NOVARTIS

Clinical Development

LEE011/Ribociclib/Kisquali®

CLEE011XDE01 / NCT03096847

A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole

RIBECCA

Statistical Analysis Plan (SAP)

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30-OCT-2019	After 3rd interim analysis, before final analysis	• post-hoc multivariate analysis for neutropenia and AST/ALT elevations included, • programming details added Sensitivity analyses added (in-/excluding centers with relevant inspection finding)	Final Version 2.0	• 2.13 Other exploratory analyses • Several
22-Apr-2020	After Data Review Meeting	Final decision rules for Populations	Final version 3.0 (22-Apr-2020)	Section 5.8: Table 1, Table 2

Table of contents

List of abbreviations

aBC	Advanced Breast Cancer
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
β-hCG	β-subunit of hCG gonadotropin – free hCG gonadotropin
BLRM	Bayesian Logistic Regression Model
CBR	Clinical benefit rate
CISH	Chromogen-in situ-Hybridisierung
CNS	Central nervous system
CR	Complete response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed tomography
DDI	Drug-Drug-Interaction
DFS	Disease-free survival
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ER	Estrogen receptor
FAS	Full Analysis Set
FISH	Fluoreszenz-in-situ-Hybridization
FSH	follikelstimulierendes Hormon
GBM	Glioblastoma multiforme
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MTD	Maximum Tolerated Dose
NCI-CTCAE	National cancer institute – common terminolgy criteria for adverse events
NCRNPD	neither complete response nor progressive disease
PD	Progressive disease
PFS	Progression Free Survival
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information

PgR	Progesterone receptor
PR	Partial Response
QTcF	QT corrected for HR using Fridericia's method
ORR	Overall response rate
OS	Overall survival
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable disease
SISH	silver-in situ-Hybridisation
SmPC	Summaries of Product Characteristics
SOD	Sum of Diameter
SOP	Standard Operating Procedure
TTF	Time to treatment failure
TTP	Time to Progression
UNK	Unknown

1 Introduction

This statistical analysis plan describes the final and the three pre-planned interim analyses.

It is based on the 4th amendment of the study protocol, dated 05-JUN-2019.

1.1 Study design

This was a national, multi-center, open-label, phase IIIb trial to determine the efficacy and safety of treatment with ribociclib (LEE011) plus letrozole in patients with HR+, HER2-negative advanced (recurrent or metastatic) breast cancer.

In this trial a total of 500 patients from 100 centers were planned to be recruited.

The study was designed as an open-label, single-arm trial, hence no randomization took place.

The primary efficacy and safety analysis was conducted on all patient data at the time all patients who are still receiving study drug will have completed at least 24 weeks of treatment (or discontinued prematurely). The additional data for any patients continuing to receive study drug past these times, as allowed by the protocol, was further summarized in a report once these patients completed the study.

Three interim analyses were planned during the study. The first interim analysis was conducted one year after the first patient has been enrolled and included a preliminary analysis on safety. The second interim analysis was conducted 12 months after LPFV in the 30% pretreated and premenopausal cohort (=Cohort B, see section 2.2.1 Subgroup of interest) and included a preliminary analysis on safety, efficacy and quality of life. The third interim analysis took place 6 months after the last patient had been recruited into cohort A (see section 2.2.1 Subgroup of interest) and included a preliminary analysis on safety and efficacy.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in the table below (in accordance with Table 3-1 from the protocol).

Primary Objective	Endpoint
The primary objective of this study is the assessment of the **clinical benefit rate after 24 weeks** for the total population and for cohorts A and B separately: 1. Cohort A: postmenopausal women and men who received no prior treatment for advanced disease. (70% group) 2. Cohort B: pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (30% group)	Clinical Benefit Rate (CBR) after 24 weeks of treatment as defined by RECIST 1.1 as percentage of patients with CR, PR or SD until week 24 or longer as well as patients with NCRNPD >24 weeks for patients with non-measurable disease

Secondary Objectives	Endpoint
To assess the **clinical benefit rate (CBR) after 24 weeks** among Cohort B1 and B2: - Cohort B1: pre- and perimenopausal women without prior therapy for advanced disease - Cohort B2: pre-, peri- and postmenopausal women and men who were pretreated for advanced disease	Clinical Benefit Rate (CBR) after 24 weeks of treatment as defined by RECIST 1.1 as percentage of patients with CR, PR or SD until week 24 or longer as well as patients with NCRNPD >24 weeks for patients with non-measurable disease
Progression-free survival (PFS) for the three different populations: Cohort A, Cohort B1, Cohort B2	PFS based on radiologic assessment by investigator using RECIST 1.1 criteria (e.g. median PFS, PFS rate at 12 and 18 months)
Overall survival (OS) for the three different populations, defined as the time from date of start of treatment to date of death due to any cause.	Overall survival (OS) (e.g. OS rate at 12 and 24 months)
Overall response rate (ORR) for the three different populations, defined as complete response or partial response as defined by RECIST 1.1	Overall Response Rate (ORR) after 24 weeks
To evaluate the **safety and tolerability** of ribociclib in combination with letrozole (and goserelin in premenopausal patients)	Frequency/severity of AEs AEs of special interest: Frequency, severity, frequency per patient, time to Event, duration of Event and recurrence Laboratory values
To evaluate **patient reported outcomes** for health related quality of life	Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30 Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30

