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Clinical Development & Medical Affairs

SOM230 (Pasireotide) LAR and RAD001 (Everolimus)

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Multicenter 3-arm trial to evaluate the efficacy and safety of Pasireotide LAR or Everolimus alone or in combination in patients with well differentiated neuroendocrine carcinoma of the lung and thymus -LUNA Trial

RAP Module 3 – Detailed Statistical Methodology

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Amendment 1.0	09-Feb-2016	Section 3.4.1 (Core phase analysis) – clarification is added on safety follow up data inclusion for patients who do not enter extension phase.
Amendment 1.0	09-Feb-2016	[redacted]
Amendment 1.0	09-Feb-2016	[redacted]
Amendment 1.0	09-Feb-2016	[redacted]
Amendment 1.0	09-Feb-2016	Section 10.15 (Vital signs): Clarification is added on the value classification (low/normal/high) for baseline and post-baseline measurements. This classification is needed for the shift table output.
Amendment 1.0	09-Feb-2016	Sections 3.2, 7.4, 7.5 – Clarification added that for tumor response related assessments, confirmation of response is required.
Amendment 1.0	09-Feb-2016	[redacted]
Amendment 1.0	09-Feb-2016	Section 5.3 – Clarified that partial end dates will be imputed to derive prior/concomitant status.
Amendment 1.0	09-Feb-2016	Section 6.3.3 – Table 5 - Brackets for posterior probability intervals updated for consistency with cumulative distribution function. Specified seed to be used for random draws.
Amendment 1.0	09-Feb-2016	[redacted]
Amendment 1.0	09-Feb-2016	[redacted]
Amendment 1.0	09-Feb-2016	Section 10.1 – Changed terminology ‘clinically notable adverse events’ to ‘adverse events of special interest’.
Amendment 2.0	10-Oct-2018	Sections 1 and 9.6.2 – Updated using latest version of protocol.
Amendment 2.0	10-Oct-2018	[redacted]
Amendment 2.0	10-Oct-2018	Section 3.4.2 – Updated to clarify that PFS endpoint will be analyzed on PP Set as well in extension phase analyses.
Amendment 2.0	10-Oct-2018	Section 3.5 – Updated to indicate that protocol deviations will

Version	Date	Changes
		be re-evaluated and PP Set will be used in extension phase analyses as well.
Amendment 2.0	10-Oct-2018	Section 5.2 – Amended list of outputs which will be repeated based on subset of patients entering extension phase.
Amendment 2.0	10-Oct-2018	Section 7.1 – Updated to clarify that PFS endpoint will be analyzed on PP Set as well in extension phase analyses.
Amendment 2.0	10-Oct-2018	Section 7.3 – Clarification added that endpoint is analyzed up to 12 month only.
Amendment 2.0	10-Oct-2018	Section 7.4 – Updated to indicate that endpoint will be rerun during extension phase analyses based on cumulative data.
Amendment 2.0	10-Oct-2018	Section 7.5 – Clarification added that endpoint is analyzed up to 12 month only.
Amendment 2.0	10-Oct-2018	Section 7.6 – Clarification added that endpoint is analyzed up to 12 month only.
Amendment 2.0	10-Oct-2018	Section 7.7 – Updated to indicate that endpoint will be rerun during extension phase analyses based on cumulative data.
Amendment 2.0	10-Oct-2018	Section 7.8 – Updated to indicate that endpoint will be rerun during extension phase analyses based on cumulative data.
Amendment 2.0	10-Oct-2018	[redacted]
Amendment 2.0	10-Oct-2018	Section 10 - Updated general statement on extension phase analyses to clarify that analyses performed after extension phase will include cumulative data.
Amendment 2.0	10-Oct-2018	Section 10.1 – Added description of two new AE summary tables.
Amendment 2.0	10-Oct-2018	Section 10.1 – Updated process of groupings of adverse events of special risk.
Amendment 2.0	10-Oct-2018	Section 11 – Clarification added that DMC analyses were performed during core phase only.
Amendment 3.0	15-Aug-2019	Section 3.4.2 – Removed duration of response analysis from extension phase analysis and added clarification that all analyses and data reporting after extension phase will be reported in the extension phase CSR only.
Amendment 3.0	15-Aug-2019	Section 3.6 – Added note on the subset of patients who entered extension phase and listed the analyses for which this subset will be used.
Amendment 3.0	15-Aug-2019	Section 5.2 – Removed prior therapy analyses from the list of analyses that are repeated for extension phase analysis.
Amendment 3.0	15-Aug-2019	Section 5.4.2 – Removed duration of exposure categories.
Amendment 3.0	15-Aug-2019	Section 5.4.3 – Updated the description of relative dose intensity summary table.
Amendment 3.0	15-Aug-2019	Section 7.4 – Removed statement of repeating duration of response endpoint analysis at the time of extension phase analysis.
Amendment 3.0	15-Aug-2019	[redacted]

Version	Date	Changes
		[redacted]
Amendment 3.0	15-Aug-2019	[redacted]
Amendment 3.0	15-Aug-2019	Section 10.9 – Removed shift table of ECHO or MUGA scan and added clarification that only baseline results will be presented in a summary table.
Amendment 3.0	15-Aug-2019	Section 10.16 – Added description of bar chart displaying the percentage distribution of ECOG performance score.
Amendment 3.0	15-Aug-2019	Section 5.4.3 – Relative dose intensity categories have been added.
Amendment 3.0	15-Aug-2019	Section 10.16 – Slight update in sentence describing bar charts provided for ECOG performance score.
Amendment 3.0	15-Aug-2019	Section 3.8 – Further details added on review of protocol deviations before extension phase database lock.
Amendment 3.0	15-Aug-2019	Section 5.2 – Clarification added that prior long acting analogue therapy and prior antineoplastic therapy summaries will be repeated during extension phase analyses based on the subset of Full Analysis Set who entered extension phase where prior therapy data is collected in core phase.
Amendment 4.0	01-Apr-2020	Section 5.3 – Added statement that concomitant medication table created as part of extension phase analyses will be repeated excluding any patient with missing Safety Follow-up assessments during Extension phase.
Amendment 4.0	01-Apr-2020	[redacted]
Amendment 4.0	01-Apr-2020	Section 10.5 – Added statement that tables created as part of extension phase analyses will be repeated excluding any patient with glucose, insulin and HbA1c assessment missing page during Extension study phase.

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List of Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid
AC	Atypical carcinoid
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BAL	Bronchoalveolar lavage
BOR	Best overall response
BPFS	Biochemical progression free survival
BR	Biochemical response
BRR	Biochemical response rate
BUN	Blood urea nitrogen
CgA	Chromagranin A
CR	Complete response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computer tomography
CTC/CTCAE	Common Toxic Criteria/Common Toxic Criteria for Adverse Events
DBL	Database lock
DBR	Duration of biochemical response
DCR	Disease control rate
DI	Dose intensity
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic Case Report/Record Form
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
EOCS	End of core study
EOEP	End of extension phase
EOT	End of treatment
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
FPFV	First patient, first visit
FVC	Forced vital capacity
GGT	Gamma-glutamyl transpeptidase
H0	null hypothesis
H1	alternative hypothesis
HbA1c	Hemoglobin A1c subtype (glycated hemoglobin)
HDL	High density lipoprotein
IGF	Insulin-like growth factor
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
i.m.	Intramuscular
INR	Internation Normalized Ratio
ITT	Intent-to-Treat
K-M	Kaplan-Meier
LAR	Long-Acting Release
LDL	Low density lipoprotein
LLN	Lower limit normal
LPLV	Last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mTOR	mammalian target of rapamycin
MUGA	Multiple-Gated Acquisition
NA	Not Applicable
NCI	National Cancer Institute
NET	Neuroendocrine Tumor
NEU	Neutrophils

p.o.	per os/by mouth/orally
PD	Progressive Disease
PFR-9	Progression-free at Month 9
PFS	Progression-free survival
PFT	Pulmonary function test
PI3K	Phosphoinositide 3-kinase
PP	Per-Protocol
PR	Partial Response
PTT	Partial prothrombin Time
RAP	Reporting Analysis Plan
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase SSC
TC	Typical carcinoid
T3	Tri-iodothyronine
T4	Levothyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper Limit Normal
Unsch	Unscheduled visit
UNK	Unknown
WBC	White Blood Cell
WHO	World Health Organization

1 Statistical methods planned in the protocol

This Report Analysis Plan (RAP) contains details of the statistical methods that will be applied for the final analyses to be incorporated into the CSR. This document is based on the clinical trial protocol version no. 5 dated November 7, 2016.

The purpose of this study is to assess the efficacy and safety of pasireotide long-acting release (LAR) and everolimus alone or in combination.

The rationale for this study is based on both preclinical and clinical considerations:

- Combined inhibition of the IGF-1-, the PI3K- and the mTOR-pathways by pasireotide and everolimus may control tumor growth more effectively than either compound alone.
- Combination of everolimus with sandostatin LAR seems to improve progression free survival in NET patients. Thus the combination of everolimus with pasireotide LAR might result in even better tumor control.

This is a prospective, multicenter, randomized, open-label, 3-arm, phase II study with a single-stage design in each arm to evaluate the efficacy and safety of pasireotide LAR and everolimus alone or in combination in the treatment of patients with well differentiated neuroendocrine carcinoma of lung and thymus.

The number of evaluable patients enrolled is targeted to be 120 with 40 patients randomized to each arm as follows:

- Arm 1 treatment with pasireotide LAR (SOM230) (60 mg/month i.m.),
- Arm 2 treatment with everolimus (RAD001) (10 mg/day p.o.), and
- Arm 3 treatment with pasireotide LAR (60 mg/month i.m.) and everolimus (10 mg/day p.o.)

Randomization is stratified by histological grade of well-differentiated tumor (typical carcinoid (TC) vs. atypical carcinoid (AC)) according to the World Health Organization (WHO) classification and line of treatment (1^{st} line vs. others).

The study is designed to assess the activity, safety, and tolerability of the therapy with pasireotide LAR and/or everolimus in each arm separately following a Fleming single-stage design. Each arm is independently evaluated using the decision rules given in the sample size calculation (see Section Determination of sample size).

This study consists of a core study and an extension phase. Patients will receive treatment with study drug(s) for a period of 12 months or until one of the following occur:

- radiologically documented disease progression
- start of new cancer therapy
- intolerable toxicity
- withdrawal of consent

- discontinuation due to any other reason.

Patients will be considered to have completed the core study after the 12 month evaluation has been performed. Patients who are presenting clinical benefit from the treatment with combination or monotherapy with pasireotide LAR and everolimus are permitted to continue treatment after the 12 month treatment period until progression as long as they do not fulfill any of the study discontinuation criteria or as long as the Clinical Trial ceases to be in the interests of the health of the Clinical Trial Patients, or until the pasireotide and/or everolimus development programs is discontinued, whichever comes first.

