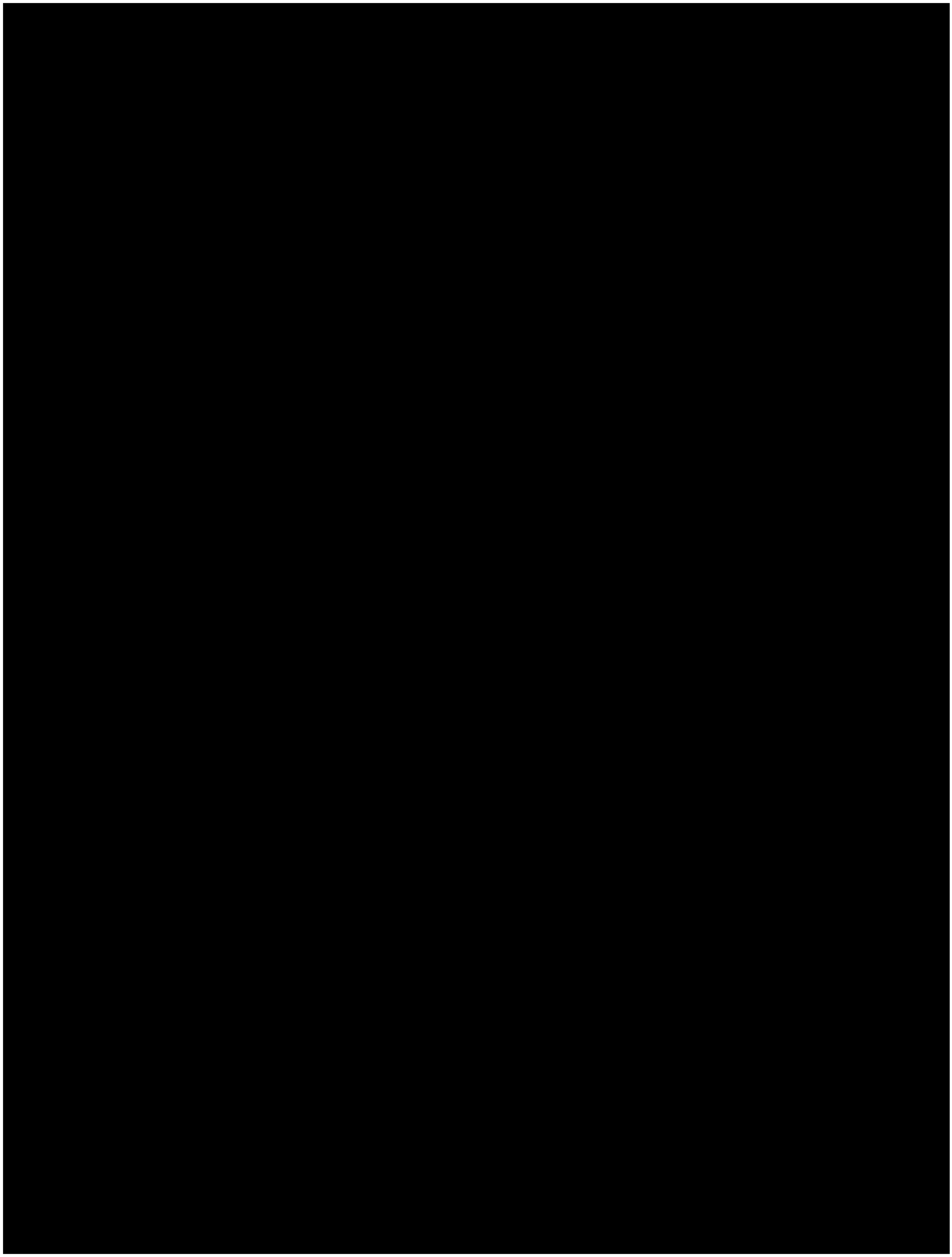
Week	Day	Scheduled Time Point	Dose Reference ID§		PK Sample No	Sample Volume (mL)
20	1	3 h post-dose ± 30 min	2	-	107	2
After 28***	1	Pre-dose/0 h*	3	12	108+	2
After 28***	1	3 h post-dose ± 30 min	3	-	109+	2
Anytime		Unscheduled	151+		1001+	2

* Pre-dose samples should be obtained within 30 minutes before administration of alpelisib dose, and within 22-26 hours after the last dose the participant received prior to the collection of the pre-dose (trough) sample. PK blood samples collected before 3 hours post-dose must be collected within ± 10 minutes from the scheduled time point, while samples collected 3 hours post-dose and later may be collected within ± 30 minutes from the scheduled time point.
** The 24 hours post-dose sample should be collected 24 hours (± 2 h) after the dose administered on Week 17 Day 1, and within 30 minutes before administration of next alpelisib dose on Week 17 Day 2.
***After Week 28, only for participants who had dose escalation, PK sampling is planned at the next scheduled visit that will occur at least 4 weeks after each dose escalation.
+ Additional samples may be collected due to additional dose escalations and/or safety observations; Refer to Lab manual for naming conventions.

§ For the PK Pre-dose samples, the actual date and time of administration of the previous dose of alpelisib should be recorded with appropriate dose reference ID as indicated in the above table. The dose reference ID “1" is for the alpelisib dose administered on Week 17 Day 1. The dose reference ID "2, 3" is for the alpelisib dose administered on study day visit. The dose reference ID "10, 11, 12" is for the previous alpelisib dose the participant received prior to the collection of the PK Pre-dose sample. The dose reference ID “20” is for the alpelisib dose taken on Week 17 Day 2.

[redacted]





[redacted]

8.5.4 Imaging

Imaging in this study will be performed as part of primary/secondary/[redacted] objectives and will also be used as a safety assessment. The methods for assessment and recording are specified in the Section 8.3 and Section 8.4.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.5.5 Lung function assessment

Spirometry testing will be performed for Groups 1, 2 and 5 according to the American Thoracic Society guidelines (Miller et al 2005, Graham et al 2019) at screening to assess participants' eligibility for the study and as detailed in the assessment schedule (Table 8-2 and Table 8-3).

The same spirometry equipment should be used for all assessments performed by a participant. Where possible the same technician should perform the assessment for an individual participant during the study.

The following spirometry measurements will be collected and recorded:

- FVC, forced vital capacity
- FVCPP, percent predicted forced vital capacity
- FEV1, forced expiratory volume in 1 second
- CO, diffusion capacity of lung for CO

Spirometry will be performed in all participants in Groups 1, 2 and 5 at screening, and then when clinically indicated. In those participants, who have pulmonary function affected by PROS at baseline, spirometry will be performed at efficacy assessment time points (please refer to Section 8.3.2).

Spirometry will not be performed in participants in Groups 3 and 4 (less than 6 yrs old). Instead of spirometry measurement, to assess these pediatric participants' eligibility for the study, chest MRI images will be used and participants with documented or suspicious pneumonitis or interstitial lung disease based on MRI images at time of informed consent will not be eligible.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration). Decision on study treatment discontinuation can be done by either the participant or the Investigator in the absence of disease progression or unacceptable toxicities.

The Investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Adverse event or laboratory abnormalities requiring permanent discontinuation of study treatment as per Section 6.5
- Progressive disease (except conditions allowing to continue study treatment beyond progression as defined in a Section 6.1.5.1)
- Protocol deviation that results in significant risk to participant's safety
- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2)
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding (except the case when retrospectively the AE/SAE led to emergency unblinding is not considered related to the study treatment)
- Study terminated by Novartis

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participant who discontinues from study treatment agree to return for the End of Treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to details in the Emergency breaking of treatment code in Section 6.6.2.

For the participants who discontinue from study treatment for reasons other than death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, safety follow-up assessments must continue after study treatment discontinuation and End of Treatment assessments.

9.1.1.1 Replacement policy

No replacements will be needed.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Withdrawal of informed consent

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and only when a participant:

- Explicitly requests to stop use of their data.

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts).

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly

document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent /exercise data privacy rights should be made as detailed in the assessment table (refer to Table 8-2 and Table 8-3).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (instructions will be provided to the Investigator for contacting the participant, when the participant should stop taking drug and when the participant should come for a final visit) and treated as a participant who discontinued from study treatment (see Section 9.1.1). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the study.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant, regardless of study period, finishes their study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

The primary analysis will be performed after all ongoing participants from Groups 1 and 2 have completed 48 weeks of treatment or discontinued earlier. For participants of Group 1 and Group 2, the Core Period (Week 1-Week 24), Extension 1 (Week 25-48) and Extension 2 (Week 49 - up to 5 years of total duration of study treatment) are considered.

[redacted]

End of Study (EoS) will occur when all participants have reached the 5 years long term treatment period, unless the participant discontinues earlier.

The end of the study for a given participant is defined as when the participant permanently discontinues study treatment with alpelisib and all the end of study procedures are completed. The end of the overall study is defined as the time point when data collection will stop in all five age groups and the final analysis of the study will occur.

For the participants participating in the study and still deriving clinical benefit from alpelisib, every effort will be made to continue provision of study treatment after 5 years of total duration of study treatment. Please refer to Section 6.1.5 for more details on PTA.