Exploratory Objectives (out of scope of this statistical analysis plan)	**Endpoint**
[redacted]	Analysis methods and endpoints will be used that resemble the current scientific standard at the time of analysis. Such analyses will be described in a separate analysis plan

2 Statistical methods

2.1 Data analysis general information

The data were analyzed by [redacted]. Analysis was carried out using the SAS (Statistial Analysis System) software, version 9.2, 2009, SAS Institute Inc., Cary, North Carolina, USA.

Interim analyses were carried out by [redacted] as well. The analyses were based on definitions within this SAP and RAP 7.1 and the tables generated for the particular interim analyses were marked in RAP 7.2.

The first interim analysis included a preliminary analysis of safety (as well as baseline characteristics). The second interim analysis included a preliminary analysis of safety, efficacy and quality of life. The third interim analysis included a preliminary analysis of safety and efficacy. The primary efficacy and safety analysis was conducted on all patient data at the time all patients who are still receiving study drug had completed at least 24 weeks of treatment (or discontinued prematurely). The additional data for any patients continuing to receive study drug past these times, as allowed by the protocol, were further summarized in a report once these patients completed the study.

In general, categorical variables were summarized by absolute and relative frequencies. Continuous variables were summarized by descriptive statistics (number of non-missing observations, mean, standard deviation, minimum, median and maximum). Time-to-event data including rates of affected patients were assessed using the Kaplan-Meier method. The primary aim of this trial was in estimation rather than significance testing of statistical hypotheses. Thus, mainly statistical estimators along with appropriate two-sided 95% confidence intervals were used. However, changes from baseline were explored using suitable statistical tests for paired samples. No adjustment for multiplicity was done due to the exploratory nature of the trial.

The data from all participating centers were combined, so that an adequate number of patients was available for analysis and the factor center was included in the analysis of the primary endpoint.

2.1.1 General definitions

Study treatment: The combination of drugs including investigational drug ribociclib as well as letrozole and goserelin acetate.

On-treatment period: Period the patient was exposed to any study treatment, i.e from the first administration of any study treatment at or after C1/D1 to the last administration of any study treatment (for ribociclib and letrozole documented on the Treatment Completion CRF and for Goserelin documented on the Dosage Administration record but not later than the End-of-study visit (see 5.2.1)

2.2 Analysis sets

The **Enrolled Patient Population (ENR)** includes all patients who signed an informed consent regardless whether they received study treatment or not.

The **Full Analysis Set (FAS)** comprises all patients to whom study treatment has been assigned. Patients with critical findings by an inspection were excluded.

The **Safety Set (SAF)** includes all patients who received at least one dose of study treatment.

The **Per-Protocol Set (PPS)** consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. During the data review meeting the violations against the CSP were identified and assessed as relevant for analysis (called “major”) or not (“minor”). The PPS may be analyzed if a substantial number of patients was not compliant with the requirements of CSP. This decision will be done during a data review meeting before analysis.

2.2.1 Subgroup of interest

All results of this study were displayed for the total population and for cohorts A, B, B1 and B2 separately (each cohort is displayed in a separate column):

- **Cohort A**: Postmenopausal women and men who received no prior treatment for advanced disease.
- **Cohort B**: Pre-, and perimenopausal women who received no prior treatment for advanced disease (**B1**) as well as pre-, peri- and postmenopausal women and men who received prior therapy (**B2**). According to exclusion criteria only patients with no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease were included.

Cohorts:	Postmenopausal women or men	Pre- or perimenopausal women
Treatment naive	**A**	**B1**
Pre-treated	**B2**	**B2**

Further subgroups of interest may be analyzed for selected endpoints. These subgroups were:

- Men
- Pre- and perimenopausal women

across all cohorts.

During review of analysis tables it will be defined which tables will be additionally produced for the further subgroups.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline characteristics were summarized for the Full Analysis Set (FAS). Baseline characteristics include prior medication, past/current medical conditions and disease history.