The end of the study is defined as the last visit two years after treatment start of the last randomized patient or when all patients have progressed whichever comes earlier.

Data will be analyzed by [redacted] according to the data analysis section 10 of the study protocol which will be available in Appendix 16.1.1 of the Clinical Study Report (CSR).

2 Discrepancies between RAP and protocol-specified analyses

The following discrepancy exists between the Reporting Analysis Plan (RAP) and the study protocol version 05, dated 7th November 2016. This discrepancy has become apparent during development of the RAP.

[redacted] At the RAP review stage it was decided that 95% confidence intervals will be displayed instead following template conventions and presentation methods for other parameters.

3 Statistical and analytical plans

3.1 Primary objective

- To evaluate the efficacy of pasireotide LAR and everolimus alone or in combination in progressive patients with a well differentiated neuroendocrine tumor of the lung or thymus. The primary endpoint is defined as the proportion of patients who are progression-free at 9 months, according to response evaluation criteria in solid tumors (RECIST V.1.1).

3.2 Secondary objectives

- To assess overall progression-free survival (PFS) throughout the study in patients with a well differentiated neuroendocrine tumor of the lung or thymus. The endpoint **"progression-free survival (PFS)"** is defined as the time from first study drug administration to objective tumor progression or death from any cause, according to RECIST V. 1.1.
- To assess the **disease control rate** of pasireotide LAR and everolimus alone or in combination, at 12 months, in patients with a well differentiated neuroendocrine tumor

of the lung or thymus. Disease control rate is defined as the proportion of patients showing a best overall response of complete (CR) or partial (PR) response or stable disease (SD) according to RECIST V.1.1

- To assess the time to response, duration of response, objective response rate and best overall response of pasireotide LAR and everolimus alone or in combination during 12 months of treatment in patients with a well differentiated neuroendocrine tumor of the lung or thymus. The endpoint **"time to response"** is defined as the time from start of treatment to the first objective tumor response (PR or CR) observed, according to RECIST V.1.1. The endpoint **"duration of response"** is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause. Tumor response will be analyzed using the criteria of confirmation, i.e. patients will need to have confirmed CR or PR overall assessment before PD or end of core phase measured at least 4 weeks apart each other to be included in the subset of responders. The endpoint **"objective response rate"** is defined as the percentage of patients showing a best overall response of CR or PR according to RECIST V.1.1. criteria. Objective response rate will be summarized at 9 months and again at 12 months. The endpoint of "**best overall response**" is defined as the best response recorded from the start of the treatment until disease progression/recurrence, taking as a reference for PD the smallest measurements recorded since the treatment started.
- To assess the biochemical response rate (BRR), duration of biochemical response (DBR) and biochemical progression-free survival (BPFS) of pasireotide LAR and everolimus alone or in combination in patients with a well differentiated neuroendocrine tumor of the lung or thymus. The endpoint **"biochemical response rate (BRR)"** is the percentage of patients showing normalization, i.e. return to within normal ranges, or a decrease of ≥ 30% from baseline of serum Chromogranin A (CgA) concentrations compared to baseline. The endpoint of **"duration of biochemical response (DBR)"** is defined as the time from the first documentation of biochemical response to the first documentation of biochemical progression (defined as an increase of serum CgA levels ≥ 25% versus baseline) or to death due to any cause, whichever occurs first. The endpoint of **"biochemical progression free survival (BPFS)"** is the time from the first study drug administration to the first documentation of biochemical progression or to death due to any cause, whichever occurs first. Biochemical progression is defined as an increase of serum CgA levels ≥ 25% versus baseline. Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed.
- To assess the safety and tolerability of pasireotide LAR and everolimus alone or in combination as measured by rate and severity of adverse events in patients with a well differentiated neuroendocrine tumor of the lung or thymus. Safety will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in vital signs, ECG tracings and laboratory results (hematology, blood chemistry) will be reported.

3.4 Data included in the analysis

The data will be analyzed by Novartis and/or [redacted] Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation. It is planned that the data from participating centers in this protocol will be combined within each of the arms, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, [redacted], where applicable. Time to event data will be analyzed using the Kaplan-Meier methodology and will be presented as Kaplan-Meier plots and Kaplan-Meier estimates.

Efficacy and safety analyses will be conducted on all patient data, both from the core study and extension phase. Note that the analysis carried out at the end of the core study will be of primary importance with analysis at the end of the extension phase being exploratory only.

3.4.1 Core phase analysis

For the core analysis, the data cutoff will be the 12 month or end of core phase evaluation and the analysis will take place after the last randomized patient has completed the 12 Month evaluation, or discontinued the study treatment due to progression or start of new anti-cancer therapy.

Only data from the 12 month core phase will be used in the core analyses, any data from the extension phase will be excluded. For patients who do not enter extension phase, safety follow up data (if available) will be included in the core analyses.

All events with start date before or on the 12 month evaluation date and with an end date after the 12 month end date will be reported as '*continuing at the end of the core phase*'. The same rule will be applied to events starting before or on the 12 month evaluation date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the 12 month evaluation date will not be imputed and therefore will not appear in the listings.

Imputation of end date will be performed with the 9 or 12 month evaluation date when needed for specific analyses e.g. exposure and dose intensity computation.

3.4.2 Extension phase analysis

For each arm, a final analysis on all data collected, including data from the core phase – unless otherwise specified - will be performed once the last patient discontinues the study treatment. All this data will be listed.

Only PFS analyses and all safety analyses will be repeated at the end of the extension phase since no changes are expected to the core data after the core analysis is performed. A formal check will be carried to demonstrate no change, or to document if any changes. All TLFs will not be rerun during the formal check, if any change is detected in the data, then it will be documented in the CSR. All analyses and data reporting performed after extension phase is completed will be reported in the extension phase CSR only.

3.5 Patients and treatments

The number and percentage of patients in each analysis set and each stratum split by treatment group will be summarized using the total number of patients randomized as the denominator for percentages. A listing of this information will also be provided based on all randomized patients. This will include the population flags, whether they were included or excluded from that specific population.
Protocol deviations severity codes defined in VAP Module 3 will lead to patient classification into the analysis sets as follows:

Severity Codes	Actions
0	Exclude from all efficacy analysis (including FAS)
1	Exclude from Per-Protocol analysis

Table 1 - Analysis set exclusions based on severity codes

Analysis set	PD severity codes that cause a patient to be excluded	Non-PD criteria that cause a patient to be excluded
Full	0	Did not receive at least one dose of study drug
Safety	NA	Did not receive at least one dose of study drug, or did not have at least one post-baseline safety assessment
Per-Protocol	0, 1	NA

A frequency tabulation of the protocol deviations leading to exclusion from analysis sets will be presented based on the number of patients in the full analysis set along with an associated listing for the core phase analyses. This listing will include the severity, the deviation code and the related description. Protocol deviations will be re-evaluated at the end of extension phase, therefore frequency table will be rerun at the end of extension phase based on

cumulative data. A listing will also be created displaying all protocol deviations recorded during the whole study.

3.6 Full Analysis Set (FAS)

The full analysis set consists of all patients who received at least one dose of study drug**.** Following the intent-to-treat (ITT) principle, patients will be analyzed according to the treatment and stratum they were assigned to at randomization. Disposition, demography and analyses of disease history will be repeated at the time of extension phase analysis based on those subset of full analysis patients, who started extension phase.

3.7 Safety Set

The safety set consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety set. Patients will be analyzed according to the study treatment (regimen) they actually received. Patients who received, during the whole treatment period, a treatment different from the one assigned at randomization will be analyzed according to the actual treatment received. Patients who received a non-randomized treatment for part of the trial will be analyzed as having received both treatment arms i.e. will be counted in the Pasireotide LAR and everolimus group.

3.8 Per-Protocol Set

The per-protocol set consists of all patients from the full analysis set without major protocol violations. Appendix 1 of VAP module 3 lists all major protocol violations.

The per-protocol set definition will be finalized prior to database lock and might be revised prior to extension phase database lock after the review of protocol violations collected during the whole study.

3.9 Assessment windows, baseline and post-baseline definitions, missing data handling

3.9.1 Assessment windows

Patients will be assessed at baseline (day -28 to -1) and will then attend up to 16 visits during the core study with a separate assessment being completed at the end of the core study (EOCS) (12 months), either completion or early withdrawal. Those patients presenting with clinical benefit and not experiencing unacceptable toxicity at the 12 month visit will continue into the extension phase until progression occurs. They will attend visits every 3 months with a separate assessment being completed at the end of the extension phase (EOEP) when progression occurs, patient withdraws or two years after treatment start of the last evaluable patient. All patients who discontinue study treatment must have safety evaluations 56 days after the last dose of pasireotide LAR or everolimus, whichever comes last. This includes those who didn't enter extension phase due to disease progression at week 52. Endpoints (i.e. EOCS and EOEP) will be summarized as per scheduled visits. Any data from unscheduled

visits (Unsch), will be listed. Early withdrawal visits will continue to be displayed at the EOCS visit i.e. it will not be re-mapped to the most appropriate visit.

Visits will be labeled as follows: Baseline, Day 1, Day 15, Day 21, Day 29, Day 49, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337, EOCS, 3 Mths Extn, 6 Mths Extn, 9 Mths Extn, 12 Mths Extn, 15 Mths Extn,…., EOEP, Safety FU, Unsch.

The tumor assessments will be time-slotted using the time windows displayed in Table 2.

Table 2 - Time windows for tumor assessments

Time Window	Planned Visit Timing		Time Window Definition				
Week 12	Study Day 85	(Week 12)	]0; 126]	days	or	]0; 18]	weeks
Week 24	Study Day 169	(Week 24)	]126; 210]	days	or	]18; 30]	weeks
Week 36	Study Day 253	(Week 36)	]210; 294]	days	or	]30; 42]	weeks
Week 48	Study Day 337	(Week 48)	]294; 351]	days	or	]42; 50]	weeks
Week 52	Study Day 365	(Week 52)	]351; 379]	days	or	]50; 54]	weeks
Week 64	Study Day 449	(Week 64)	]379; 491]	days	or	]54; 70]	weeks
Week k	Study Day x x= k*7+1 ;	(Week y) y=k	]x-43; x+41]	days	or	]y-6; y+6]	weeks
Study Day 1 = start of study treatment date							

Similarly to tumor assessments, week-based time windows [redacted]. If more non-missing results fall into a specific time window, then the one will be chosen which is closer to the optimal study day of the specific time window.

[redacted]

[redacted]

3.9.2 Baseline and post-baseline definitions

For ***efficacy evaluations***, the last available assessment before or at date of start of study treatment is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations include also ECOG performance status.

For ***safety evaluations*** (i.e. laboratory and vital signs), the last available assessment before or at date of start of study treatment is taken as "baseline" assessment.

If patients have no value as defined above, the baseline result will be missing.