10 Safety monitoring, reporting and committees

During the COVID-19 pandemic that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible, regular phone or virtual calls will occur (at the time of every scheduled visit or more frequently if needed) for safety monitoring and discussion of the participant's health status until the participant can again visit the site.

The Investigator and any qualified designees are responsible for managing the safety of individual participants. They are also responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and for following up all AEs and SAEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided below (Sections 10.1.1, Section 10.1.2 and Section 10.1.3).

For the investigational product, information about adverse drug reactions and how to manage them can be found in the Investigator's Brochure (IB) and in Section 6.5.2. Information about adverse drug reactions can also be found in the product information for marketed products.

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. This includes events reported by the participant

(or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on study related medical questions or problems.

Once screening procedures start, all AEs per the description below (inclusive of SAEs) will be captured as adverse events. The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 4.03). Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version, including Grade 5 (Death related to AE). Grade 5 (Death related to AE) will be used in assessment of AEs to comply with CTCAE grading. Information about deaths will be collected through the appropriate eCRF page.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the study drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of groups, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, and the outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2) for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following

- Dose not changed
- Dose Reduced/ re-escalation
- Drug interrupted/permanently discontinued

6. Its outcome (i.e., recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently as necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcomes.

Progression of PROS (including fatal outcomes), if documented according to the protocol, should not be reported as a serious adverse event, except if the Investigator considers that progression of PROS is related to study treatment.

Adverse events separate from the PROS progression (i.e., thromboembolic event at time of progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- social reasons and respite care in the absence of any deterioration in the participant's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For participant monitoring and to better understand potential etiologies, the Investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data. All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective of if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions

regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

Information about all SAEs is collected and recorded on the eCRF: all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, Novartis may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female study participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcome should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not they are associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.1.6 Off-site procedures (for Netherlands only)

At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures performed at an off-site location (Section 6.5).

One or more of the following elements may be implemented to support off-site visits:

- Telephone contacts (when applicable)
- Fasting Glucose self-monitoring using standard self-tests, where locally allowed
- Off-site HealthCare Professionals (OHP)
- Source Data Collection

Procedures for off-site visits utilizing the above listed elements are further detailed in a separate manual(s) provided to the sites participating in the off-site visits.

- Off-site training manual
- Site guidance

The off-site procedures will be utilized in certain countries and sites as determined by protocol needs, if Sponsor allows, and based on national and local/site regulations.

Participants, that the investigator identifies as suitable for off-site visits, must provide informed consent (Optional consent for activities that may be done outside of the study site.)

The following conditions must be met for off-site visits to take place:

- Off-site visits may occur during the study for fasting glucose plasma assessments
- If the participant suffers from either (1) a severe AE or an SAE (possibly related to study medication), and/or (2) any concurrent medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risks, then the participant must resume the on-site visits. The participant may resume the off-site visits when, based on the Investigator's judgment, there are no further safety risks for the participant.

10.1.6.1 Responsibility of Investigator oversight of off-site activities

Procedures that are performed off-site remain under the oversight of the investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP, and will ensure the rights, safety, and wellbeing of participants. This includes the following (including, but not limited to):

- the identification, management and reporting of AEs and SAEs are performed in accordance with the protocol and applicable regulations
- verification that OHPs have appropriate qualifications, training, and experience to successfully conduct off-site procedures
- source data collected off-site are reviewed and evaluated in a timely manner
- the investigator or delegate is available to be contacted by the OHP if any issues or concerns are noted during an off-site visit
- where relevant, the investigator or delegate will be present by phone for a portion of the off-site visit to support the physical examination.

The off-site healthcare professionals will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use.

10.1.6.2 Responsibility of OHPs

Any issues or safety concerns identified by the OHP will be promptly communicated to the investigator or delegate according to a pre-defined communication plan.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

For liver safety monitoring guidelines, please refer to the Section 6.5.2.1.

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical study, including the site Investigators participating in the study. The DMC will be formed prior to the randomization of the first participant and will assess at defined intervals the progress of a clinical study, safety data and recommend to Novartis whether to continue, modify, or terminate a study.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between Novartis and the DMC.

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising Investigators participating in the study, i.e., not being members of the DMC, a patient advocate and Novartis representatives from the Clinical study Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical study team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

Monitoring strategy, methods, responsibilities, and requirements are provided in the monitoring plan. Details may include definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring)

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

11.1 Data collection

All data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Safety laboratory assessments, PK [redacted] samples drawn during the course of the study will be collected from the Investigator sites and sent to the Novartis designated central laboratory for processing. The laboratory results will be sent electronically to Novartis (or a designated CRO).

Imaging data used for PROS lesions assessments will be collected at the sites, transmitted to a designated vendor for centralized analysis, quality control, as well as further processing and data reconciliation. It will be prospectively reviewed by a blinded independent review committee (BIRC).

PRO data collected using an electronic tablet device will be documented into a separate study-specific vendor database supplied and managed by a designated vendor. All PRO data will be sent electronically to Novartis personnel (or a designated CRO).

Randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study primary analysis at Week 48 or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate for primary analysis at Week 48, the database until Week 48 will be locked **and the treatment codes will be unblinded** and made available for data analysis. Final database lock will be declared after Week 240 (i.e., once LPLV is achieved at Safety Follow-up/End of Study). Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis/representative will review the protocol and data capture requirements (i.e., eSource

DDE or eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in the monitoring guidelines.

The Investigator must maintain source documents (source data) that support the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete and verifiable from source documents; that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits.

Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Primary safety and efficacy analysis (including analysis of key secondary objectives) will be conducted on all participant data (in Groups 1 and 2) at the time all participants who are still receiving study treatment will have completed at least 48 weeks of treatment or discontinued earlier.

[redacted]

Data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis. Data will be summarized using descriptive

statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, and efficacy, safety, and PK measurements.

Study data will be analyzed and reported in a primary CSR based on all participants' data up to the time when all participants in Groups 1 and 2 have completed at least 48 weeks of study treatment or discontinued earlier. [redacted]

All summaries, listings, figures and analyses will be performed by age group and treatment arm (unless otherwise specified).

Screen failure participants, as described in Section 8.1.2, and the reasons for not starting the study treatment will be reported in a listing but will not be included in any analyses.

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP).

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The main efficacy and safety analyses will focus on the randomized participants in Groups 1 and 2. [redacted].

The **Full Analysis Set (FAS)** for Groups 1 and 2 comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment and age group they have been assigned to during the randomization procedure. The analysis set considered for the analysis of the primary endpoint is a subset of the FAS (FAS - BYL719) and comprises all participants to whom alpelisib has been assigned by randomization.

[redacted]

The **Safety Set** includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received.

The **Pharmacokinetic analysis set (PAS)** includes all participants who receive at least one dose of alpelisib and provide at least one evaluable PK concentration. Participants will be analyzed according to the treatment received.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data, including disease characteristics, will be listed and summarized descriptively by age group and treatment arm for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by age group and treatment arm.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to alpelisib and placebo, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by age group and treatment arm.

The number of participants with dose adjustments (either dose increase for response optimization purpose, or reductions, interruption, or permanent discontinuation) and the reasons will be summarized by age group and treatment arm, and all dosing data will be listed.

12.4 Analysis of the primary estimand(s)

The primary objective is to demonstrate the efficacy of alpelisib based on the proportion of participants randomized to the alpelisib treatment with a confirmed objective response by BIRC in the pediatric (6-17 years old; Group 2) or in the adult (≥ 18 years old; Group 1) groups (multiple primary endpoints).

12.4.1 Definition of primary estimand(s)

The primary efficacy variable of the study is the proportion of participants randomized to alpelisib achieving confirmed objective response, where response is based on

- achieving ≥ 20% reduction from baseline in the sum of target lesion volumes (1 to 3 target lesions, assessed by MRI by BIRC), provided that none of the individual target lesions has ≥ 20% increase from baseline and in absence of progression of non-target lesions and without new lesions. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response.

Refer to Section 12.4.3 for handling of intercurrent events and Section 12.4.4 for handling of missing values.

Analysis of the primary endpoint will be performed in each of Groups 1 and 2.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be based on data from the FAS - BYL719 for Groups 1 and 2 respectively. The study will be declared positive if at least one of the two primary null hypotheses can be rejected.

In order to conserve the overall type-1 error (one-sided level of significance of α=0.025) in testing multiple hypotheses, an alpha split with a graphical gate-keeping approach will be implemented based on the graphical multiple testing procedure as described in Section 12.5.1.1.

A confirmed response rate of 15% or less is considered "as insufficient" level of efficacy for the proposed participant population. Please refer to details in this Amendment rationale 01 for the threshold for futility (updated from 35% to 15%). For the primary analysis, the following statistical hypotheses will be tested based on the exact binomial distribution:

- H_1 (Group 1): $H_{01}: p_{BYL} \leq 0.15$ *vs.* $H_{A1}: p_{BYL} > 0.15$
- H_2 (Group 2): $H_{02}: p_{BYL} \leq 0.15$ *vs.* $H_{A2}: p_{BYL} > 0.15$

where p_{BYL} is the confirmed objective response rate on alpelisib in the Groups 1 and 2, respectively.