2.3.1 Patient disposition

Patient disposition was summarized for all patients by absolute and relative frequency of patients completing the study phases screening, treatment and study completion. Reasons for discontinuation were shown for the Enrolled Patient Population (ENR) for screening resp. the Full Analysis Set (FAS).

The number of patients per visit and the number of on-treatment visits were given for the FAS.

Frequencies of major (=leading to exclusion from per-protocol population) and minor protocol violations were reported.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration (days) of study treatment exposure for patients who took at least one dose of any of the components of the study treatment was calculated as the difference between the last and first day of drug application +1 day. For details see 5.2.1.

The duration includes the periods of temporary interruptions for any reason. Additionally, duration of drug exposure was summarized using descriptive statistics separately for ribociclib, letrozole and goserelin, respectively.

The cumulative dose, dose intensity (DI) and relative dose intensity (RDI) were summarized by cohort. Cumulative dose is defined as the total dose given during the study treatment exposure. For patients who did not receive the respective drug the cumulative dose was set to zero (in case of goselerin for pre- and perimenopausal patients only). The dose intensity (DI) for patients with non-zero duration of exposure is defined as cumulative dose / duration of exposure. For patients who did not receive any drug, the DI was set to zero. Planned dose intensity (PDI) is the assigned dose in mg/day prescribed by the investigator to be given to patients. Relative dose intensity (RDI) is defined as DI divided by PDI. The DI and RDI were summarized separately for each of the study treatment components, but using the duration of the whole study treatment exposure, not the duration of each of the components. In addition, for combinations, the RDI was calculated as mean RDI of each of the study treatment components on a per-patient basis.

Ribociclib interruptions (defined as null doses for any reason except “as per protocol”) were displayed by the number of affected patients, the total duration and frequencies of study drug interruptions. The total duration was calculated by end date – start date of interruption (for any reason except “as per-protocol”) + 1 day. All interruptions of a patient are summed up to the total duration (for any reason except “as per protocol”)

Frequencies of the number of patients with ribociclib dose reduction (defined as dose > 0 mg but lower than the previous dose) as well as the number of dose reductions by reason were given. Additionally, dose reductions and dose interruptions were tabulated in combined fashion. In the combined summary, the dose interruptions were considered as dose reductions to 0 mg and therefore all reductions/interruptions were labeled as reductions and tabulated in one table.

These analyses were performed for the Safety Set (SAF).

2.4.2 Prior, concomitant and post therapies

Regarding the prior treatment for advanced breast cancer, the number, type, setting and best response of regimes before study were evaluated. The type was classified by WHO ATC level 2 and preferred name. Radiotherapies and surgeries were analysed similarily.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be coded according to the WHO Drug Reference List and summarized by ATC class and preferred term using frequency distributions.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objective of this study was the assessment of the clinical benefit rate after 24 weeks.

The **Clinical Benefit Rate (CBR)** is the proportion of patients with a best overall response of confirmed complete (CR) or partial (PR) response or stable disease (SD) or non-complete response, non-progressive disease (NCRNPD) within Week 24. The best overall response for

each patient is determined from the sequence of investigator overall lesion responses until week 24 according to RECIST 1.1. To be assigned a best overall response of CR at least two determinations of CR at least 4 weeks apart before progression are required. To be assigned a best overall response of PR at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) are required. To be assigned a stable disease, two determinations of SD at least 12 weeks apart (and not qualifying for PR or CR) are required.

Patients with best overall response "unknown" will be summarized by reason for having

unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early (≤6 weeks after randomization)
- PD too late (>12 weeks after randomization and not qualifying for CR, PR, or SD)

Special (and rare) cases where BOR is unknown due to both early SD and late PD

will be classified as "SD too early"

During data review. i.e. before analysis, the number and reasons for best responses falling into the category "unknown" according to RECIST 1.1 criteria are investigated. In addition, the impact of confirmation of response on the outcome in the context of the visit schedule and assessment timepoints will be assessed. If necessary, further sensitivity analyses were defined to adjust for this uninformative category.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria will be carefully reviewed during the data review meeting. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in an UNK (unknown) overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified based on the available information. Potential discrepancies between the modality used and overall lesion response (e.g. change in modality but response is different from 'Unknown') will be queried during the data validation process."

Additionally, the CBR at EOT was determined.

2.5.2 Statistical hypothesis, model, and method of analysis

In this single-arm trial, the primary objective is to estimate the CBR. Therefore, no statistical hypothesis or model is underlying the analysis.

The CBR (best overall response of CR or PR or SD or NCRNPD) as well as individual response categories (CR, PR, SD, PD, NCRNPD or unknown) will be summarized using frequency tables together with their associated two-sided exact 95% confidence intervals (Clopper-Pearson method).