3.9.3 Missing data handling

Throughout the study reasonable attempts will be made to limit the amount of missing data. However the majority of missing data will not be imputed. The only exceptions to this are for the RECIST calculations, see the table in the Primary efficacy evaluation section and censoring for the time to analyses detailed in the secondary efficacy evaluation sections.

4 General Strategies of Data Presentation

All categorical data will be summarized by frequencies and percentages. Where categorical data is missing, a 'Missing' row will be included at the bottom with frequencies and percentages for it also presented.

Continuous data will be summarized with either standard descriptive statistics (i.e. the number of non-missing data points, arithmetic mean, standard deviation, minimum, median and maximum), or will be collapsed into categorical data and summarized as categorical data.

Day 1 is relative to the treatment start date and is calculated as date of interest – treatment start date + 1. For visits/events occurring prior to treatment start date the '+1' will be excluded, so the day before day 1 is day -1.

5 Patient Disposition, background and demographic characteristics

5.1 Patient disposition

All patient disposition outputs will be performed on the full analysis set.

The number of patients who received study drug, completed the core study and entered extension phase will be summarized. For patients who discontinued their reason for discontinuing will be presented. This will be summarized for the core study and the extension phase separately.

A listing will include details of patients' last known date of study medication, whether they completed or discontinued and the primary reason for any discontinuation for both the core study and extension phase (if applicable), whether the patient is followed up for post treatment evaluation and death date if applicable.

A separate listing will also be presented which only includes screening failure patients. This will include the reason for screening failure.

5.2 Demographics and baseline characteristics variables

Demographics and baseline characteristics will be summarized using the full analysis set. The demographics of age (both numeric and categorical (<65 & >=65)), sex, race, body mass index and Eastern Cooperative Oncology Group (ECOG) performance status (World Health Organization (WHO)) at baseline will be summarized. A listing will also be provided summarizing this information along with the height (cm), weight (kg) and child-bearing potential for women.

An additional listing will provide details of the pregnancy test, both at screening and post-baseline (including extension phase pregnancy test results as well). This will include the visit, sample date, the method (serum, urine) and the result (negative, positive).

The baseline stratification factors (i.e. histologic grade and treatment line) will be cross-classified, tabulated and listed against the stratification factors actually used at randomization (contained in the IVRS dataset).

Diagnosis and extent of cancer will also be summarized and listed. This will include primary site of cancer (lung, thymus), KI67 index categories, functional status of tumor (functioning, non-functioning), histologic grade as recorded on the eCRF (typical, atypical), treatment line (first line, others) time since initial diagnosis of primary site in months, type of lesions at baseline (target only, non-target only, both target and non-target), the presence of metastatic disease (yes, No) and if present the location of this. Time since initial diagnosis of primary site will be calculated as the date of the baseline visit minus the dates of initial diagnosis of primary site divided by 30.4375. Partial dates will be handled in the following way: where the day is missing e.g. XXAPR74 then the day will be imputed as 01, e.g. 01APR74, where the date and month are missing XXXXX73 then the day will be imputed as 01 and the month as JAN, e.g. 01JAN73. A listing will also present this information along with the date of first diagnosis.

Relevant medical history/current medical conditions will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by system organ class and MedDRA preferred term. Separate summary tables will be provided for past medical condition and current medical condition. A current medical condition will be those on the CRF that are flagged as an active problem. A listing of all relevant medical history/current medical conditions will be presented. This will include reported term, preferred term and system organ class, the diagnosis/surgery date and whether or not it is still an active problem.

History of prior long-acting somatostatin analogue therapy will be summarized, identifying any use of octeotride or lanreotide, as well as summarizing exposure to prior somatostatin analogues, in terms of both summary statistics and categorical frequencies (<6 months, ≥6 months - <2 years, ≥2 years - <5 years, ≥5 years). Duration of exposure (months) will be calculated as (end date of somatostain analogue therapy – start date of somatostatin analogue therapy + 1) / 30.4375. A listing summarising the long-acting somatostatin therapies will also be presented.

Prior antineoplastic therapies will also be summarized overall, and separately by therapy type (Medications (solid tumor), Radiotherapy, Surgery/local or regional therapy). The medications (solid tumor) table will include if any prior antineoplastic regimens occurred and

if so the number, setting and best response at last treatment. The radiotherapy table will summarize if any prior radiotherapy occurred and if so the location, along with the setting and best response at last radiotherapy. The surgery/local or regional therapy table will include if any prior surgery occurred, the time since last surgery, procedure at last surgery and whether there was any residual disease. All these summaries will be based on the full analysis set. Listings will also be provided for each of the therapy types separately. The listing for medications (solid tumor) will include regimen number, medication, route, setting, number of cycles, start date, end date, best response, the duration of response and the date of progression. The listing for Radiotherapy will include location, start date, end date, cumulative dose and unit, setting, best response, method and whether or not the patient had received radiotherapy to 30% or more of their bone marrow. The listing for Surgery/local or regional therapy will include the procedure, the date of surgery and the residual disease.

Basic demographic data, disease history, prior long acting somatostatin analogue therapy and prior antineoplastic therapy summaries (overall, surgery, radiotherapy and medication, where data is collected in core phase) will be repeated for extension phase analyses displaying data on only the subset of patients entering extension phase.

5.3 Concomitant Medications

Prior and concomitant medications will be collected throughout the study and will be coded according to the latest version of the WHO Drug Reference List. The actual medication listed on the CRF along with the coded name, Anatomical Therapeutic Chemical (ATC) classes, reason, start date, stop date, dose, unit, frequency, route and a flag for prior/concomitant status will be listed. The prior/concomitant flag will be identified using the end date of the medication; if the end date is prior to the start of study treatment then the medication is defined as prior, otherwise it is concomitant. Partial end dates will be imputed and flagged in the listing. Details are provided in RAP Module 8.1. A frequency tabulation for the concomitant medications will be presented for each of the ATC levels and coded medications for both core phase and extension phase analyses. This will be based on the full analysis set. Table will be repeated during extension phase analyses excluding patients missing Safety Follow-up assessments during Extension study phase.

5.4 Study Medication

5.4.1 Dose reductions or interruptions

Exposure to study treatment, relative dose intensity, dose reductions and interruptions will be summarized after completion of core phase and extension phase. Dosages may be adjusted for a number of reasons, see the protocol for details.

The number of patients who have dose reductions or interruptions, the number of dose reductions or interruptions, as well as their reasons, will be summarized by treatment. This will be done for all reductions or interruptions together and then summarized just for reductions and again just for interruptions. The number of dose reductions/interruptions will be the sum of the number of reductions and the number of interruptions. A patient who reduced their dose to zero will be counted only once in the dose reduction/interruption summaries, i.e. not counted once as a reduction and counted again as an interruption.

If a patient moves from a higher than protocol planned dose down to the planned dose then this is not be counted as a reduction, however if they move directly from a higher than planned dose down to a lower than protocol planned dose or the planned dose on a less frequent regimen, then this is counted as a reduction.

Everolimus

Interruption: An interruption is defined as a 0mg/0tablets dose given on one or more days or a 0mg/0tablets record entered for a weekly dosing schedule.

Reduction: A reduction is defined as a decrease in dose from the protocol planned dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. A decrease to zero will not be counted as a reduction. For example, in the sequence 10mg – 0mg – 5mg, only the 5mg dose will be counted as a reduction. A decrease in frequency of administration which results in a lower cumulative dose is also counted as a reduction, e.g. in the sequence 10mg od – 5mg od – 5mg qod, two reductions will be counted.

Pasireotide LAR

Interruption: An interruption is defined as a 0mg dose entered for a monthly dosing schedule or the time between two Pasireotide LAR administrations being more than 31 days (28 days + 3 days).

Reduction: A reduction is defined as a decrease in dose from the protocol planned dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. A decrease to zero will not be counted as a reduction.

Combination arm

Dose reductions and interruptions will be calculated separately for both Pasireotide LAR and Everolimus treatments.

5.4.2 Duration of exposure

Everolimus

The following algorithm will be used to calculate the duration of Everolimus exposure:

Duration of exposure (weeks) = (min(date of last administration of Everolimus, date of data cut-off) – (date of first administration of Everolimus + 1)) / 7.

The duration includes the periods of temporary interruption.

Pasireotide LAR

The following algorithm will be used to calculate the duration of Pasireotide LAR exposure:

Duration of exposure (weeks) = (min(date of last administration of Pasireotide LAR +27, date of death, date of data cut-off) – date of first administration of Pasireotide LAR + 1) / 7.

Combination arm

The duration of exposure in the combination arm will be computed for the individual components separately and combined. The exposure for the individual components will be

calculated using the methods above. The duration of exposure to the study treatment for the combined treatment will be calculated as follows:

Duration of exposure (weeks) = (last date of exposure to any study treatment component– date of first administration of study treatment + 1) / 7.

With the last date of exposure to any study treatment component defined as: max (min(date of last administration of Pasireotide LAR +27, date of death, data cut-off date) for Pasireotide LAR, min(date of last Everolimus administration, data cut-off date) for Everolimus).

Summaries of the exposure to each treatment i.e. duration (weeks) of application of study medication will be presented for the safety set.

The total number of patients who received each component will be summarized, with the combination arm being split into three (Pasireotide LAR, Everolimus and Both). Duration of study treatment exposure will be summarized with means of descriptive statistics.

5.4.3 Relative dose intensity

Relative dose intensity (RDI) will be summarized separately for each study drug and is defined as follows:

RDI = DI (dosing unit / unit of time) / PDI (dosing unit / unit of time).

Dose intensity (DI) is defined as follows:

DI (dosing unit / unit of time) = Cumulative dose (dosing unit)/Duration of exposure (unit of time).

For patients who did not take any drug the DI is by definition equal to zero.

For both Pasireotide LAR and Everolimus the unit of time will be weeks.

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the Dose Intensity.

PDI = 10 mg/day = 70 mg/week for Everolimus.

PDI = 60mg per 28 days = 15 mg/week for Pasireotide LAR.

In the combination arm, RDI will be summarized separately for each component, but using the duration of the study treatment exposure, not the duration of each of the components.

Cumulative dose is defined as the total dose taken by the patient during the study treatment exposure and will be summarized for each of the study treatment separately.

For Everolimus total dose = sum of all rows on the dosage administration record of (actual dose * (date of end of medication – date of start of medication + 1(only '+1' if end date not the same as the start date of the next dose)). If the date of end of medication is missing or after the cut-off date then the cut-off date will be used instead. Note that actual dose is the daily dose a patient has taken, if a dose is taken every other day instead then the daily dose will be halved.

For Pasireotide LAR total dose = sum of all doses recorded on the dosage administration record CRF page.

Mean and median relative dose intensity will be displayed along with exposure summaries. Summary of actual dose intensity, categories of relative dose intensity (<70%, 70 - <90%, 90 - <100% and >=100%) and cumulative dose received summary will be displayed in a separate table.