The primary null hypothesis will be rejected based on the probability of obtaining the observed confirmed objective response rate under a binomial distribution with underlying parameter p_0 =0.15 at the appropriate α-level governed by the graphical gatekeeping procedure described in Section 12.5.1 and Figure 12-1. With a total of 52 participants, if 15 or more confirmed responses are observed (observed confirmed objective response rate of 28.8%, lower bound of the 97.5% CI exceeding 15%), the null hypothesis will be rejected at a one-sided α/2= 0.0125.

Confirmed objective response rates in Groups 1 and 2 will be summarized using descriptive statistics (N, %) along with 2-sided exact 100(1-2α_i)% confidence interval (CI) (Clopper-Pearson exact method), where α_i corresponds to the appropriate α-level adjusted for multiple testing.

12.4.3 Handling of remaining intercurrent events of primary estimand

The primary analysis will account for different intercurrent events as explained in the following:

a. participants discontinuing treatment prior to confirmation of response: Classified as a non-responder
b. participants receiving surgery as a rescue therapy for any PROS lesions (target or other) prior to confirmation of response: Classified as a non-responder

12.4.4 Handling of missing values not related to intercurrent event

The primary efficacy variable is confirmed objective response. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response. Additional details on handling of missing scans will be provided in the SAP.

12.4.5 Supplementary analysis

The primary endpoint will be summarized and reported for the following subgroups, if there are enough participants in each category allowing such analysis:

- Age (6-11 years; 12-17 years)
- Gender
- Mutation type (as assessed locally)
- PROS syndrome (e.g., CLOVES, Klippel-Trenaunay syndrome (KTS))
- Lesion type (e.g., vascular, adipose)

Forest plots (response rate, 95% CI) will be produced to graphically depict the treatment effect estimates in different subgroups. Further supplementary analysis may be documented in the SAP.

12.4.6 Sensitivity analyses for primary endpoint/estimand

Sensitivity analysis (including potential analyses to assess the impact of COVID-19 pandemic if applicable) may be documented in the SAP.

12.5 Analysis of secondary endpoints/estimands

The analysis of secondary endpoints will be performed by age group and treatment arm. Periods defined based on pre- and post- switch of treatment will be considered for the analyses.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The FAS will be used for all analyses in this section.

12.5.1.1 Key secondary estimand(s)

The key secondary objective is to demonstrate the efficacy of alpelisib based on the comparison of the proportion of participants achieving response at Week 16 with alpelisib versus placebo in Groups 1 or 2.

The key secondary analysis will be based on data from the FAS for Groups 1 and 2 respectively.

Definition of key secondary estimand(s)

A similar definition of response described for the primary efficacy variable in Section 12.4.1 will be used for the key secondary efficacy variable, using response at Week 16 instead of confirmed objective response. Participants who had a missing/non-evaluable radiological assessment at Week 16 will be considered as non-responders for the calculation of the key secondary efficacy variable. Handling of intercurrent events will be done as described for the primary estimand in Section 12.4.3: Instead of confirmed objective response for the primary, Week 16 will be considered for the key secondary estimands.

Statistical model, hypothesis, and method of analysis

The following statistical hypotheses will be tested

- H_3 (Group 1): H_{03}: $p_{BYL,W16} \leq p_{PBO,W16}$ vs. H_{A3}: $p_{BYL,W16} > p_{PBO,W16}$

- H_4 (Group 2): H_{04}: $p_{BYL,W16} \leq p_{PBO,W16}$ vs. H_{A4}: $p_{BYL,W16} > p_{PBO,W16}$

where $p_{BYL,W16}$ is the response rate on alpelisib at Week 16 and $p_{PBO,W16}$ is the response rate on placebo at Week 16. The analysis to test these hypotheses will consist of a Fisher's exact test at the appropriate α-level governed by the graphical gatekeeping procedure described below and in Figure 12-1.

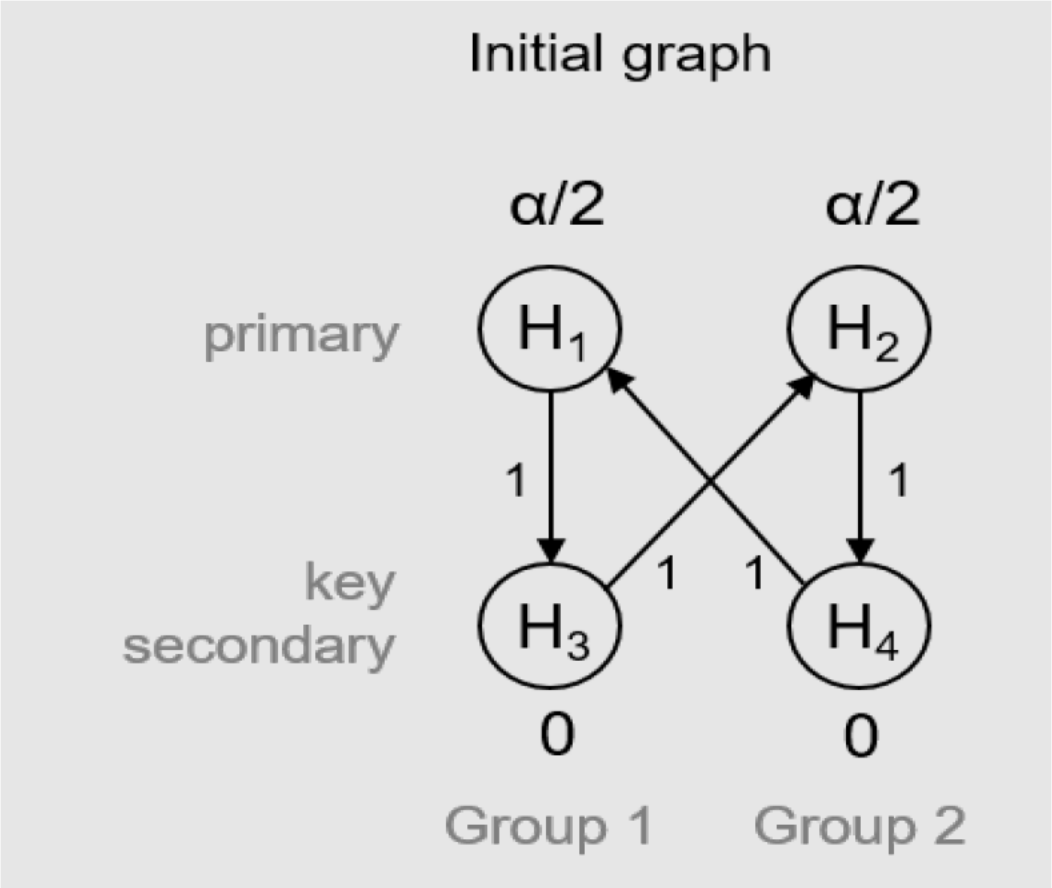
Response rates at Week 16 in Groups 1 and 2 will be summarized using descriptive statistics (N, %) along with 2-sided exact 95% confidence interval (CI) (Clopper-Pearson exact method). The difference between treatment arms (alpelisib - placebo) in response rates at Week 16 will be presented together with 2-sided 95% confidence interval (unadjusted for multiple testing), separately for Groups 1 and 2.

Sequentially rejective graphical procedure for multiple testing

The 4 null hypotheses (primary hypotheses H_1 and H_2 described in Section 12.4.2; key secondary hypotheses H_3 and H_4 described above) are tested using the graphical approach to sequentially rejective multiple test procedures proposed by Bretz et al 2009. Significance levels α_i, i=1,…,4, are initially defined such that they sum up to α. The 2 primary hypotheses H_1 and H_2 are allocated with the levels $\alpha_i = 1/2\alpha$, i=1 or 2, where $\alpha = 0.025$ (one-sided), i.e., the two primary hypothesis are considered equally important. For the 2 key secondary hypotheses H_3 and H_4, $\alpha_i = 0$, i=3 or 4, i.e., the key secondary hypothesis is not tested until its parent primary hypothesis is rejected.

The procedure then is as follows: Test the hypotheses H_i, i=1,…,4, each at its local significance level α_i. If a hypothesis H_i is rejected, remove H_i from the graph and propagate its level to other hypotheses according to a pre-specified rule represented by a directed, weighted graph. Update the reduced graph and repeat the testing step for the remaining, non-rejected hypotheses with the updated local significance levels. The procedure is repeated until no further hypothesis can be rejected. The procedure is fully determined by the initial graph given below and an updating algorithm, see Bretz et al 2009.