The Full Analysis Set will be used for the primary efficacy analysis, the per-protocol set will serve as sensitivity analysis. Further, selected analysis tables (see RAP module 7.1) were desplayed as sensitivity analysis for a modified FAS population which inexcludes patients from centers with a relevant inspection finding.

2.5.3 Handling of missing values/censoring/discontinuations

Since the definition of the primary variable was derived from tumor assessments based on RECIST 1.1 criteria, these criteria apply for the handling of missing values in tumor assessments. 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 (see protocol, Post-text supplement 1). If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be ‘unknown’ unless progression was seen. Patients with a best overall response assessment of unknown (UNK) were not be regarded as ‘responders’ but were included in the denominator for the calculation of the ORR for the FAS.

For patients who took other anti-neoplastic drugs their efficacy data will be censored so that the tumor assessments made after the administration of the other anti-neoplastic drugs are not included in the primary efficacy analyses. Sensitivity analysis including these observations may be performed if decided during data review meeting.

2.5.4 Supportive analyses

CBR until Week 24 were additionally presented for the Per-protocol Set (PPS). Furthermore, the CBR were summarized by subgroups (cohorts A, B, B1 and B2) for the FAS and PPS, respectively.

2.5.4.1 Time to reponse (CR or PR)

Furthermore, the time to overall response (CR or PR) were analyzed by Kaplan Meier curve and Kaplan meier statistics for the total population and for cohorts. The time to overall response is the time between date of start of treatment until first documented response (CR od PR). Patients who did not achieve a confirmed PR or CR will be censored:

- At maximum follow-up (i.e. FPFV to LPLV used for analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)

2.5.4.2 At last adequate tumor assessment date otherwise Duration of response (DoR)

DoR applies only to patients whose best overall response was CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of event defined as the first documented progression or death due to underlying cancer. In other words, the start date will be determined using the time the response was first determined and not using the time the response was confirmed. If a patient has not had an event, duration is censored at the date of last adequate tumor assessment. DoR will be summarized for the total population and the cohorts separately. Distribution of duration of response will be estimated using the Kaplan-Meier method and the median response duration will be presented along with 95% confidence interval only if there are sufficient numbers of events.

2.6 Analysis of the key secondary objective

No 'key' secondary objective was defined.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

2.7.2 Statistical hypothesis, model, and method of analysis

The following secondary efficacy variables were analyzed in an explorative manner for the full analysis set (FAS): overall response rate (ORR) by Week 24, progression-free survival (PFS) and overall survival (OS).

ORR within Week 24

The ORR within Week 24 was derived from the sequence of overall lesion responses as described for the primary efficacy variable. The ORR by Week 24 was summarized using frequency tables presenting absolute and relative frequencies together with appropriate confidence intervals. Furthermore, the ORR at EOT was analyzed.

Progression-free survival

Progression-free survival (PFS) is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient had not had an event, progression-free survival was censored at the date of last adequate tumor assessment. Disease progression for primary efficacy endpoint derivation was assessed using the local investigator's tumor assessment (treating center's radiologist). PFS was summarized using the Kaplan-Meier method. Percentiles (25%, median, 75%) of the event time distribution were presented along with their two-sided 95% confidence interval. Additionally, Kaplan-Meier estimates for the proportions of patients progression-free by Week 48 and Week 72 were presented. The Kaplan-Meier curve (with censored patients at number of patients at risk) was displayed graphically.

Overall survival

Overall survival (OS) is defined as the time from date of start of treatment to date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last

contact. OS was summarized using the Kaplan-Meier method as described above. The Kaplan-Meier curve was displayed graphically. Additionally, the proportion of patients alive at 48 and 96 weeks were presented

2.7.3 Handling of missing values/censoring/discontinuations

Same instructions as for primary analysis

2.8 Safety analyses

The analysis of safety objectives was described in section 10.5.2.1. of the study protocol. All listings and tables are presented for the Safety Analysis Set by pretreatment group and total, i.e. cohorts A, B1, B2, B and total:

- postmenopausal women or men without prior treatment for advanced disease (cohort A)
- pre- and perimenopausal women without prior treatment for advanced disease (cohort B1)
- pre-, peri and postmenopausal women with prior treatment for advanced disease (cohort B2)

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 treatment
2. on-treatment period plus 30 days: from day of first dose of study medication to 30 days after last dose of study treatment
3. post-treatment period: starting at day 30+1 after last dose of study treatment.

Goserelin and letrozole after end of treatment were not considered as study treatment, see 5.2.1.

As a sensitivity analysis selected analysis tables (see RAP module 7.1) were desplayed for a modified SAF population which excludes patients from centers with a relevant inspection finding.