6 Efficacy evaluation

6.1 Implementation of RECIST

Tumor response and disease progression will be evaluated according to the Novartis guidelines based on RECIST 1.1 criteria (enclosed in protocol Appendix 1), unless otherwise noted.

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below. This information will be captured on the CRF.

Table 4 - Evaluation of overall lesion response

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non PD	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1,2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] This overall lesion response also applies when there are no non target lesions identified at baseline.

[2] Once confirmed PR was achieved, all these assessment are considered PR.

A listing of the tumor assessments and responses will be presented for the full analysis set after completion of core phase and extension phase analyses. This will include evaluation number, type of lesion (target, non-target, new), overall assessment, number, location, measurement method, evaluation date, longest diameter (cm), lesion status and an overall lesion response as per the investigator. Patients who discontinue study treatment after 12 months of treatment without evidence of progression or for reasons other than disease progression will continue to have tumor evaluation assessments unless consent is withdrawn. These will be flagged in this listing.

Another listing of lesion locations and descriptions will also be produced for the full analysis set. This will include the evaluation number, the type of lesion (target, non-target, new), the

number, the evaluation date, the location, the description, the measurement method and the measurement method detail.

For each time to event assessment, the assessment date is calculated as follows:

- the latest of all measurement dates for assessment with overall lesion response = CR, PR, SD or UNK.
- the earliest of all measurement dates for assessments with overall lesion response = PD.

6.2 Source for overall lesions response

The tumor endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. Of note, no central review is planned in this study, however all scans will be locally stored. If the decision is taken at a later point to perform a central review, then the RAP will be amended.

Investigator (local radiology) reported overall lesion response at each assessment will be recorded on the eCRF and will be used for the primary endpoint derivation.

6.3 Primary efficacy evaluation

6.3.1 Variable

The primary efficacy endpoint is defined as the proportion of patients who are progression-free at Month 9 (PFR-9) based on RECIST V. 1.1.

All CT scans and MRI will be assessed and validated at the local sites throughout the trial.

The investigator evaluation of overall lesion response will be used for the assessment of the primary efficacy endpoint.

Patients with CR, PR or SD at Month 9 will be considered as “progression-free”.

Patients with missing tumor assessment, or with overall lesion response “unknown” at Month 9 will be considered as “non progression-free”, unless any of the following assessments at week 48 or week 52 indicate CR, PR or SD, in which case the patient will be considered as progression-free at Month 9.

Patients discontinuing the study for any reason prior to the 9 month assessment will be considered as “non progression-free”.

6.3.2 Statistical Hypothesis, model and analysis

Single-stage phase II trials are frequently undertaken to determine whether a new procedure or treatment is likely to meet a basic level of efficacy before comparing it with the standard technique in a larger randomized phase III trial. This study is of a single stage design, which is defined as follows. Let p_0 be the highest proportion of patients progression-free at Month 9 which would indicate that the procedure or treatment is clearly ineffective, and p_1 be the minimum required proportion of patients progression-free to show that the procedure or treatment is effective. The trial tests the null hypothesis H0 that the proportion of patients progression-free, p, is less than or equal to p_0 against the alternative hypothesis H1 that p is greater than or equal to p_1. It consists of entering a predetermined number of patients and

deciding in favor of p_0 or p_1 based on the success rate observed by using an appropriate cut-off between p_0 or p_1. In a single-stage design, if the number of responses is greater than or equal to R+1, the hypothesis that p is less than or equal to p_0 is rejected. If the number of responses is less than or equal to R, the hypothesis that p is greater than or equal to p_1 is rejected.

In this trial, p0 and p1 have been set equal to 0.20 and 0.45, respectively. Forty (40) patients are planned to be randomized in each treatment group. If the number of responses is 13 or more, the hypothesis that $p \leq p0 = 20\%$ is rejected with a target alpha error rate of 5% and an actual alpha error rate of 4.3%; if the number of responses is 12 or less, the hypothesis that $p \geq p1 = 45\%$ is rejected with an actual beta error rate of 4%.

In the case where more than 40 patients are randomized to one arm, the required number of responses to reject the null and alternative hypotheses will be computed using the methodology described in Fleming's paper [Fleming 1982]. R Codes below compute the cutoff (RstarPlus1) to reject the null hypothesis for different sample sizes.

For example, with 41 patients, the required number of responses to reject the null hypothesis is still 13 responses, and with 42 patients the required number is 14 responses.

```
fleming <- function(n){
p.0   <- 0.2
Z     <- qnorm(0.95)
N     <- n
s     <- round(N * p.0 + Z * sqrt((N * p.0 * (1 - p.0)))) + 1
thres <- list(N = N , RstarPlus1  = s)
return(thres)

}

n <- 40:45
f <- sapply(n, fleming)
f

##            [,1] [,2] [,3] [,4] [,5] [,6]
## N          40   41   42   43   44   45
## RstarPlus1 13   13   14   14   14   14
```

Each arm will be independently evaluated using the above decision rule.

If the null hypothesis is rejected for more than 1 arm the selection of the best arm will be based on a risk/benefit evaluation and guided by a Bayesian evaluation described below.

The number and percentage of patients progression-free at Month 9 (PFR-9) will be presented for the FAS together with their confidence interval. An ***exact binomial confidence interval*** (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper & Pearson, 1934].

The same computations will be repeated for each stratification factor by stratum.

6.3.3 Supportive analyses

To further support the decision process, a Bayesian analysis will be performed to estimate the proportion of patients who are progression-free at Month 9 for each treatment arm.

Vague prior beliefs about the PFR-9 distribution reflecting the current uncertainty about the efficacy of Everolimus and Pasireotide alone or in combination in the study will be summarized in prior distributions. Minimally informative Beta distribution priors ([Neuenschwander, Branson and Gsponer 2008]) with prior median equal to the clinical threshold for futility (20%) will be utilized.

The parameter values of the prior distribution for PFR-9 by arm are summarized in table 5 and table 6 summarizes the corresponding prior distribution that PFR-9 falls within the pre-specified efficacy intervals

Table 5 - Prior parameters for minimally informative Beta distribution of PFR at 9 months

Prior parameters	
α	β
0.431	*1*

Table 6 - Summary of prior distribution of PFR at 9 months

Efficacy intervals **Prior probabilities (%) that PFR is in interval:**			**Mean**	**SD**	**Quantiles**		
Unacceptable	**Moderate**	**Substantial**			**2.5%**	**50%**	**97.5%**
[0, 20%]	(20%, 45%]	(45%, 100%]					
0.500	*0.209*	*0.291*	*0.301*	*0.294*	*<0.001*	*0.2*	*0.943*

The posterior distribution of the PFR-9 is the update of the prior distribution with all the available data from the FAS upon completion of the 9 month follow up. The posterior distribution will be used to derive the probability that the true rate lies in the pre-specified efficacy intervals.

In order to guide the selection of the best treatment for further development, for each treatment arm selected by the Fleming procedure, the probability that the treatment is the best will be evaluated based on the posterior distributions of the PFR-9.

For example, if two treatments A & B are selected using the Fleming single stage method with 13 and 14 successes respectively, the posterior probability of being the ‘best’ treatment is 0.4 and 0.60 respectively for treatment A and treatment B, based on a total of 40 patients per arm and prior distributions of the rate as defined above. The computations are based on Monte Carlo simulations i.e. draws from the posterior Beta distributions of the rates. At each iteration of the simulations, the two treatment rates are compared and the frequency of a treatment coming up better is computed.

If more treatment arms are selected by the Fleming single stage method then 10000 draws will be performed from the posterior Beta distributions to decide on the best treatment arm. A random seed of 43985 will be used.

The number and percentage of patients progression-free will be presented additionally for the PP set, together with the appropriate exact confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) [Clopper & Pearson, 1934].

Results of supportive analyses will be interpreted purely exploratory.

7 Secondary efficacy evaluations

7.1 Progression-free survival (PFS)

The progression-free survival (PFS) is defined as the time from first study drug administration to objective tumor progression or death from any cause (including extension phase data, if applicable at the time of the extension phase analyses). If a patient has not had an event, PFS is censored at the date of the last adequate tumor assessment. PFS will be analyzed in the FAS and PP set (for both core and extension phases) by presenting the Kaplan-Meier curve and estimators.

The Kaplan-Meier estimate of the PFS survival function will be constructed and displayed by treatment arm overall and per stratum for the core phase analyses and extension phase analyses. The plots will also display the number of patients at risk every 3 months. Median PFS for each treatment arm will be obtained along with 95% confidence intervals calculated by SAS procedure LIFETEST using method of Brookmeyer and Crowley (1982). 25% and 75% percentiles will be calculated as well. K-M event-free probability estimates with 95% confidence intervals using the Greenwood formula will be summarized as well at the following time points: 3, 6, 9, and 12 months. This analysis will be repeated for the FAS set after completion of the extension phase and interpreted exploratory. The progression-free survival analysis after extension phase will take into consideration evaluations during extension phase as well, if a patient has not had an event (discontinued for other reason than PD or death or trial was ended), PFS is censored at the date of the patient's last adequate tumor assessment in study.

Time to progression and death will be listed per patient presenting the start and end date of treatment, the progression status (Y/N), progression date, last progression-free date, death status (Y/N), date of death along with principal cause of death and date of last adequate tumor assessment which is used for censoring.

7.2 Disease Control Rate

The endpoint of disease control rate (DCR) is defined as the proportion of patients showing a best overall response of CR or PR or SD during the core study (12 months) according to RECIST V 1.1. The disease control rate will be calculated for the full analysis set. An ***exact binomial confidence interval*** (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper & Pearson, 1934].

7.3 Time to Response

Time to response is defined as the time from start of treatment to the first objective tumor response (PR or CR) observed up to 12 months (i.e. core phase) according to RECIST V. 1.1 criteria. Patients who did not achieve a confirmed PR or CR will be censored using one of the following options:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case, the PFS event is the worst possible outcome as it means the patient cannot subsequently respond.
- At last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding.

Time to response will be explored by presenting the Kaplan-Meier curve and estimators along with associated 95 percent confidence intervals, the number with the event and the number censored for the full analysis set.

7.4 Duration of Response

Duration of response is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause. The start date is the date of first documented response (CR or PR) during core phase and the end date and censoring is defined the same as that for time to progression. The duration of response will be summarized for the subset of patients who had confirmed response. Duration of response will be explored by presenting the Kaplan-Meier curve graphically and presenting the number of patients with the event, the number censored, the estimators and associated 95 percent confidence intervals. The results from this analysis should be interpreted with caution since treatment bias could be introduced, as only those patients with a response will be included and the number may vary between treatments.