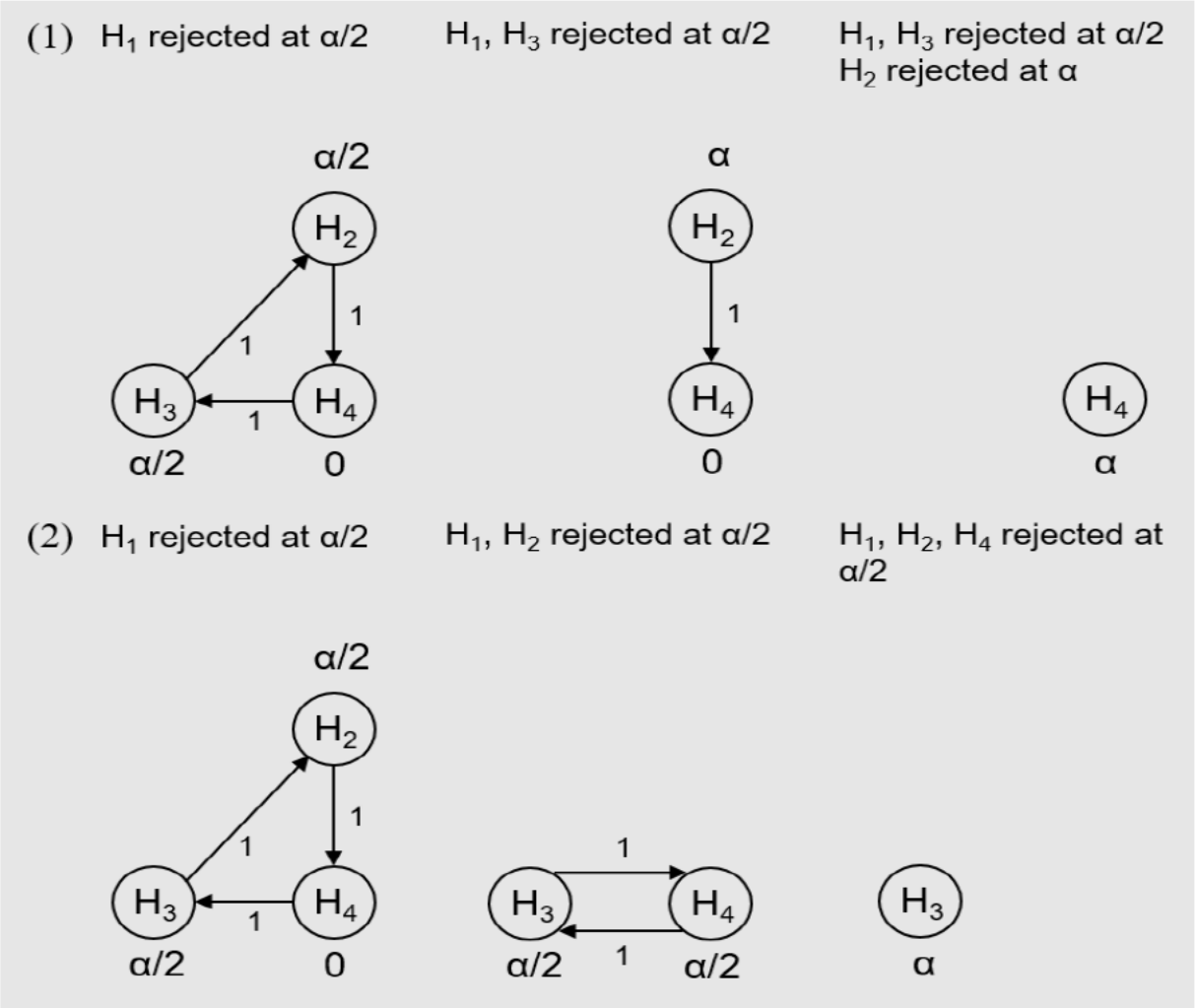
Figure 12-1 Graphical gatekeeping procedure to test procedure to test primary and key secondary endpoints in order to control overall type I error.



Edges with initial weights 0 (e.g. from $_4$ to H_3) are not displayed in the graph. Initial significance levels and initial graph will be updated as per the updating algorithm in Bretz et al 2009

This particular gatekeeping procedure can be interpreted as a Bonferroni-Holm test applied to the hierarchical pairs of primary and key secondary hypotheses (H_1, H_3) and (H_2, H_4) (Maurer et al 2011). To illustrate the sequentially rejective graphical procedure, Figure 12-2 displays two example rejection sequences. Note that in case more than one hypothesis could be rejected at a particular step, the algorithm guarantees that the sequence of rejection has no influence on the test decision (Bretz et al 2009). For instance, if one of the primary hypotheses can be rejected at α/2 (say Group 1), this level is first shifted entirely to its descendant key secondary hypothesis. If this can be rejected at level α/2, its level is shifted and added to the level of the remaining, nonparent primary hypothesis (Group 2) which in turn now can be tested at full level α. After the potential rejection of this second primary hypothesis, its descendant secondary hypothesis then can be tested at level α (example 1 in Figure 12-2).

Figure 12-2 Example rejection sequences for the sequentially rejective graphical procedure



Two example rejection sequences based on the initial graph in Figure 12-1.

Sensitivity and supplementary analyses for the key secondary estimands

The key secondary endpoint will be summarized and reported for the same subgroups described in Section 12.4.5 for the primary estimand, if there are enough participants in each category allowing such analysis. Further sensitivity and supplementary analysis may be documented in the SAP.

12.5.1.2 Other secondary endpoints

Changes in PROS lesions

Changes in PROS lesion volume (via BIRC) over time will be reported in the following ways

- The proportion of participants with response (as defined in Section 8.3) at each scheduled assessment visit.

- The actual and percentage change from baseline in the sum of target lesion volumes, the sum of MRI-measurable non-target lesion volumes, the sum of all MRI-measurable lesion (target and non-target) volumes.

Changes in other non-target lesions (via BIRC) will be reported in the following ways

- The proportion of participants with changes in non-target lesions.
- The proportion of participants with new lesions.

Overall clinical response

The proportion of participants with overall clinical response reported as improvement, stable or worsening of clinical condition, as assessed by the Investigator (see Section 8.3) will be summarized descriptively and/or graphically displayed.

Duration of response

This analysis only applies to participants who are on treatment with alpelisib and who achieve response. Duration of response (DOR) is defined as the time from first documented response until progression of PROS lesions by BIRC or death. The start date is the date of first documented response (Section 8.3), and the end date is defined as the date of first documented progression of PROS lesions by BIRC or death. Participants continuing without an event will be censored at the date of last adequate PROS lesion assessment prior to cut-off.

Time to treatment failure

This analysis only applies to participants who are on treatment with alpelisib. Time to treatment failure (TTF) is defined as the time from randomization/alpelisib treatment start date until the discontinuation of study treatment due to lack of efficacy (including unsatisfactory therapeutic effect, disease progression) or safety reasons (including adverse events, death). Participants who complete the study or discontinue study treatment for other reasons (e.g. discontinuation due to Participant/Guardian decision, technical problems) will be censored at the date of last study treatment received.

Changes in symptoms and complications/comorbidities associated with PROS

Changes in symptoms and complications/comorbidities (i.e., walking impairment, cardiac/pulmonary/renal function, pain, Karnofsky/Lansky performance status) will be summarized descriptively and/or graphically displayed as appropriate. For each complication/comorbidity, only participants who have this reported as being present at baseline will be included in the analysis. When new symptoms/complications/comorbidities appear at any time of study therapy, they will be assessed for clinical significance and reported as adverse events when applicable.

Healthcare visits/hospitalization due to PROS, surgeries to manage PROS

Healthcare visits/hospitalizations and surgeries related to PROS during on-treatment period, will be summarized in the following ways

- Proportion of participants with healthcare visit/hospitalized due to PROS, and the number and duration of hospitalizations required
- Proportion of participants requiring surgery due to PROS, and the number of surgeries
- The proportion of participants where an anticipated PROS surgery is avoided due to improvement.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by age group and treatment arm. [redacted].

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period will be further divided in order to separately present safety summaries according to study periods. For instance, safety summaries based on data from the period from randomization up to Week 16 in order to compare safety between alpelisib and placebo.

Adverse events

All information obtained on adverse events will be displayed by age group, treatment arm and participant.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment) will be summarized.

All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

All vital signs data will be summarized by age group, treatment arm and visit/time.

12-lead ECG

PR, QRS, QT, QTcF and RR intervals will be obtained from triplicate 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced.

All ECG data will be summarized by treatment and visit/time.

Clinical laboratory evaluations

Laboratory data will be summarized by age group and treatment arm. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE v4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE v4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Change from baseline in selected laboratory tests will also be summarized by visit and/or displayed graphically.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in other laboratory tests over time or box plots might be specified in the analysis plan.

Specific analyses to assess the impact of renal (as part of efficacy) and liver function tests will be described in the analysis plan.

Other safety evaluations

Growth, bone/dental development and sexual maturation

Data on growth, bone/dental development and sexual maturation (Tanner stage) will be summarized for children and adolescents.

Height and Body Mass Index (BMI) will be summarized at 6-month intervals, using the standard deviation scores (SDS, also called z-score), velocity and velocity SDS. SDS will be calculated based on published referenced height and BMI information.

Height/BMI SDS and height/weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window, as well as by presenting number of participants with SDS values lower/higher than 5th/95th percentiles respectively. All height/BMI SDS, velocity and velocity SDS data will be listed.

Data on bone/dental development will be summarized descriptively.

Sexual maturation will be monitored by Tanner staging. The age at which Tanner Stages 2-5 are achieved by gender will be summarized descriptively. All Tanner stage data will be listed.

Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

PROS-related hospitalizations and surgeries will be analyzed as part of efficacy objectives.

12.5.3 Pharmacokinetics

PAS will be used in all PK data analysis and PK summary statistics.