2.8.1 Adverse events (AEs)

Summary tables for adverse events (AEs) include only AEs that started or worsened during the on-treatment period plus 30 days, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed in CSR section 16.2. Absolute and relative frequencies for patients with AEs collected during the pre-treatment and post-treatment period are presented.

The following analyses are presented for the different types of AEs:

	Incidence (frequency table)	**Two-level frequency table** **SOC x PT (MedDRA)**	**Patient data Listing** **(section 14.3.1)**	**Maximum severity** **(frequency table)**	**Time to event**	**Dur-ation of event**	**Recurrence/ frequency of events per patient**
Treatment emergent AEs	X	X		X			
Treatment emergent serious AEs	X	X	X	X	X	X	X
Treatment emergent non-serious AEs	X	X					
TEAE with suspected drug relation to ribociclib	X	X					
TEAE leading to permanent discontinuation of study drug	X	X					
TEAE of special interest	X	x	x		X	X	X
Death (in pre-/on-/post-treatment period)	X		X				

The **incidence frequency table** presents the number, percentage and 95% confidence for occurrence of at least one event of the respective AE type. This table is separated by each of the observation period (pre-/on-/post-treatment) and total. Denominator (for each period) is the number of patients in the Safety Analysis Set (SAF).

The **two-level frequency table** calculates absolute and relative frequencies for MedDRA System Organ Classes (SOC) and Preferred Terms (PT) within SOCs. Again, the number of patients in SAF is used as denominator and each event is counted only once in the respective category. The MedDRA version currently available at time point of analysis is used for decoding.

The **frequency table for maximum severity** analyses the maximum CTC-AE grade and display n and % for each category (total, SOC, and PT). Again, the number of patients in SAF is used as denominator and each maximum severity is counted only once in the respective category.

All patient data are listed in CSR section 16.2. Additionally **data listings** relevant for safety assessment are presented in section 14.3.2. Here, the patient identification, the verbatim term given by the investigator, MedDRA preferred term and system organ class, start/end dates,

severity, seriousness, relationship to study drug and action taken are listed. The AE onset will also be shown relative (in number of days) to the date of initial dose.

2.8.1.1 Adverse events of special interest / grouping of AEs

The following (S)AEs of special interest were defined:

- Neutropenia (MedDRA Code 10029354)
- Hepatobiliary toxicity, defined as grade 3 or 4 increases in ALT or/and AST (MedDRA Codes: 10001551, 10003481)
- QT prolongation (MedDRA Code 10014387)

In addition, the time to occurrence from start of study drug to the (first) onset of a TEAE of special interest (TEAESI) is analysed by sample statistics as well as the duration (start – end + 1 day). Further the number of TEAESI occurring in one patients during on-treatment period is displayed.

2.8.2 Deaths

The number of deaths in the pre-, on- and post-treatment period plus 30 days were displayed as absolute and relative frequencies with 95% confidence intervals. Deaths are listed by patient.

2.8.3 Laboratory data

Normal laboratory values were not documented in the CRF. Abnormal laboratory parameters that induced clinical signs or symptoms, required therapy or required changes in study drug(s) constituted an adverse event and were recorded on the Adverse Events CRF. These relevant laboratory values associated with an adverse event were listed only.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG results were summarized using frequency distributions by visit.

2.8.4.2 Vital signs

Vital signs were summarized descriptively by visit for baseline and all post-baseline time points and change from baseline to these time points.

2.8.4.3 ECOG Performance Status

The ECOG Performance Status was summarized using frequency distributions by visit. Shifts from baseline value to worst (i.e. the highest) post-baseline value were summarized using frequency distributions.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

Not applicable

2.11 Patient-reported outcomes

Health-related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 and BR23 questionnaires.

Descriptive statistics was used to summarize the individual item and scored sub-scale scores of QoL data at each scheduled assessment time point. Patients were included if they completed at least one questionnaire item. Additionally, change from baseline in the domain scores at the time of each assessment was summarized. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period were included in the change from baseline analyses (assessments after disease progression were excluded).

The time (from start of study drug) to 10% deterioration in EORTC QLQ-C30 was analysed by sample statistics.

2.12 Biomarkers

Analysis of Biomarker was described in a stand-alone analysis plan document.

2.13 Other Exploratory analyses

Multivariate regression analysis to identify prognostic factors for Neutropenia respectively AST/ALT increase.

This analysis was not foreseen in the study protocol but included on request of the principal investigator for the presentation of interim and final results.