7.5 Objective Response Rate

The objective response rate is defined as the proportion of patients showing a best overall response of CR or PR during the core study (i.e. up to 12 months) according to RECIST V. 1.1 criteria. For the assessment of SD as best overall response, there is no specific time needed from baseline as the first tumor evaluation takes place after 12 weeks (at Visit 8) from randomization thus conforming the required minimum time of 6 weeks from randomization based on RECIST 1.1 guidelines. Therefore, the best overall response is interpreted as the best response recorded from the start of the treatment until disease progression/recurrence, death from any cause or until the patient withdraws consent, whichever is earliest. In order to have a best overall response of CR or PR, response must be confirmed by another response assessed at least 4 weeks after the initial response. The objective response rate will be calculated at 12 months and displayed with 95 percent exact binomial confidence intervals (implemented using SAS procedure FREQ with EXACT statement for one-way tables) [Clopper & Pearson, 1934]. Frequencies of each response will also be included. This will be carried out for all patients in the full analysis set.

7.6 Biochemical Response Rate

The endpoint of BRR is defined as the percentage of patients showing normalization, i.e. return to within normal ranges, or a decrease of ≥ 30% from baseline of serum Chromogranin A (CgA) concentrations compared to baseline. The parameter of biochemical response will be summarized by arm with frequency counts, percentages and 95% exact confidence intervals. Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed, with a response being defined as normalization or a ≥ 50% reduction of 5HIAA levels from baseline.

Patients who are within normal range at baseline will be excluded from the tables. The endpoint of BRR will be analyzed based on core phase data only.

Absolute and relative changes from baseline for each of CgA and 5-HIAA will be summarized by arm for the full analysis set up to Visit 4 of extension phase. Any data collected after Visit 4 of extension phase will not be summarized or listed in the CSR.

A listing containing the CgA and 5-HIAA results will be presented along with the visit, sample date, analyte name (CgA, 5-HIAA) and analyte nature/type (DNA, RNA, Protein).

[redacted]

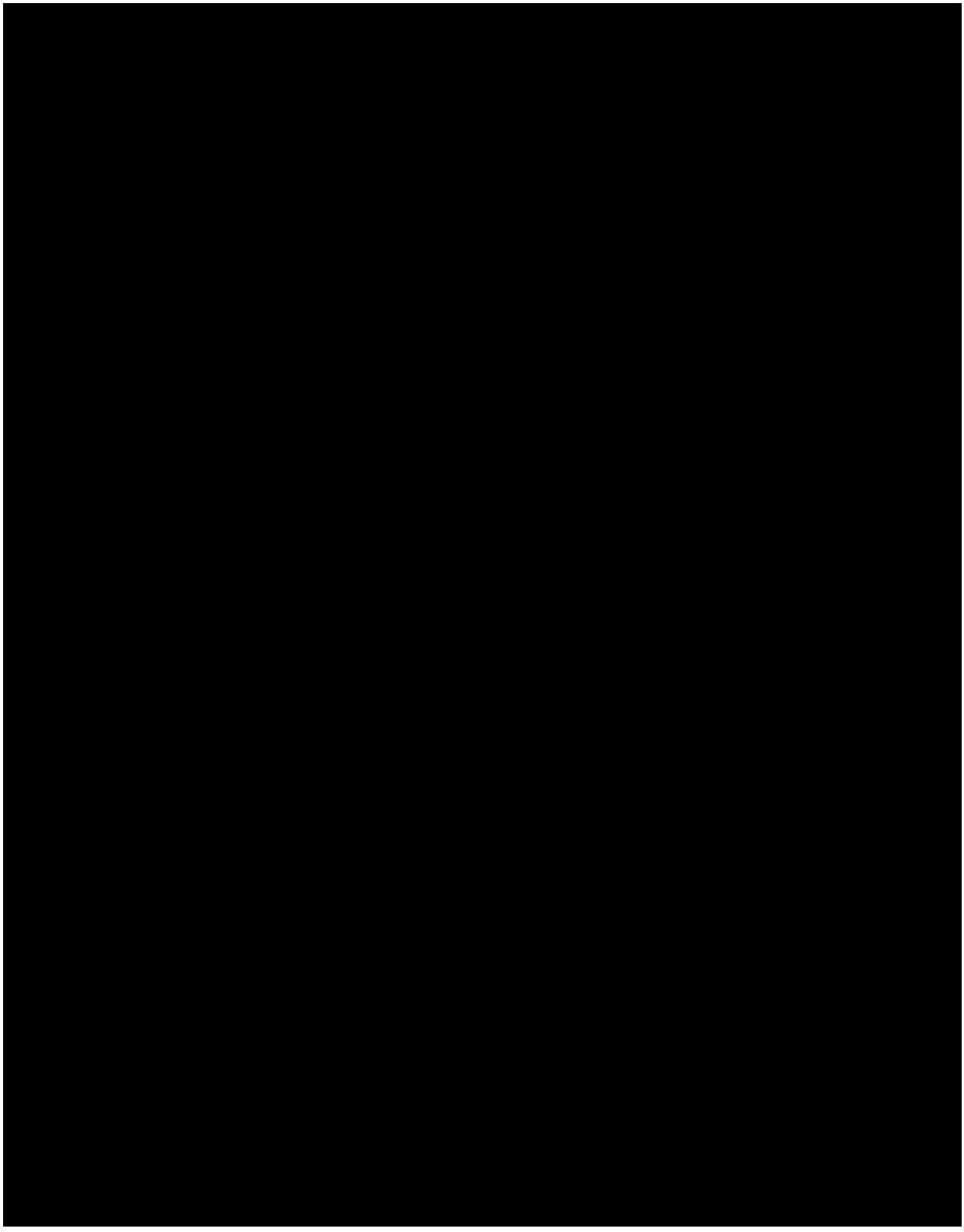
7.7 Duration of Biochemical Response

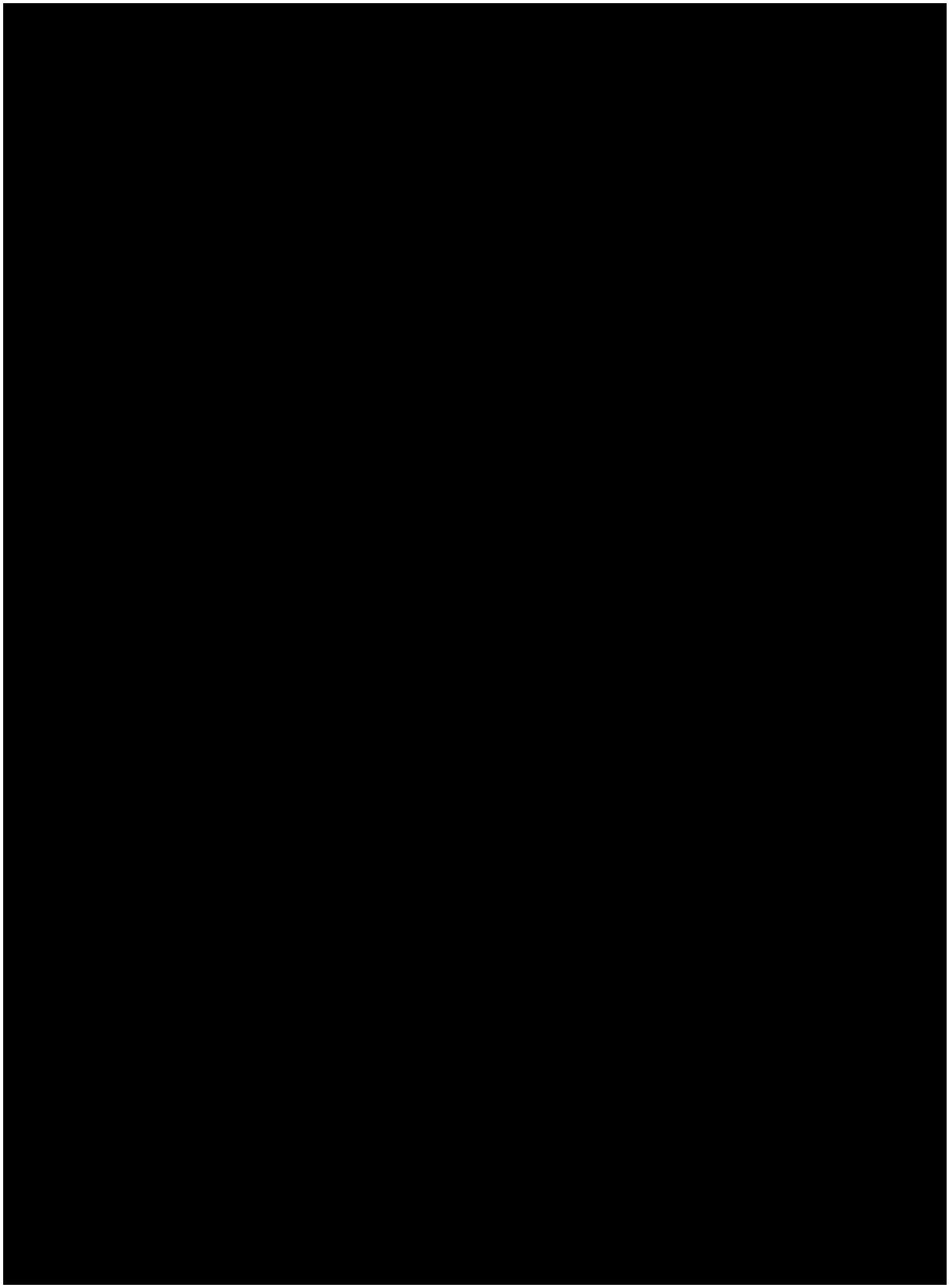
Duration of biochemical response (DBR) is defined as the time from the first documentation of biochemical response during core phase to the first documentation of biochemical progression or death due to any cause, whichever occurs first (including extension phase data, if applicable at the time of the extension phase analyses). Biochemical progression is defined as an increase of serum CgA levels ≥ 25% compared to baseline. DBR data will be censored on the date of the last CgA assessment on study for patients who do not have biochemical progression and who do not die due to any cause while on study. DBR will be summarized for the subset of patients from the full analysis set who had biochemical response, patients with CgA levels within normal range at baseline will also be excluded from the table. This will be explored using the Kaplan-Meier method, graphically presenting the Kaplan-Meier curve and also tabulating the number with the event, the number censored and the estimators along with 95 percent confidence intervals. The analysis of this endpoint will be repeated based on cumulative study data at the time of extension phase analyses.