Alpelisib plasma concentration data will be listed by age group/dose, participant, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

The PK parameters (Table 12-1) will be calculated from individual plasma concentration versus time profiles using non-compartmental analysis (Phoenix WinNonlin). Cmax and Ctrough are primary PK parameters; AUClast, AUCinf, Tmax, T1/2, CL/F and Vz/F may be evaluated as secondary PK parameters if data permit. PK parameters will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is *Tmax* where median, minimum, and maximum will be presented.

Table 12-1 Pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration (mass x volume^{-1})
Ctrough	The trough observed concentration is the concentration that is just prior to the beginning, or at the end, of a dosing interval (mass x volume^{-1})
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time).
CL/F	The total body clearance of drug from the plasma (volume x time^{-1})
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)

12.5.4 Patient reported outcomes

The patient-reported global impression of symptom severity and BPI worst pain intensity item are identified as the primary PRO measures of interest. Change from baseline in scores at Week 16 will be assessed on treatment with alpelisib as compared to placebo in pediatric (12 to 17 year old) and adult (≥ 18 year old) populations. Full details of the derivation of the endpoints and corresponding analyses will be defined in the SAP.

The FAS will be used for analyzing PRO data. No multiplicity adjustment will be applied.

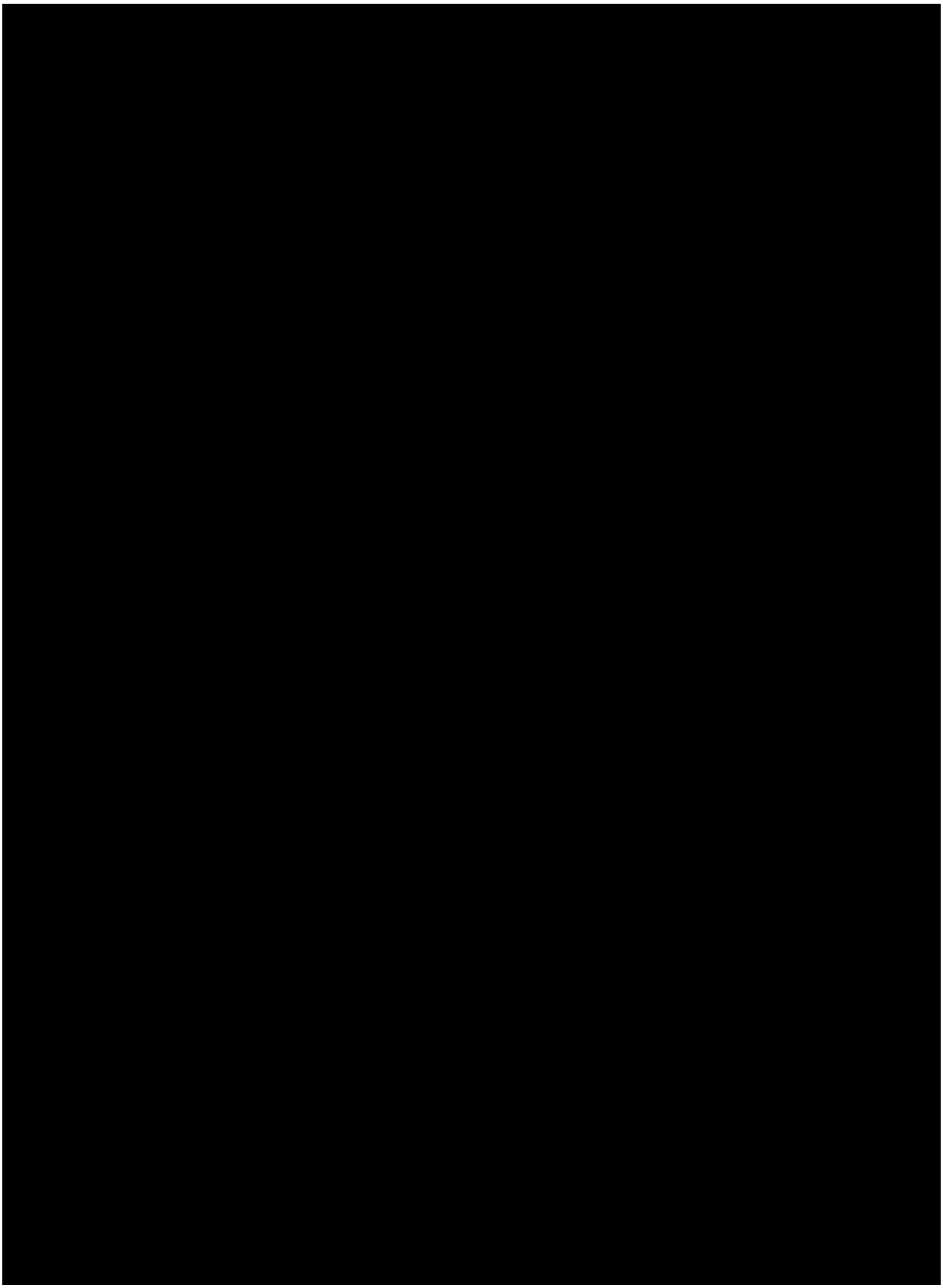
The change from baseline will be summarized and/or graphically displayed at scheduled assessments for the following PRO measures:

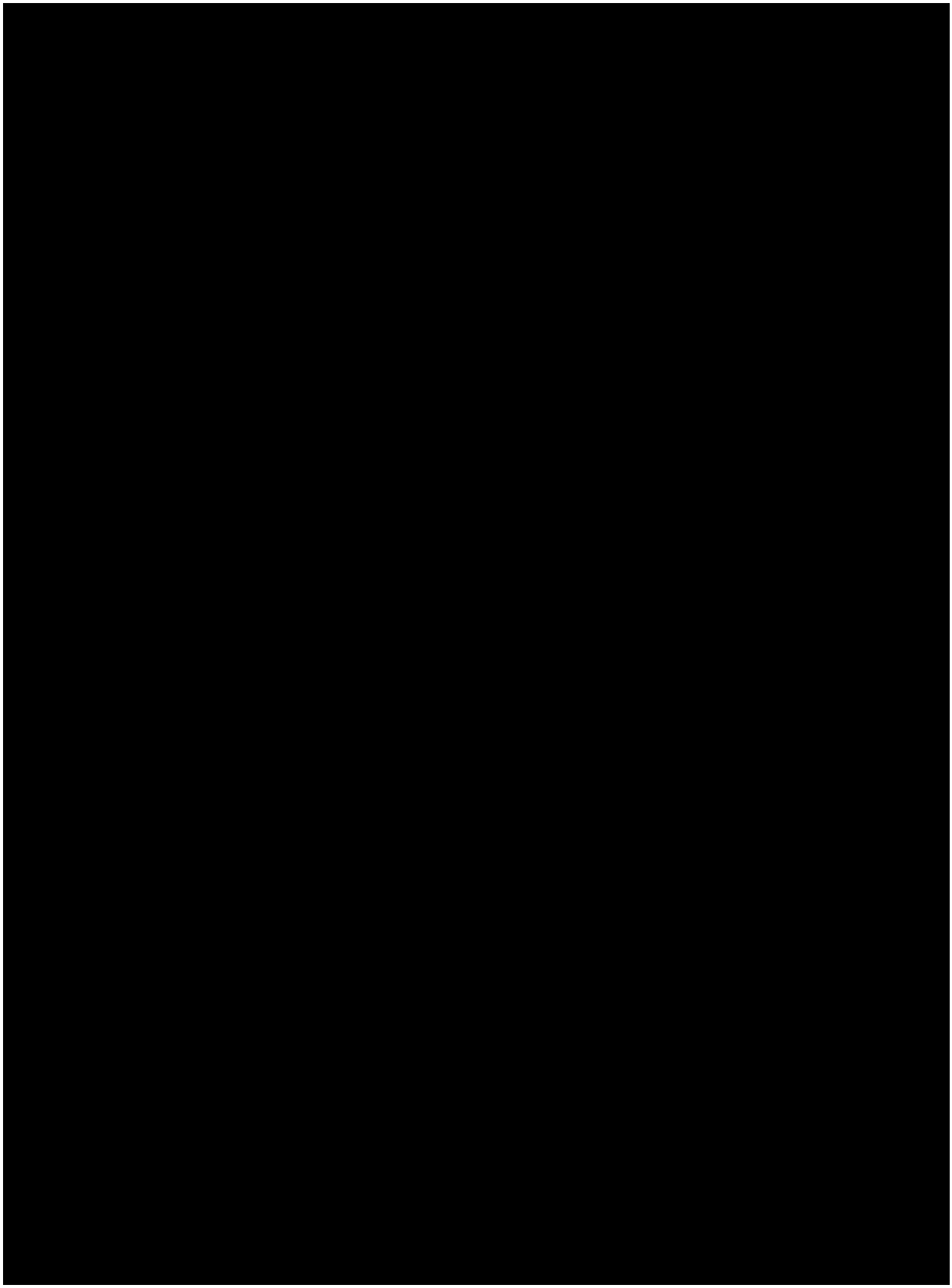
- Patient Global impression of symptom severity item
- Worst Pain intensity, item from the BPI, as collected with the PRO Diary
- Pain interference with general activity in the past 24 hours, as collected with the PRO Diary
- Location of pain, as collected with the PRO Diary
- Type of pain, as collected with the PRO Diary
- Dyspnea items, as collected with the PRO Diary
- PROMIS Profile domains

Age appropriate versions of the PRO tools will be used as described in Table 8-8 and Table 8-9. For the analysis, PRO scores based on adult self-reports (≥ 18 years old), child self-report (12-17 years), child reports with parent/caregiver assistance (3-11 years old) and parent/caregiver reports (<12 years old) will be presented separately.