Two separate multivariate regression analyses were calculated for these interesting events (dependent variables):

1. Neutropenia, selected from AE data set via PTs “neutropenia” and/or “neutrophil count decreased”
2. Increase in ALT or AST: Selected from AE dataset via PTs “ALANINE AMINOTRANSFERASE INCREASED” and/or “ASPARTATE AMINOTRANSFERASE INCREASED”

The following effects (without interactions) were investigated by Type 3 estimates and Wald’s confidence intervals for Odds ratios:

- Age at baseline (categorical): <60 years, 60-70 years, and >= 70 years
- BMI at baseline (categorical, rounded to integers): < 20, 20-25, 26-29, and >30 kg/m²
- Presence (no vs. yes) of bone metastases at study start
- Use of chemo therapy as prior antineoplastic medication (no vs. yes)
- Therapy line: 1st, 2nd, and >= 3rd

2.14 Interim analysis

Three interim analyses were planned during the study. The first interim analysis was conducted one year after the first patient has been enrolled and included a preliminary analysis on safety. The second interim analysis was conducted 12 months after LPFV in the 30% pretreated and premenopausal cohort and included a preliminary analysis on safety, efficacy and quality of life. The third interim analysis took place 6 months after the last patient had been recruited and included a preliminary analysis on safety and efficacy.

3 Sample size calculation

Sample size assumptions in this study for postmenopausal patients without prior treatment for advanced disease are based on the data from the CLEE011X2107 study (Juric, poster presented at ASCO 2016), which enrolled a similar patient population.
Regarding patients in later than first lines and pretreated premenopausal patients, assumptions are based on Cristofanilli et al 2016 - PALOMA-3 final analysis.
It is expected that the CBR (based on local assessment) by week 24 is in a range as reported for the CLEE011X2107study for the ribociclib + letrozole group (CBR = 79%, 95% confidence interval [59% to 92%]).
Using the lower limit of the CI (59%) as a pessimistic estimate for the CBR by week 24, a sample size of 500 produces a two-sided 95% confidence interval with a width equal to 8.6 percentage points (the associated 95% CI is [54.7% to 63.3%]). When using the same CBR as observed (CBR 79%), a sample size of 500 produces a two-sided 95% confidence interval with a width equal to 7.2 percentage points (the 95% CI is [75.4% to 82.6%]). Using the upper limit of the CI (92%) as an optimistic estimate for the CBR, a sample size of 500 produces a two-sided 95% confidence interval with a width equal to 4.8 percentage points (the 95% CI is 89.6% to 94.4%]). Assuming an estimated rate of 70% to be recruited in the subgroup of postmenopausal first line patients resulting in a sample size of 350 patients, the width of the confidence interval will be between 10.4 percentage points (pessimistic scenario) and 5.6 percentage points (optimistic scenario).
Regarding the subgroup of second or further treatment lines and premenopausal patients, assuming an estimated rate of 30% to be recruited, and further based on the data as presented by Cristofanili et al. (CBR 67%, 95% CI [61.3% to 71.5%]), the resulting precision based on 150 patients leads to a width of the resulting 95% confidence interval between 15.6 percentage points (pessimistic scenario) and 14.4 percentage points (optimistic scenario).

Thus, a sample size of 500 patients allows estimating the CBR in this patient population with reasonable precision.

4 Change to protocol specified analyses

Additionally to protocol specified analyses, the time to and duration of RECIST response was analysed for the full analysis set (FAS).

5 Appendix

5.1 Definition of efficacy variables

Progression:

1. ds.eotdreasn = 4 (Main reason for ribociclib discontinuation = progressive disease)
2. ds.eotprdi1n = 1 (Radiologic progression according to RECIST 1.1) OR
3. ds.eotprdi3n = 1 (Clinically symptomatic progress) OR
4. zr.recoveran = 4 (Overall lesion response = Progressive Disease) OR
5. zr.recnewln=1 (New Lesion)

Progression date:

1. ds.eotcprdt (date of clinically symptomatic progress) OR
2. Date of Evaluation where zr.recoveran = 4 or zr.recnewln = 1

Response:

3. zr.recoveran (Overall lesion response)

Assessment Date:

4. zr.tlesdt (Date of image or examination, Target Lesion Assessment)
5. zr.ntlesdt (Date of image or examination, Non-Target Lesion Assessment)
6. zr.nlesdt (Date of image or examination at which new lesion appeared)

Date of Death:

7. sc.deathdt

Date of last contact:

8. sc.eoslcdt

Start of treatment = first administration of Ribociclib or Letrozole:

9. min(min(zq.ribostdt), min(zq.letrstdt))

5.1.1 Clinical Benefit Rate (CBR) until week 24

Best overall response in (CR, PR, SD, NCRNPD):

1. zr.recoveran = 1; at least two determinations of CR at least 4 weeks apart before progression OR
2. zr.recoveran = 2; at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
3. zr.recoveran = 3; two determinations of SD at least 12 weeks apart (and not qualifying for PR or PD)

4. zr.recoveran = 5

Tumor evaluations are scheduled for baseline, Cycle 4 and cycle 7 etc. (every 12 weeks). Thus, to assess the CBR at week 24 the first two post-baseline evaluations have to be considered. Additionally it has to be checked that no progression occurred during the following 4 weeks. Deviations against the time schedule is investigated and assessed during the data review meeting.