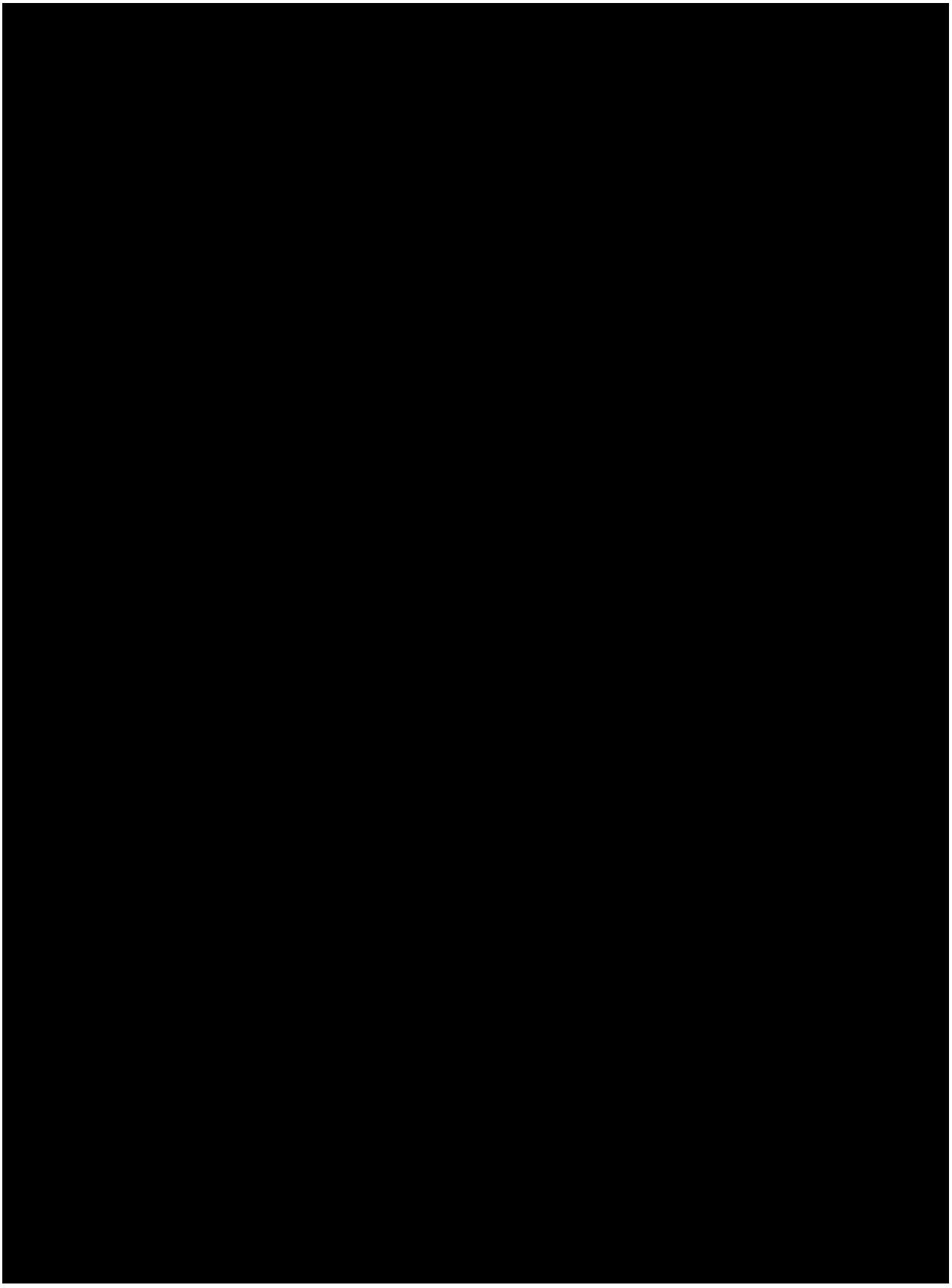
7.8 Biochemical Progression-free Survival (BPFS)

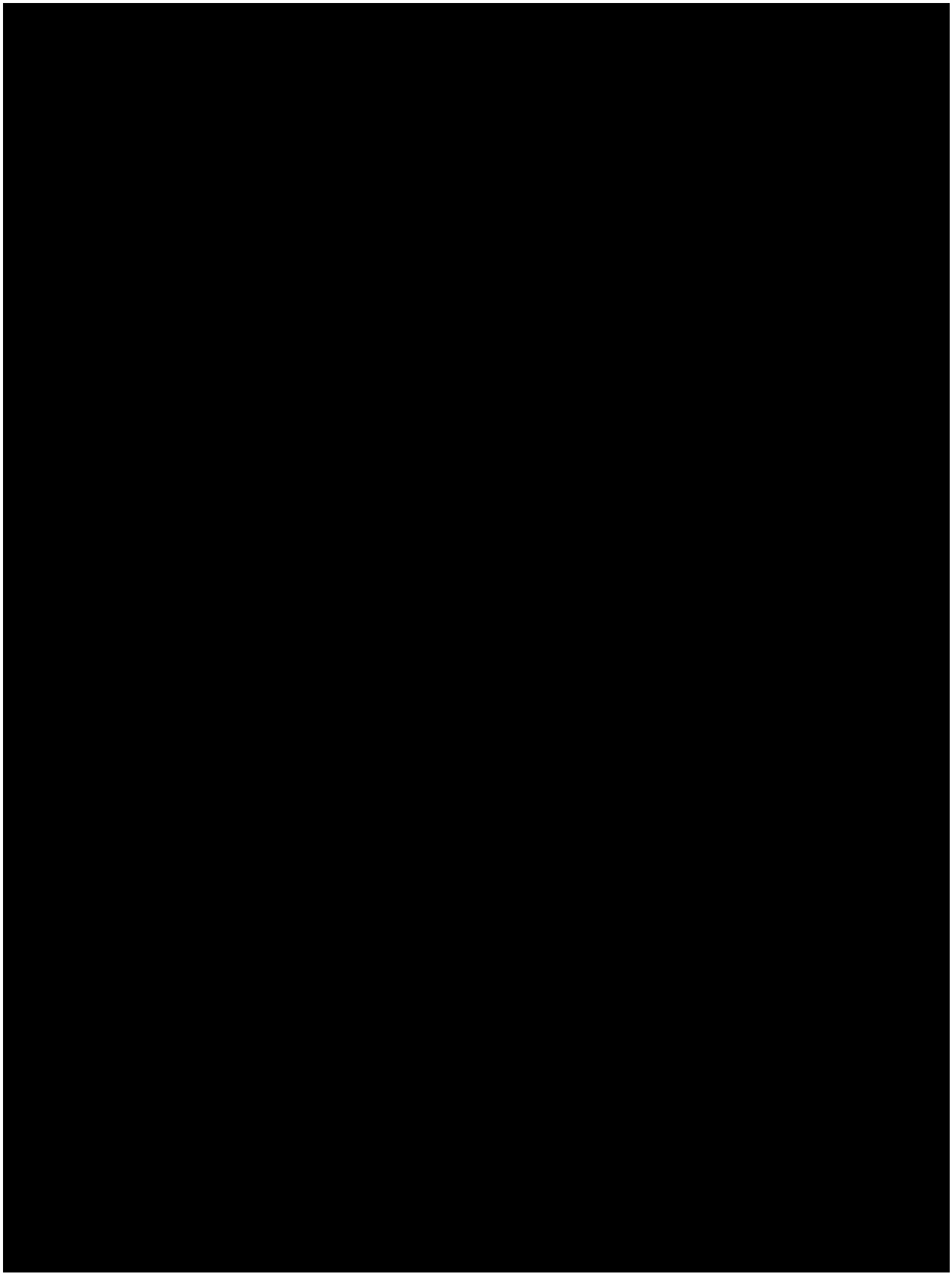
Biochemical progression free survival (BPFS) is the time from the first study drug administration to the first documentation of biochemical progression or to death due to any cause, whichever occurs first (including extension phase data, if applicable at the time of the extension phase analyses). Biochemical progression is defined as an increase of serum CgA levels ≥ 25% versus baseline. BPFS data will be censored on the date of the last CgA assessment on study for patients who do not have biochemical progression and who do not die due to any cause while on study. BPFS will be analyzed in the FAS set by presenting the Kaplan-Meier curve and estimators. The table used will be similar to that described for PFS.

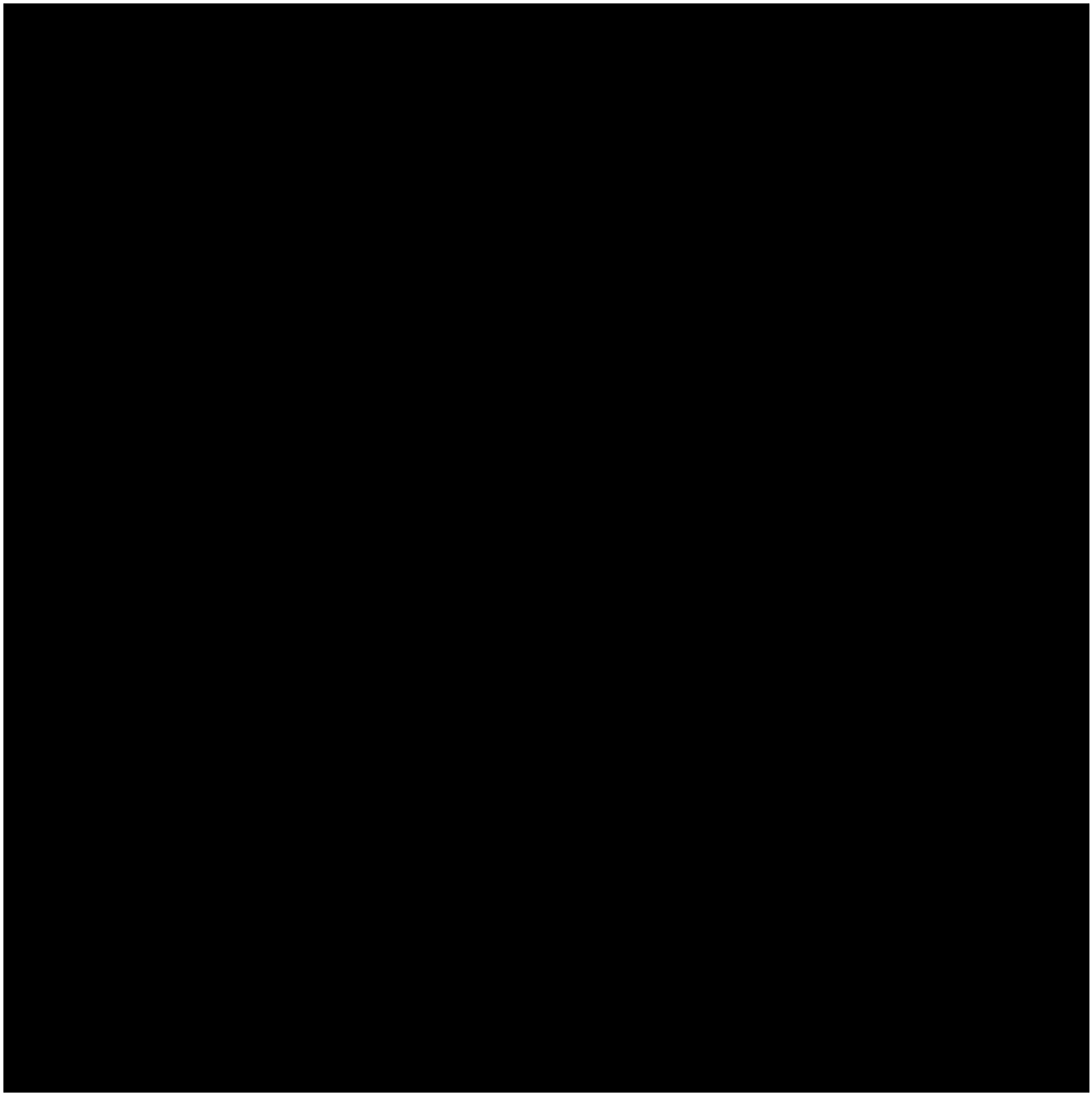
The analysis of this endpoint will be repeated based on cumulative study data at the time of extension phase analyses.