Further details will be provided in the SAP.

[redacted]





[redacted]

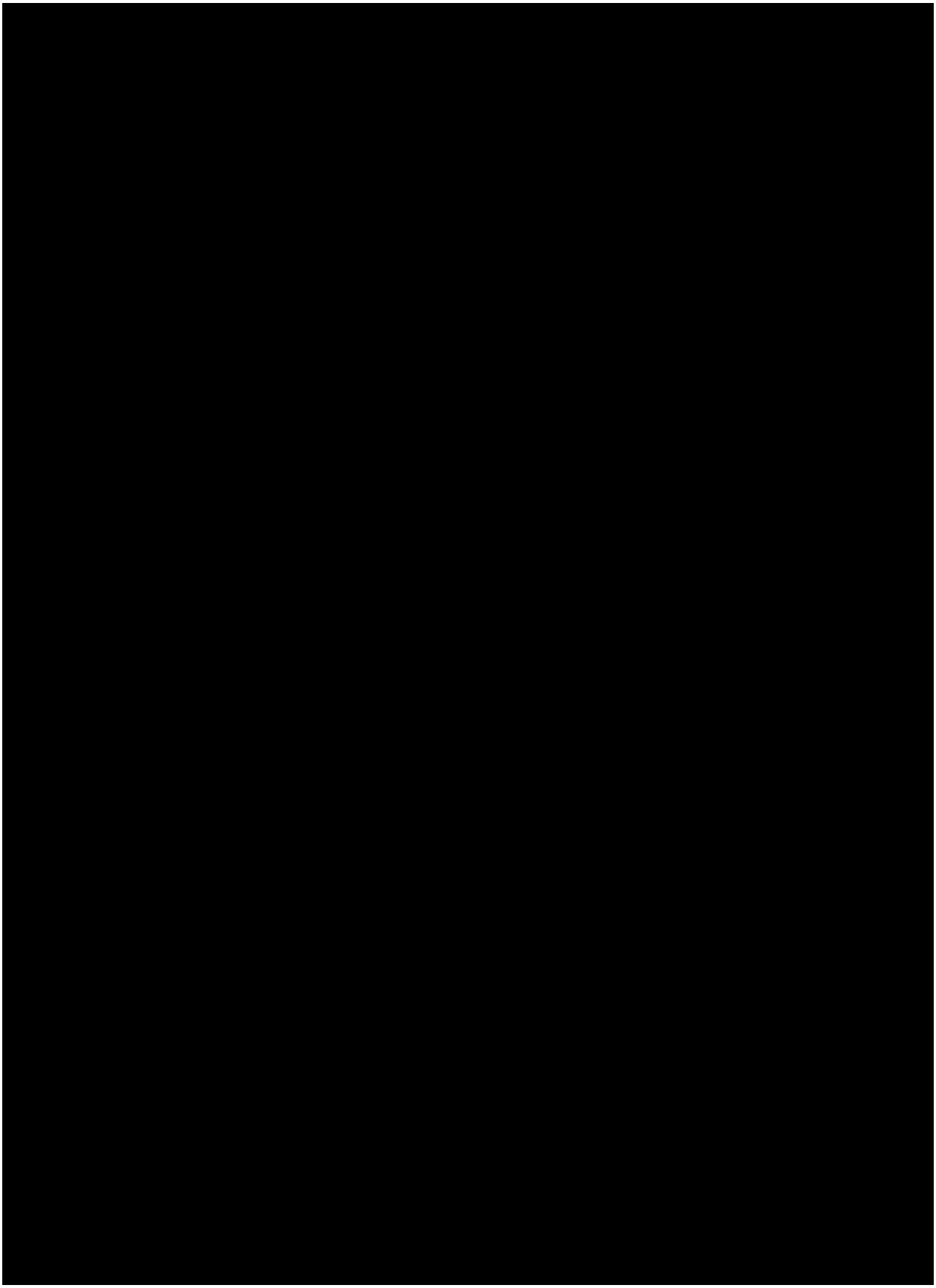
12.7 Interim analyses

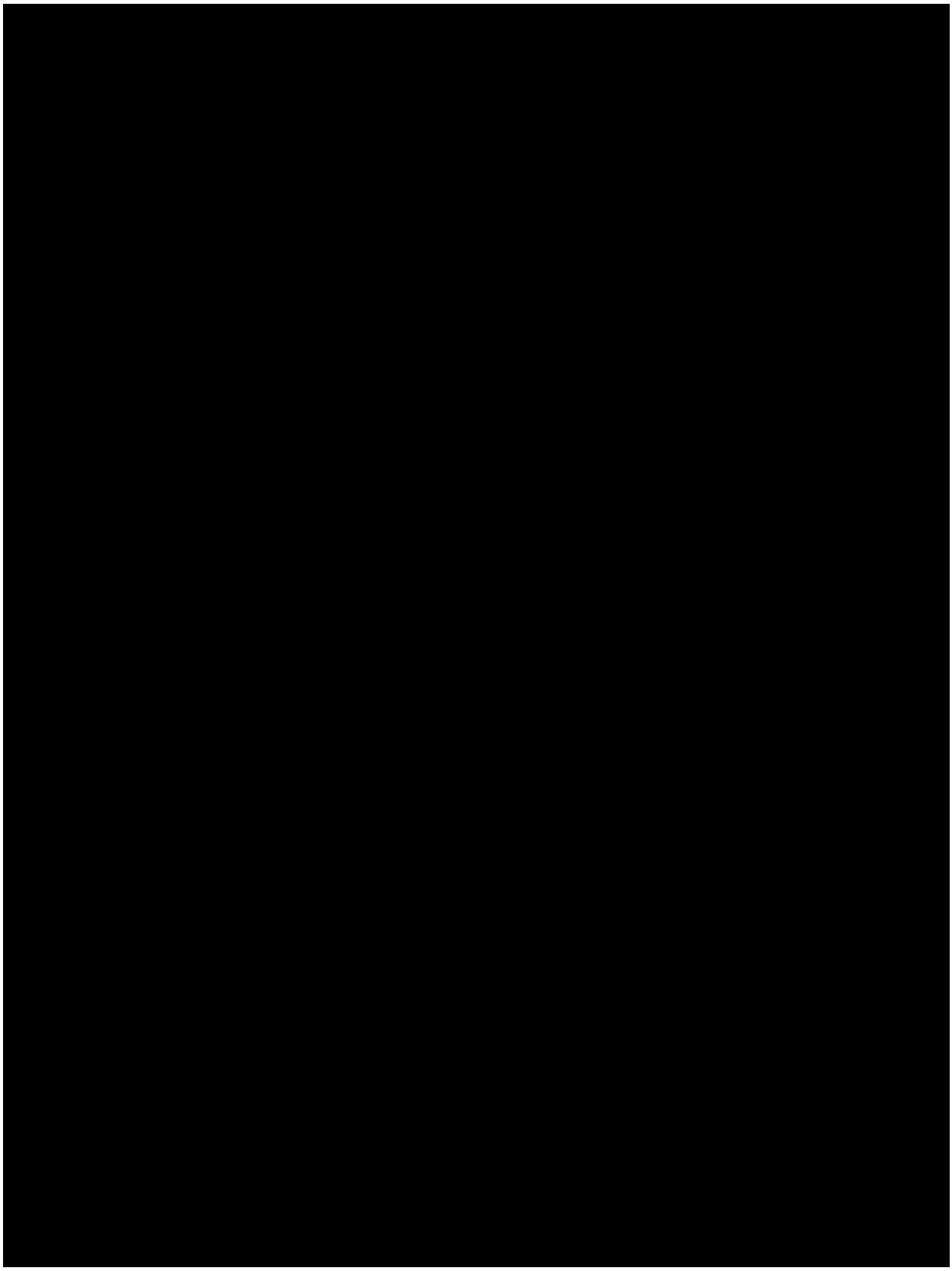
Interim analyses are planned for the monitoring of safety data by the DMC, and will be performed at defined intervals during the course of the study (see Section 10.2.2). Such safety analyses do not inflate type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