5.1.2 Overall response rate (ORR) by week 24

Similar to 5.1.1, but the best overall response must be in in (CR, PR)

5.1.3 Progression-free survival

Start date = Start of treatment (first administration of Ribociclib or Letrozole)

End date = First date of progress or date of death or (if no event) date of last tumor assessment

5.1.4 Overall survival (OS)

Start date = Start of treatment (first administration of Ribociclib or Letrozole)

End date = Date of death or (if no event) date of last contact

5.2 Definiton of safety variables

5.2.1 Duration of study treatment exposure

For ribociclib and letrozole the duration of exposure (days) = date of last administration of ribociclib resp. letrozole – date of first administraton of ribociclib resp. letrozole + 1 day. The first administration of the study treatments ribociclib and letrozole are taken from the respective Dosage Administration Record, i.e. the date of first dose > 0 at/after C1/D1. The date of last administration of the study treatments ribociclib and letrozole are taken from the Treatment Completion CRF. In case of ongoing treatment, resulting in missing end days on Treatment Completion CRF, the end date is substituted hierarchy by:

- End date of last administration with dose >0 of ribociclib resp. letrozole on the Dosage Administration record before End-of-Treatment-visit
- If the end date of the last administration with dose >0 of ribociclib resp. letrozole on the Dosage Administration is missing (normally because “ongoing” is ticked) the date of the last visit during the on-treatment period (C1/D1 to End-of-treatment) is used to substitute the end date.

For goselerin the duration of exposure (days) = date of last administration of goselerin – date of first administraton of goselerin + 1 day. The first administration of the study treatment goselerin is taken from the respective Dosage Administration Record, i.e. the first dose > 0 at/after C1/D1. The end of the third component goselerin is not asked at the Treatment Completion CRF and must be derived from the Dosage Administration record therefore. Goselerin may be continued in combination with a follow-up therapy and may be documented on the Dosage Administration Record, although it is no longer a study treatment. For this reason

the date of last goselerin administration is the last dose > 0 administered until the End-of-treatment visit.

The exposure to study treatment is displayed for each of the third components separately, and in combination. For combination, called "exposure to any of the study treatments", the first start date and the last end date of the study treatments is used for calculation.

The duration of exposure includes the periods of temporary interruption (of any component of the study treatment for any reason).

5.2.2 Cumulative dose

Cumulative dose (mg) = total dose given during study treatment exposure

For patients who do not receive any drug the cumulative dose is set to zero.

5.2.3 Dose intensity (DI)

Dose intensity (mg/day) = cumulative dose (mg) / duration of exposure of study treatment (days)

For patients who do not receive any drug the dose intensity is set to zero.

5.2.4 Planned dose intensity (PDI)

Planned dose intensity (mg/day) = total daily dose pescribed

5.2.5 Relative dose intensity (RDI)

Relative dose intensity (mg/day) = dose intensity (mg/day) / planned dose intensity (mg/day)

5.2.6 Mean relative dose intensity (mean RDI)

Mean relative dose intensity (mg/day) = mean of the relative dose intensity per patient by study treatment component

5.2.7 Adverse events of special interest

- Neutropenia = AE term: MedDRA Preferred Term "Neutropenia" (10029354)
- Hepatobiliary toxicity = AE term: MedDRA Preferred Term "Alanine aminotransferase increased" (10001551) or "Aspartate aminotransferase increased" (10003481), Toxicity grade "Grade 3" or "Grade 4"
- QT prolongation = AE term: MedDRA Preferred Term "Electrocardiogram QT prolonged" (10014387)

5.3 Programming rules

5.3.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days).

When no post-baseline tumor assessments was available, the date of first application of treatment was used as end date (duration = 1 day) when time was to be censored at last tumor assessment, i.e. time to event variables can never be negative.

5.4 Imputation rules

5.4.1 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must have been completed with day, month and year.
If one or more investigation dates was incomplete but other investigation dates were available, this/these incomplete date(s) was/were not considered for calculation of the assessment date (and assessment date was calculated as outlined in Section 3.2.7). If all measurement dates had no day recorded, the 1st of the month is used.

If the month was not completed, for any of the investigations, the respective assessment was considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment was not available, this assessment was not used for any calculation.

5.4.2 Incomplete dates for last known date patient alive or death

All dates must have been completed with day, month and year. If the day was missing, the 15th of the month was used for incomplete death dates or dates of last contact.