10 Safety evaluation

For all safety analyses, the safety set will be used. All safety analyses and listings will be rerun after completion of the extension phase based on cumulative study data from both core and extension phases. The assessment of safety will be based primarily on the frequency of AEs and laboratory abnormalities. Other safety data (e.g. gallbladder assessments) will be summarized appropriately.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient'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 56 days after last dose of study medication

3. Post-treatment period: starting at day 56+1 after last dose of study medication.

The listings will all contain a flag to identify which period the event occurred in.

10.1 Adverse Events

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded on the CRF. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through both the "Study evaluation completion – core" form or the "Study evaluation completion – extension phase" form and "Adverse Event" form. Table and listing of deaths will be created based on the "Adverse Event" form primarily including all reported adverse events with "fatal" outcome indicating end date of adverse event as date of death. Fatal adverse events will be flagged appropriately indicating if the adverse event ended within the 56-day window after end of study treatment. In case of missing adverse event end date, death will be considered as occurring within 56 days from last treatment day. A supplementary listing will also be added created based on "Study evaluation completion – core" form or the "Study evaluation completion – extension phase" forms displaying information related to study discontinuation if death was reported to be the reason for discontinuation. **Treatment-emergent** AEs (TEAEs) are AEs that started or worsened during the on-treatment period. Adverse event tables will include only TEAEs. All safety data (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.

Adverse events will be coded using the most recent version of the medical dictionary for regulatory activities (MedDRA) available at the time of each analysis. The incidence of all grades of treatment-emergent adverse events and grades 3 or 4 TEAEs will be summarized by system organ class only and by system organ class and preferred term for all TEAEs regardless of study drug relationship, as well as by system organ class and preferred term for serious treatment-emergent AEs regardless of study drug relationship, TEAEs suspected to be related to study drug (related to Pasireotide LAR, related to Everolimus, related to both and/or undistinguishable), for TEAEs requiring dose adjustment or study drug interruption and for TEAEs leading to study drug discontinuation separately. Non-serious TEAEs will be tabulated for preferred terms and system organ classes with >5% recorded in any treatment group. Incidence of TEAEs will also be summarized by system organ class, preferred term and maximum severity (based on CTC grades) for all TEAEs, for those related to study drug and for serious TEAEs separately. On treatment deaths will also be tabulated using system organ class and preferred term. In all summaries, at each level of summarization (system organ class, preferred term) patients will only be counted once regardless of how many times it has occurred.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on non-serious TEAEs with an incidence >=5% and on serious TEAEs, deaths and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class and preferred term:

- a single occurrence will be counted if there is <1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is >1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE/ SAE suspected to be related to study treatment/ non SAE has to be checked in a block e.g. among AEs in a <=1 day gap block, if at least one SAE is occurring then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by system organ class and preferred term.

All information pertaining to the AE noted during the study will be listed by treatment group and patient, detailing verbatim given by the investigator, the preferred term, the abbreviated system organ class, start date, end date, duration, severity (CTCAE grade), relationship to study drug (not suspected, suspected to be related to SOM, suspected to be related to RAD, suspected to be related to both and/or undistinguishable), action taken (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable) and outcome (recovered, recovering/resolving, recovered/resolved with sequelae, not recovered/resolved, fatal, unknown). The AE onset will also be displayed relative (in number of days) to the day of the first dose of study medication. AEs occurring before start of study drug or 57 or more days after the discontinuation of study medication will not be considered as treatment-emergent and will not be included in AE summary tables but will be listed only. This listing will be repeated for the subsets of serious TEAEs, TEAEs leading to study drug discontinuation and TEAEs requiring dose adjustment or study drug interruption.

All deaths will be listed by treatment group and patient detailing principal cause given by the investigator, the preferred term the date of last dose and the date of death. The day of last dose and day of death will also be displayed relative to the day of the first dose of study medication. The number of days since last dose will also be presented, calculated as death day – day of last dose + 1.

Grouping of adverse events of special interest

Specific groupings of adverse events of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with everolimus or pasireotide treatment (i.e. where everolimus or pasireotide may influence a common mechanism of action responsible for triggering them) or adverse events which are similar in nature (although not identical).

Adverse event groupings can be defined through e.g. the use of Preferred Terms (PT), High Level Terms (HLT) or System Organ Classes (SOC) or through a combination of these three components.

Adverse event groupings will be performed by Novartis and the created adverse event risk analysis dataset will be forwarded [redacted] to generate summary tables. Summaries of the adverse events of special interest by specific grouping term and preferred term will be produced. These summaries will be repeated for adverse event groupings related to everolimus and pasireotide treatment separately. These will be produced for all adverse events of special interest regardless of study drug relationship as well as for adverse events of special interest suspected to be related to study drug including summaries for all CTC grades and CTC grades 3 or 4.

10.2 Laboratory values

All laboratory values will be converted into SI units; for laboratory tests covered by the CTCAE version 4.0 (see National Cancer Institute (NCI) 2009), the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a 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, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

All summaries will be produced separately for each lab category (hematology, biochemistry and urinalysis). Hematology includes hemoglobin, hematocrit, platelets and total white blood cell count (WBC, absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils). Biochemistry includes sodium, potassium, chloride, bicarbonate, creatinine, total protein, uric acid, blood urea nitrogen (BUN), calcium, magnesium and phosphate. Urinalysis includes pH, protein, glucose, blood, ketones and leukocytes. They will be tested using a dipstick. In some cases urea results will be collected rather than BUN. In these cases urea will be converted to BUN using the following conversions:

BUN (mg/dL) = Urea (mg/dL) / 2.14

BUN (mmol/L) = Urea (mmol/L) / 2

Shift tables using CTCAE grades will be produced for hematology and biochemistry separately to compare baseline and the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding grade and at least one non-missing post baseline value as the denominator.

For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification will be produced to compare baseline to the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding level and at least one non-missing post baseline value as the denominator.

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly important for neutrophils and lymphocytes, as the CTC grading is based on the absolute counts).

The method to convert the value is as follows: for each patient, the original laboratory value (%) is divided by 100 and multiplied by the WBC count, e.g. for neutrophils (NEU):

NEU count = (WBC count) * (NEU %value / 100)

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If the % range is missing and the absolute range is missing, then the pre-defined normal range as reported in the Merck manual (FRM-0015557 Laboratory value references) will be used.
- If the absolute range is NOT missing (% range is or isn't missing), then the absolute range provided by the site will be used.
- If the % range is NOT missing and the absolute range is missing, then the % normal limits (i.e. lower limit normal (LLN) and upper limit normal (ULN)) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for NEU:

  LLN for NEU count = (LLN for WBC count) * (LLN for NEU % value/ 100)

  ULN for NEU count = (ULN for WBC count) * (ULN for NEU % value / 100)

A listing will be presented for all hematology, biochemistry and urinalysis laboratory data, with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges. A separate listing will be created presenting the laboratory normal ranges for the collected parameters by laboratory identification number and laboratory group.

10.3 Hepatitis screening and evaluation

In certain instances, patients must be tested for Hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBsAb, and HBcAb as well as Hepatitis C. These instances are described in the protocol.

For the parameter of HBV-DNA where the result is recorded as negative, positive or not done at multiple visits, frequencies of these results will be produced for baseline and each post-baseline visit. Percentages will be calculated using the number of available patients at that visit, for the particular treatment group. A similar table will be produced for the HCV RNA-PCR parameter.

For the parameters of HBsAg, HBsAb and HBcAb where the result is recorded as negative, positive or not done at baseline only, the frequencies of these results will be produced by treatment.

A listing will be presented by treatment showing the visit, sample date, laboratory number, laboratory name, HBV-DNA (negative, positive, not done), HBsAg (negative, positive, not done), HBsAb (negative, positive, not done), HBcAb (negative, positive, not done) and HCV RNA-PCR (negative, positive, not done). HBV-DNA and HCV RNA-PCR are the only tests carried out post-baseline and only in certain circumstances.

10.4 Liver function tests

The liver function tests carried out will be albumin, serum glutamic oxaloacetic transaminase (aspartate aminotransferase) (SGOT (AST)), serum glutamic pyruvic transaminase SSC

(alanine aminotransferase) (SGPT (ALT)), total bilirubin (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0 x ULN), alkaline phosphatase and gamma-glutamyl transpeptidase (GGT). For patients treated with pasireotide LAR: the Day 21 and Day 49 liver function tests should be available and assessed prior to dosing on Day 29 (2nd LAR injection) and Day 57 (3rd LAR injection). The coagulation parameters of international normalized ratio (INR) will be determined at baseline, at Visits 2, 5, 7, 8, then every 8 weeks in the core study and every 3 months in the extension phase. It will be determined also at Visits 4 and 6 for patients treated with pasireotide LAR. The partial thromboplastin time (PTT) will be determined only at baseline.

A shift table using CTCAE grades will be produced for these parameters, with the exception of PTT as it is captured as baseline only, to compare baseline and the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding grade and at least one non-missing post baseline value as the denominator.

For laboratory tests where CTCAE grades are not defined, a shift table using the low/normal/high/(low and high) classification will be produced to compare baseline to the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding level and at least one non-missing post baseline value as the denominator.

A frequency table will be created presenting number of patients with elevated liver chemistry tests based on worst post-baseline values for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase parameters. Categories of elevated tests will be defined with regards to the upper or lower normal ranges, whichever is applicable. Percentages will be calculated using the number of patients in the safety analysis set.

A listing will be presented showing the visit sample date, laboratory number, laboratory name, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, GGT, total bilirubin, direct bilirubin, indirect bilirubin, INR and PTT split by treatment.

10.5 Glucose, insulin & HbA1c

A shift table using CTCAE grades will be produced for these parameters to compare baseline and the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding grade and at least one non-missing post baseline value as the denominator.

For laboratory tests where CTCAE grades are not defined, a shift table using the low/normal/high/(low and high) classification will be produced to compare baseline to the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding level and at least one non-missing post baseline value as the denominator.

Tables created as part of the extension phase analyses will be repeated excluding patients missing glucose, insulin and HbA1c assessment during Extension study phase.

A listing will be provided split by treatment arm summarizing this information and will include visit, sample date, laboratory number, laboratory name, glucose, insulin, HbA1c and a flag to indicate whether it was taken whilst fasting.