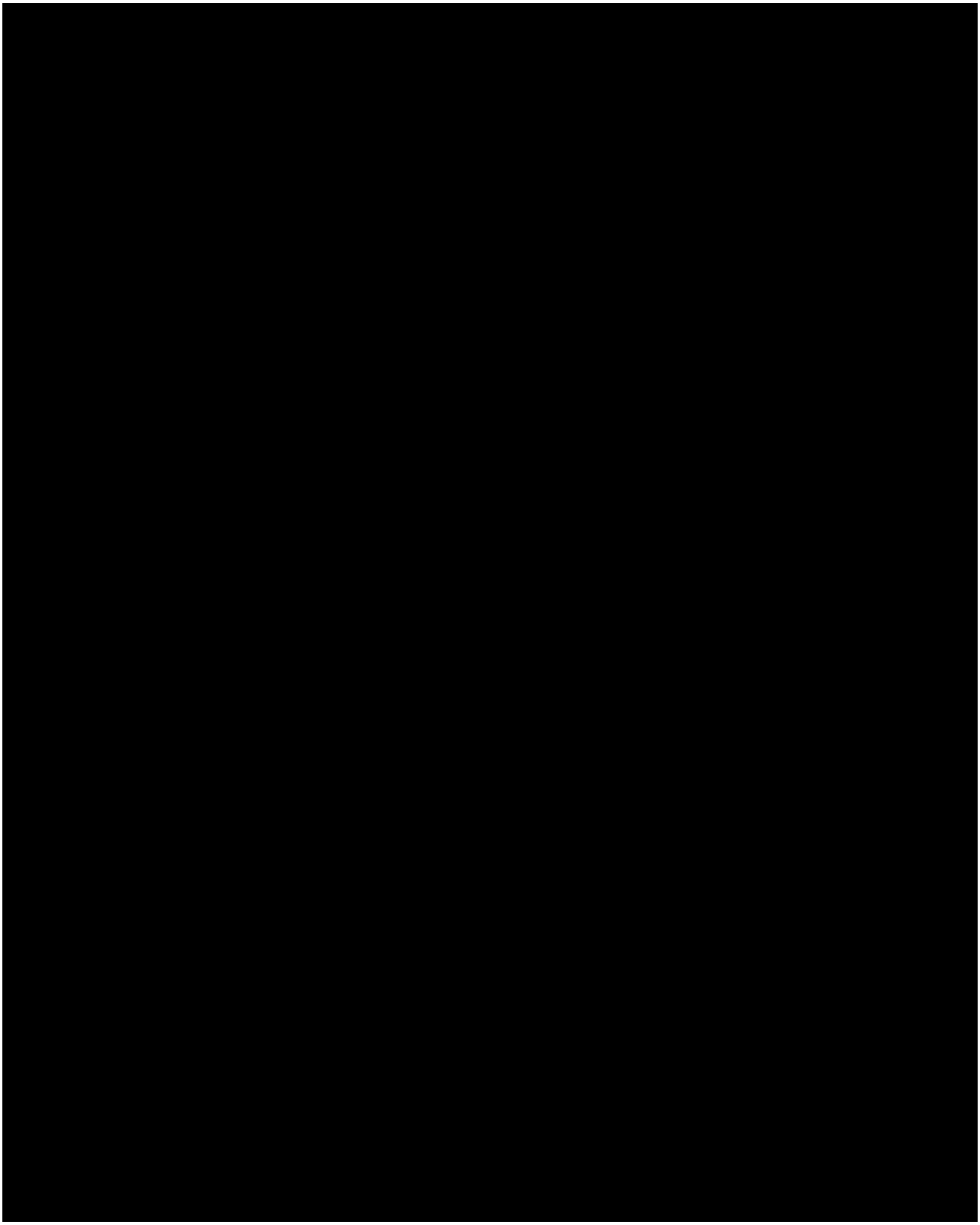
No formal interim analysis is planned on efficacy data for this study. The primary analysis will be performed after all participants in Groups 1 and 2 have completed Week 48 or discontinued prior to Week 48. [redacted]

A final analysis will be performed after all participants have completed the study (or discontinued earlier). Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point.

[redacted]







13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the

Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines

- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, Investigational Directions for Use (IDFU), and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a study, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the study protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as ClinicalTrials.gov and as required in CTIS public website. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results, such as the Novartis clinical study results website and all required Health Authority websites (e.g., ClinicalTrials.gov, CTIS public website etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the study Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results or primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of Investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical study. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant or their legally authorized representative must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

13.6 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modification to these requirements with Novartis.

- Thank You Letter – at study start and End of study
- Plain language trial summary – after CSR publication
- Individual study results – after CSR publication

- Trial Feedback Questionnaire (TFQ) – at Week 1 Day 1, Week 48 and Week 264 (End of Study Treatment)

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances, including incidental collection, is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

Adams DM, Trenor CC, Hammill AM, et al (2016) Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. Pediatrics; 137(2):e20153257.

Ader, Deborah N. (2007) Developing the Patient-Reported Outcomes Measurement Information System (PROMIS); 45(5):S1-S2.

Bretz F, Maurer W, Brannath W, et al (2009) A graphical approach to sequentially rejective multiple test procedures. Stat Med p. 586-604.

Busaidy NL, Farooki A, Dowlati A, et al (2012) Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. J. Clin. Oncol. p. 2919-28.

Canaud C, Gutiérrez JCL, Irvine A, et al (2021) EPIK-P1: Retrospective chart review study of patients (pts) with PIK3CA-related Overgrowth Spectrum (PROS) who have received alpelisib (ALP) as part of a compassionate use programme [abstract]. Annals of Oncology; 32 Suppl 5:S1297.

Caron PJ, Bevan JS, Petersenn S, et al (2014) Tumor shrinkage with lanreotide Autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J. Clin. Endocrinol. Metab. p. 1282-90.

Cella D, Choi SW, Condon DM, et al (2019) PROMIS® Adult Health Profiles: Efficient Short-Form Measures of Seven Health Domains. Value Health; 22(5):537–44.

Cleeland C (2009) The Brief Pain Inventory, user Guide.

De Santis MC, Sala V, Martini M, et al (2017) PI3K Signaling in Tissue Hyper-Proliferation: From Overgrowth Syndromes to Kidney Cysts. Cancers (Basel); 9(4):30.

Fine KD, Schiller LR (1999) AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology p. 1464-86.

Fritsch C, Huang A, Chatenay-Rivauday C, et al (2014) Characterization of the novel and specific PI3Kα inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. Mol. Cancer Ther. p. 1117-29.

Graham BL, Steenbruggen I, Miller MR, et al (2019) Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am. J. Respir. Crit. Care Med. p. e70-e88.

Greulich, WW and Pyle SI (1959) Radiographic Atlas of Skeletal Development of the Hand and Wrist; 8(4):513.

[redacted]

Hernán MA, Robins JM (2020) Causal Inference: What If. 1st edition. Boca Raton: Chapman & Hall/CRC, chapter 12 and 13. //.hsph.harvard.edu/miguel-hernan/causal-inference-book/.

Hojreh A, Gamper J, Schmook MT, et al (2018) Hand MRI and the Greulich-Pyle atlas in skeletal age estimation in adolescents. Skeletal Radiol. 47(7):963-71.

Hoste G, Slembrouck L, Jongen L, et al (2019) Correction to: Unexpected Benefit from Alpelisib and Fulvestrant in a Woman with Highly Pre-treated ER-Positive, HER2-Negative PIK3CA Mutant Metastatic Breast Cancer. Clin Drug Investig. 39(1):113.

Juric D, Rodon J, Tabernero J, et al (2018) Phosphatidylinositol 3-Kinase α-Selective Inhibition with Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results From the First-in-Human Study. J. Clin. Oncol. 36(13):1291-9.

Keegan NM, Gleeson JP, Hennessy BT, et al (2018) PI3K inhibition to overcome endocrine resistance in breast cancer. Expert Opin Investig Drugs; 27(1):1-15.

Keppler-Noreuil KM, Parker VE, Darling TN, et al (2016) Somatic overgrowth disorders of the PI3K/AKT/mTOR pathway & therapeutic strategies. Am J Med Genet C Semin Med Genet;172(4):402-21.

Keppler-Noreuil KM, Rios JJ, Parker VE, et al (2015) PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am. J. Med. Genet. A; 167A(2):287-95.

Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al (2014) Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. Am. J. Med. Genet. A p. 1713-33.

Kornblau S, Benson AB, Catalano R, et al (2000) Management of cancer treatment-related diarrhea. Issues and therapeutic strategies. J Pain Symptom Manage; 19(2):118-29.

Kuentz P, St-Onge J, Duffourd Y, et al (2017) Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. Genet. Med; 19(9):989-97.

Kurek KC, Luks VL, Ayturk UM, et al (2012) Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am. J. Hum. Genet. 90(6):1108-15.

Lee CA, O'Connor MA, Ritchie TK, et al (2015) Breast cancer resistance protein (ABCG2) in clinical pharmacokinetics and drug interactions: practical recommendations for clinical victim and perpetrator drug-drug interaction study design. Drug Metab. Dispos. p. 490-509.

Leoni C, Gullo G, Resta N, et al (2019) First evidence of a therapeutic effect of miransertib in a teenager with Proteus syndrome and ovarian carcinoma. Am. J. Med. Genet. A 179(7):1319-24.

Lindhurst MJ, Parker VE, Payne F, et al (2012) Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. Nat. Genet; 44(8):928-33.

Lindhurst MJ, Yourick MR, Yu Y, et al (2015) Repression of AKT signaling by ARQ 092 in cells and tissues from patients with Proteus syndrome. Sci Rep (5):17162.

Maurer W, Glimm E, Bretz F (2011) Multiple and Repeated Testing of Primary, Coprimary, and Secondary Hypotheses. Statistics in Biopharmaceutical Research; 3(2):336-52.

Miller MR, Crapo R, Hankinson J, et al (2005) General considerations for lung function testing. Eur. Respir. J. 26(1):153-61.