5.4.3 Non-target lesion response

If no non-target lesions were identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment was considered ‘not applicable (NA)’.

5.4.4 Censoring reason

In order to summarize the various reasons for censoring, the following categories were calculated for each time to event variable based on the treatment completion page, the end of study page and the survival follow-up page.

For survival the following censoring reasons are possible:

- Alive
- Unknown/Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)

- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 3.2.7. This reason was applicable when adequate evaluations were missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

5.4.5 Study treatment

In case of missing or partial start date, the start date should be shifted to the earliest possible date, but not earlier than the C1/D1 visit, i.e. the beginning of the on-treatment period, respectively not earlier than the previous administration. Missing or partial end dates (which result often from "ongoing" answers) should be shifted forward as far as possible: At maximum to the last documented on-treatment visit, i.e. C1/D1 to End-of-treatment-visit and not later than the following administration.

5.4.6 AE date imputation

In case of missing or partial start date or end date of an AE, the start date should be shifted to the earliest possible date, but not ealier than the first intake of study drug while the end date should be shifted forward as far as possible.

5.4.7 Concomitant medication date imputation

In case of missing or partial start date or end date of a concomitant medication, the start date should be shifted to the earliest possible date, but not earlier than the first intake of study drug while the end date should be shifted forward as far as possible.

5.4.7.1 Prior antineoplastic therapies date imputation

In case of missing or partial start date or end date of a prior therapy, the start date should be shifted to the earliest possible date, but not earlier than the initial diagnosis while the end date should be shifted as far back as possible, but not later than the first intake of study drug.

5.4.7.2 Post antineoplastic therapies date imputation

In case of missing or partial start date or end date of a post therapy, the start date should be shifted to the earliest possible date, but not earlier than the first intake of study drug while the end date should be shifted forward as far as possible.

5.4.7.3 Other imputations

5.5 AEs coding/grading

Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading did not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, was used. CTCAE Grade 5 (death) was not used in this study.

5.6 Laboratory parameters derivations

Not applicable.

5.7 Statistical models

5.7.1 Primary analysis

No statistical hypothesis or model was underlying the analysis.

5.8 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
I_06	No positive hormone receptor status	Excluded form PP analysis
I_07	positive HER2 receptor status	Excluded form PP analysis
I_08	No negative HER2 receptor status	Excluded form PP analysis
E_04	Patient received any non-permitted prior medication or therapy	Excluded form PP analysis, only if medication/therapy is assessed as influencing the primary parameter in Data Review Meeting (DRM)
E_12	History or clinical evidence of central nervous system metastases not meeting the specific criteria for eligibility	Excluded form PP analysis
D_01	Patient continued with trial treatment in spite of IMP Ribociclib was interrupted for > 28 days.	Excluded form PP analysis
M_01	Non-permitted concomitant medication	Excluded form PP analysis

		(only if during DRM medication/therapy is assessed as influencing the primary parameter)
S_03	IMP (Ribociclib and letrozole) intake is not 80-120%	Excluded from PPS if leading to invalid primary enpoint (assessed additionally during DRM, although not specified in VAP Module 3)
O_03	Tumor evaluation omitted if assessed during DRM as relevant (timepoint, frequency)	
O_05	Tumor assessment method invalid or changed during course of study	Excluded form PP analysis if leading to invalid primary endpoint (assessed during DRM)
O_09	Any data for evaluating the primary endpoint is missing	Excluded form PP analysis, if leading in invalid assessment of primary endpoint (assessed in DRM)
O_10	Complete patient's study visit was omitted	Excluded form PP analysis, if leading in invalid assessment of primary endpoint (assessed in DRM)

Table 2 Subject Classification

Analysis Set	**PD ID that cause subjects to be excluded**	**Non-PD criteria that cause subjects to be excluded**
ENR	NA	Not having informed consent;
SAF	NA	Not having informed consent; Screening failure, not treated with any dose of study treatment
SAF 2 (for sensitivity analysis of AE)	NA	Not having informed consent; Screening failure, not treated with any dose of study treatment; Centers with a critical finding by audit / inspection (as assessed by Novartis "Massnahmenausschuss")
FAS	NA	Not having informed consent; Screening failure; not intended to be treated with any dose of study treatment; Centers with a critical finding by

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
		audit / inspection (as assessed by Novartis "Massnahmenausschuss")
FAS 2 (for sensitivity analysis of primary parameter)	NA	Not having informed consent; Screening failure; not intended to be treated with any dose of study treatment
PPS	I_01 – I_08 E_04, E_12, D_01, M_01, O_03, O_05, O_09, O_10	Not in FAS; not treated with any dose of study treatment

6 Reference

None.