10.6 Serum lipid profile

A shift table using CTCAE grades will be produced for these parameters to compare baseline and the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding grade and at least one non-missing post baseline value as the denominator.

For tests where CTCAE grades are not defined, a shift table using the low/normal/high/(low and high) classification will be produced to compare baseline to the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding level and at least one non-missing post baseline value as the denominator.

A listing will be provided split by treatment displaying the visit, sample date, laboratory number, laboratory name, cholesterol, triglycerides, LDL and HDL.

10.7 Thyroid function

Thyroid function tests of thyroid stimulating hormone (TSH), free T3 (tri-iodothyronine) and T4 (levothyroxine) along with B12 vitamin will be collected at baseline, week 12, week 24 and at the end of the core study. Plasma ACTH will be taken at baseline and only those patients with hypersecretion will be tested again.

A shift table using CTCAE grades will be produced for these parameters to compare baseline and the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding grade and at least one non-missing post baseline value as the denominator.

For laboratory tests where CTCAE grades are not defined, a shift table using the low/normal/high/(low and high) classification will be produced to compare baseline to the worst on-treatment value with each laboratory parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding level and at least one non-missing post baseline value as the denominator.

This information will also be presented in a listing along with the visit, sample date, laboratory number and laboratory name split by treatment.

10.8 Electrocardiograms (ECGs)

Overall ECG interpretation and details of abnormalities are collected at Screening and selected visits. The ECG QTcF result at each visit will be categorized. A shift table displaying the baseline categorized ECG QTcF result compared with the worst post-baseline categorized result will be produced. Percentages will be calculated using the number of patients with that categorized result at baseline as the denominator.

The number of patients recording notable ECG QTcF increases from baseline at least once will also be presented. Percentages will be calculated using the number of patients with both baseline and post baseline evaluations.

A listing of ECG evaluations will be presented for all patients with at least one treatment emergent abnormality i.e. where no clinically significant abnormality was present at baseline and a clinically significant abnormality was present on-treatment. This listing will include the date of ECG, clinically significant abnormality (yes, no) and abnormality descriptions.

10.9 ECHO or MUGA scan

All patients will have an echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan at screening and when it is indicated clinically during the study. A summary table of LVEF will be produced to display baseline result. This information will also be listed along with any optional post-baseline records and includes the method (ECHO, MUGA scan), the LVEF (%), the result (normal, clinically insignificant abnormality, clinically significant abnormality) and the abnormality descriptions.

10.10 Gallbladder assessment

The gallbladder evaluation, either magnetic resonance imaging (MRI) or a computer tomography (CT) scan, will be performed together with the radiological tumor assessment at baseline for all patients, on treatment only for patients treated with pasireotide LAR.

If the patient discontinues treatment, an end of core study visit MRI/CT scan has to be performed only if the end of core study visit occurred 3 months or more after the previous MRI/CT scan.

A table will be presented showing the frequencies at baseline of image performed? (yes, no), were any gallstones detected? (yes, no), was any sludge detected? (yes, no), is there any dilatation of the intra- or extrahepatic ductal system (yes, no) and if yes was it the intrahepatic ductal system or the extrahepatic dutal system, gallbladder imaging technique (CT scan, MRI) and was there any gallbladder thickening (yes, no). Percentages will be calculated based on the number of patients with available data for each of these questions.

A shift table will also be produced for gallstones detection, sludge detection, dilatation and thickening comparing the baseline result with the most extreme post-baseline result (defined as ‘yes’ if it occurs post-baseline). This will only include the treatments of Pasireotide LAR and both Pasireotide LAR and Everolimus since this data is not collected for patients in the Everolimus group.

A listing will be presented showing the visit, image performed? (yes, no), date, were any gallstones detected? (yes, no) and if yes, the location, was any sludge detected? (yes, no) and if yes, the location, is there any dilatation of the intra- or extrahepatic ductal system (yes, no) and if yes was it the intrahepatic ductal system or the extrahepatic dutal system, gallbladder imaging technique (CT scan, MRI) and was there any gallbladder thickening (yes, no).

10.11 Pulmonary function test

At baseline, prior to administration of study drug, pulmonary function tests (PFT) can be performed, if clinically indicated. During study treatment, all PFTs including spirometry, diffusion capacity for carbon monoxide (DLCO) and room air oxygen saturation at rest must be performed if the patient develops non-infectious pneumonitis. A listing split by treatment will be provided showing the spirometry date, total lung capacity, forced vital capacity (FVC), forced expiratory volume in one second (FEV1), functional residual capacity, residual capacity, was DLCO done? (yes, no) and if yes, the date and capacity, pulse oximetry done? (yes, no) and if yes the date, percent inspired oxygen and percent oxygen saturation.

10.12 Bronchoscopy

A bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL) will be performed only when medically necessary for ensuring patient care. When non-infectious pneumonitis is diagnosed, consultation with a pulmonologist should be considered.

A listing showing the assessment date, was infectious agent identified? (yes, no), was BAL done? (yes, no), was BAL cell count done? (yes, no), was alveolar hemorrhage seen? (yes, no) and if yes, the predominance (lymphocyte, eosinophil, neutrophil, dysplastic type II, malignant, other), was a transbronchial biopsy done? (yes, no) and if yes, the findings.

10.13 Chest X-ray or chest CT-scan

If the baseline scan shows signs suggestive of interstitial lung disease (ILD)/non-infectious pneumonitis, it is at the discretion of the investigator to follow the patient with appropriate chest imaging. For all other patients chest X-rays or chest CT-scans are to be performed during the study if clinically indicated e.g. if there is suspicion of non-infectious pneumonitis, in the investigator's discretion. A shift table displaying the baseline result (normal, insignificant abnormality, clinically significant abnormality) compared with the worst post-baseline categorized result will be produced. Percentages will be calculated using the number of patients with that categorized result at baseline as the denominator.

A listing split by treatment will be provided showing the X-ray/CT-scan date, the examination of the chest in the P-A and/or lateral view (normal, clinically insignificant abnormality, clinically significant abnormality) and if clinically significant, details of the abnormality.

10.14 Hepatic assessment

If certain criteria occur then one of the tests that must be carried out within **72 hours** of awareness of the abnormality is a hepatitis screen. This consists of anti-HAV (positive, negative, not done), IgM (positive, negative, not done) to confirm acute Hepatitis A, HbsAg (positive, negative, not done), Anti-HBc (positive, negative, not done), anti-HCV (positive, negative, not done) and if positive, PCR viral load, Anti-HEV ANA antibodies (positive, negative, not done), anti-smooth muscle anti-bodies (positive, negative, not done), CMV (positive, negative, not done) and EBV (positive, negative, not done). All these will be listed split by treatment arm along with the sample date, laboratory number and laboratory name.

10.15 Vital signs

Vital signs data includes weight, body temperature, respiratory rate, sitting pulse as well as sitting blood pressure (systolic and diastolic). Shift tables using the low/normal/high/(low and high) classification (as shown below.) will be produced to compare baseline to the worst on-treatment value with each vital sign parameter on a new page. Percentages will be calculated using the number of available patients at baseline with corresponding level and at least one non-missing post baseline value as the denominator. For baseline value classification (low/normal/high) the normal ranges per parameter will be taken into account (except for weight displaying only Total and Missing rows as there is no normal range defined). For post-baseline classification change from baseline will also be considered (except for respiratory rate). Only assessments obtained after start of study drug and up to 56 days after the discontinuation of study medication will be considered "on-treatment".

Table 11 - Notable abnormalities

		Notable abnormalities	
Vital signs		**Low**	**High**
Pulse (beats/min)		≤50 + decrease ≥15*	≥120 + increase ≥15*
Blood pressure (mmHg)	Systolic	≤90 + decrease ≥20*	≥180 + increase ≥20*
	Diastolic	≤50 + decrease ≥15*	≥105 + increase ≥15*
Weight (kg)		decrease of > 10% during the study*	increase of > 10% during the study*
Respiratory rate (per min)		≤12	≥25

* Refers to post-baseline value as compared to baseline value

The notable abnormality of '≥ 120 + increase ≥ 15' is interpreted as that the value at that visit is ≥ 120 and the increase from baseline is ≥ 15.

The vital signs variables of weight, body temperature, respiratory rate, sitting pulse and sitting blood pressure (systolic and diastolic) will also be listed and clinically notable values/changes from baseline will be flagged. A separate listing containing all records for patients with clinically notable abnormal vital signs will also be generated.

10.16 Eastern Cooperative Oncology Group (ECOG) performance status (WHO)

The ECOG performance status is captured throughout the study. A shift table displaying the baseline category compared with the worst post-baseline category will be produced. Percentages will be calculated using the number of patients with that category at baseline as the denominator. A listing of all ECOG records will also be produced. In addition, bar charts will be created separately for each treatment group, displaying the percentage distribution of each ECOG performance score at each scheduled visit.

11 Interim analyses

An external and independent Data Monitoring Committee (DMC) was instituted before study start. The DMC will review safety-related issues and will be entitled to make recommendations for changes in study conduct, if needed during core phase of the study. Details on the function of the DMC are reported in a separate DMC Charter. A separate Module 3, Module 7.1 and Module 8.1 have been produced with details of what will be produced for each DMC.

12 Other topics

No other topics will be studied.

13 Determination of sample size

The trial tests the null hypothesis H0 that the observed proportion of patients progression free, p, is less than or equal to p_0 against the alternative hypothesis H1 that p is greater than or equal to p_1. It consists of entering a predetermined number of patients and deciding in favor of p_0 or p_1 based on the success rate observed by using an appropriate cut-off between p_0 and p_1. If the number of responses is greater than or equal to R+1, p_0 is rejected in favor of p_1. If the number of responses less than or equal to R, p_1 is rejected in favor of p_0.

For this study let p_0 be the highest proportion of patients progression-free at Month 9 which would indicate that the treatment is clearly ineffective, and p_1 be the minimum required proportion of patients progression-free for the procedure or treatment to be effective.

Table 12 – Design features for single arm trials

p0	**p1**	**Target**		**Cut-Off R + 1**	**N**	**Actual**	
		alpha	**beta**			**alpha**	**beta**
20%	45%	5%	10%	13	40	4.3%	4%

A study requires 40 patients per treatment to decide whether the proportion responding, p, is less than or equal to p_0=20% or greater than or equal to p_1=45%. If the number of responses is 13 or more, the hypothesis that $p \leq p_0 = 20\%$ is rejected with a target alpha error rate of 5% and an actual alpha error rate of 4.3%. This indicates that the treatment is not ineffective i.e. it is likely be effective and so it is worth proceeding with a phase III trial. If the number of responses is 12 or less, the hypothesis that $p \geq p_1 = 45\%$ is rejected with a target beta error rate of 10% and an actual beta error rate of 4%. This indicates that the treatment is not effective i.e. is likely to be ineffective and so it is not worth pursuing any further.

14 References

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