Mirzaa G, Timms AE, Conti V, et al (2016) PIK3CA-associated developmental disorders exhibit distinct classes of mutations with variable expression and tissue distribution. JCI Insight; 1(9):e87623.

Mirzaa GM, Rivière JB, Dobyns WB (2013) Megalencephaly syndromes and activating mutations in the PI3K-AKT pathway: MPPH and MCAP. Am J Med Genet C Semin Med Genet p. 122-30.

Parker VER, Keppler-Noreuil KM, Faivre L, et al (2019) Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. Genet. Med; 21(5):1189-98.

Patient-reported outcomes to support medical product labeling claims(2007): FDA perspective.

Patrick DL, Burke LB, Gwaltney CJ, et al (2011) Content validity-establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument. Value Health; 14(8s):967-77.

[redacted]

Ranieri C, Di Tommaso S, Loconte DC, et al (2018) In vitro efficacy of ARQ 092, an allosteric AKT inhibitor, on primary fibroblast cells derived from patients with PIK3CA-related overgrowth spectrum (PROS). Neurogenetics; 19(2):77-91.

Sasaki T, Ishibashi Y, Okamura Y, et al (2002) MRI evaluation of growth plate closure rate and pattern in the normal knee joint. J Knee Surg; 15(2):72-6.

Solomon J. et al. (2004) Data Driven Brain Tumor Segmentation in MRI Using Probabilistic Reasoning over Space and Time. Barillot C., Haynor D.R., Hellier P. (eds) Medical Image Computing and Computer-Assisted Intervention – MICCAI 2004. MICCAI 2004. Lecture Notes in Computer Science, vol 3216. Springer, Berlin, Heidelberg.

Suzuki Y, Enokido Y, Yamada K, et al (2017) The effect of rapamycin, NVP-BEZ235, aspirin, and metformin on PI3K/AKT/mTOR signaling pathway of PIK3CA-related overgrowth spectrum (PROS). Oncotarget; 8(28):45470-83.

The EuroQol Group (1990) EuroQol--a new facility for the measurement of health-related quality of life. Health Policy; 16(3):199-208.

Tomei E. et al. (2011) Determination of bone age using MRI of hand/wrist p. Poster C-0963.

Venot Q, Blanc T, Rabia SH, et al (2018) Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature; 558:540-6.

Vijoice® (alpelisib) United States Prescribing Information, Novartis Pharmaceuticals Corporation, April 2022. Available from: DailyMed - VIJOICE- alpelisib tablet VIJOICE- alpelisib kit (nih.gov).

Wadler S, Benson AB, Engelking C, et al (1998) Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J. Clin. Oncol; 16(9):3169-78.

[redacted]

Wong DL, Baker CM (1988) Pain in children: comparison of assessment scales. Pediatr Nurs;14(1):9-17.

16 Appendices

16.1 Appendix 1: PROS diagnostic criteria

Clinical Diagnostic Criteria for PROS

Required:

- Presence of somatic PIK3CA mutation*
- Congenital or Early Childhood Onset
- Overgrowth Sporadic and Mosaic (Other terms: Patchy, Irregular)
- Features as described in either A or B

A. Spectrum (two or more features)**

1. Overgrowth: Adipose, Muscle, Nerve, Skeletal
2. Vascular Malformations: Capillary, Venous, Arteriovenous Malformation, Lymphatic
3. Epidermal Nevus

B. Isolated features

1. Large Isolated Lymphatic Malformation
2. Isolated Macrodactyly*** OR Overgrown Splayed Feet/ Hands, Overgrown Limbs
3. Truncal Adipose Overgrowth
4. Hemimegalencephaly (bilateral)/ Dysplastic Megalencephaly/ Focal Cortical Dysplasia 2[1]
5. Epidermal nevus[2]
6. Seborrheic Keratoses[2]
7. Benign Lichenoid Keratoses[3]

Abbreviations: + present; − absent; HC hydrocephalus; ID intellectual disability

*If no mutation identified, then consider as presumptive PROS

**Typically Progressive. Can manifest as: Scoliosis (Kyphosis), Limb overgrowth, CNS (HC, Cerebellar tonsillar ectopia, Chiari, Megalencephaly, Mega corpus callosum, Regional lipomatous undergrowth with overgrowth, Infiltrating lipomatosis, Wilms tumor/ovarian cystadenoma

***Other terms: macrodystrophia lipomatosa, macrodactylia fibrolipomatosis and gigantism

1. Dobyns WB, 2014 (unpublished data);

2. Hafner et al. [2007];

3. Groesser et al. [2012]

Adopted from: Kim M. Keppler-Noreuil et al., PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. Am J Med Genet A. 2015 February ; 0(2): 287–295. Keppler-Noreuil et al 2015

16.2 Appendix 2: Karnofsky performance scale index

Percentage	Characteristics
100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0%	Death.

16.3 Appendix 3: Lansky play performance scale

Grade	Characteristics
100	Fully active, normal.
90	Minor restrictions in physically strenuous activity.
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play, keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed. Moribund

16.4 Appendix 4: Tanner assessment staging scale

Figure 16-1 Sexual maturity rating (Tanner stages) of secondary sexual characteristics

Boys – Development of external genitalia
Stage 1: Prepubertal
Stage 2: Enlargement of testes and scrotum; scrotal skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker
Stage 5: Adult genitalia
Girls – Breast development
Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3: Further enlargement of breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above level of breast
Stage 5: Mature stage: Projection of papilla only, related to recession of areola
Boys and girls – Pubic hair
Stage 1: Prepubertal (the pubic area may have vellus hair, similar to that of forearms)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser, and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult in type and quantity, with horizontal upper border

16.5 Appendix 5: QT Heart rate Fridericia's Correction Formula

$$QTc(Fridericia) = \frac{QT}{\sqrt[3]{RR}}$$

16.6 Appendix 6: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or alpelisib. Please note that all lists in this appendix are not comprehensive. Please refer to regular updated online sources and the label of a concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6.2.2. In doubt, please contact the medical monitor with any questions.

16.6.1 Permitted medication to be used with caution and/or action

As described in this list of CYP substrates was compiled from the University of Washington's Drug Interaction Database (Updated April 2019). This list only meant to be used as a guide.

Table 16-1 List of CYP450 substrates to be used with caution

Category	Drug names
CYP2C9 substrates	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin and other coumarin-derivative anticoagulants
Sensitive substrates of CYP2C9	Benzbromarone, Celecoxib, Glimepiride, Glipizide, (R)/(S)-Ibuprofen, Lornoxicam, Meloxicam, Piroxicam, Tolbutamine, (S)-Warfarin
CYP2B6 substrates	
Narrow Therapeutic index substrates of CYP2B6	Meperidine
Sensitive substrates of CYP2B6	Bupropion, Efavirenz
Selected CYP3A4 substrates	
Narrow Therapeutic index substrates of CYP3A	Alfentanil, Diergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine
Sensitive substrates of CYP3A	Alfentanil, Atazanavir, Atorvastatin, Darunavir, Lumefantrine, Midazolam, Simvastatin, Triazolam
CYP3A4 substrates which are known or potential auto-perpetrators	Clarithromycin, Conivaptan, Encorafenib, Erythromycin, Diltiazem, Mifepriston, Ribociclib, Telthromycin, Troleandomycin, Verapamil
* Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increase in their exposure levels by the concomitant use of potent inhibitors may lead to serious concerns (e.g. Torsades de Pointes, QT prolongation). ** Sensitive substrates: Drug that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor. CYP3A4 substrates which are auto-perpetrators: Based on Novartis internal assessment.	

16.6.2 Prohibited Medication

Strong inducers of CYP3A4

This list of CYP inducers was compiled from the University of Washington's Drug Interaction Database (Updated April 2019). This list only meant to be used as a guide.

Table 16-2 List of prohibited strong inducers of CYP3A

Category	Drug Name
Strong CYP3A Inducers	Apalutamide, Avasimibe[1], Carbamazepine, Enzalutamide, Ivosidenib, Lumacaftor, Mitotane, Phenobarbital, Phenytoin, Rifabutin, Rifapentine, Rifampin (Rifampicin), St. John's wort (hypericum perforatum)[1]
[1] Herbal product	

Inhibitors of BCRP

The table encompasses only drugs and molecular entities for which inhibition of BCRP has been investigated and/or formally shown in vivo in a clinical DDI study. Please note that this is not an exhaustive list and only meant to be used as a guide. When in doubt, refer to the prescribing information of the drug to assess whether a potential for BCRP inhibition is described.

Table 16-3 List of prohibited BCRP inhibitors

Category	Drug Name
BCRP inhibitors - Evidence for DDI potential shown in vivo	Protease Inhibitors (e.g., Atazanavir/ritonavir[1,2], , Lopinavir/ritonavir[1,2], Tipranavir/ritonavir[1,2], Tipranavir[2] , Paritaprevir[2]), Elvitegravir/cobicistat[1,2], Curcumin[1,2], Cyclosporine[1,2], Daclatasvir[1,2], Ledipasvir[2], Eltrombopag[1,2], Gefitinib[2], Lapatinib[1], Pantoprazole[1,2]

[1] Lee et al 2015
[2] Novartis PK Sciences DDI List (January, 2018)