CONFIDENTIAL

CLINICAL STUDY REPORT

CORALLEEN

A Phase 2 Clinical Trial of multi-agent Chemotherapy or letrozole plus Ribociclib (LEE011) as neoadjuvant treatment for postmenopausal patients with Luminal B/HER2-negative breast cancer

Study code: SOLTI-1402

Study development phase: Phase II

Sponsor: SOLTI

EudraCT number: 2016-003098-17

Indication: Primary operable HR+/HER2-negative Luminal B breast cancer

Investigational medicinal product: Ribociclib (Kisqali®)

First patient first visit: 27 July 2017

Last patient last visit: 01 July 2019

Version: Final

Date: 08th June 2020

Coordinating Investigators: Dr. Aleix Prat, Hospital Clinic, Barcelona;
Dr. Joaquín Gavilá, Instituto Valenciano de Oncología, Valenciano

Sponsor signatory: Patricia Villagrasa

This study was performed in compliance with Good Clinical Practice (E6).

1 SYNOPSIS

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)		
Name of Active Ingredient: Ribociclib		

STUDY CODE:
SOLTI-1402

TITLE OF STUDY:

A Phase 2 Clinical Trial of multi-agent Chemotherapy or letrozole plus Ribociclib (LEE011) as neoadjuvant treatment for postmenopausal patients with Luminal B/HER2-negative breast cancer

INVESTIGATORS:

Dra. Cristina Saura, Dra. Begoña Bermejo, Dra. Montserrat Muñoz, Dr. Xavier González Farré, Dr Miguel Gil-Gil, Dra. Neus Ferrer, Dr. Alvaro Montaño, Dr. Yann Izarzugaza, Dr. Antonio Llombart-Cussac, Dra. Raquel Bratos, Dr. Santiago González Santiago, Dr. Eduardo Martínez, Dr. Sergio Hoyos, Dra. Beatriz Rojas, Dr. Juan Antonio Virizuela, Dra. Vanesa Ortega, Dr. Rafael López, Dra Eva Ciruelos, Dra.Lucía García Cortijo, Dr Carlos Jara and Dr. Joaquín Gavilá.

STUDY CENTRES:

Hospital Universitario Vall d'Hebron , Hospital Clínico Universitario de Valencia, Hospital Clinic de Barcelona, Hospital General de Catalunya, Institut Català d'Oncologia Hospitalet, Hospital Universitari Son Espases, Hospital Universitario Virgen del Rocío, Hospital Universitario Fundación Jimenez Díaz, Hospital Arnau de Vilanova, Centro Oncológico Internacional MD Anderson, Hospital San Pedro de Alcántara, Consorcio Hospitalario Provincial de Castellón, Hospital Rey Juan Carlos, Centro Integral Oncológico Clara Campal, Hospital Virgen de la Macarena, Fundación Privada Asil de Granollers, Complejo Universitario de Santiago de Compostela, Hospital 12 de Octubre, Hospital Quirón Madrid, Hospital Universitario Fundación de Alcorcón, Instituto Valenciano de Oncología.

PUBLICATION (REFERENCE):

J.Gavilá et al. CORALLEEN: A Phase 2 clinical trial of chemotherapy or letrozole plus ribociclib as neoadjuvant treatment for postmenopausal patients with Luminal B/HER2-negative breast cancer. Poster presented at ASCO 2017.

J.Gavilá et al. CORALLEEN: A phase 2 clinical trial of chemotherapy or letrozole plus ribociclib as neoadjuvant treatment for postmenopausal patients with luminal B/HER2-negative breast cancer.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

J.Gavilá et al. Primary results of SOLTI-1402/CORALLEEN phase 2 trial of neoadjuvant ribociclib plus letrozole versus chemotherapy in PAM50 Luminal B early breast cancer: an open-label, multicenter, two-arm, randomized study. Oral presentation at SABCS 2019.

N.Chic et al.Immune response following neoadjuvant ribociclib plus letrozole versus chemotherapy in PAM50 Luminal B early breast cancer: a correlative analysis of the SOLTI-1402/CORALLEEN phase 2 randomized trial. Poster presented at SABCS 2019

Aleix Prat et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with PAM50 Luminal B breast cancer (CORALLEEN): an open-label, two-arm, randomised, multicentre, phase 2 trial. Lancet Oncology 2019

N.Chic et al. Gene expression profiling in early breast cancer treated with neoadjuvant ribociclib plus letrozole (R+L) versus chemotherapy (CT): A correlative analysis of the SOLTI-1402/CORALLEEN phase II trial. Poster presented at ESMO Breast 2020.

STUDY PERIOD (YEARS):
2017-2019

Date of first patient first visit: 27 July 2017

Date of last patient last visit: 01 July 2019

PHASE OF DEVELOPMENT:
Phase II

OBJECTIVES:

Primary Objective

To evaluate the ability of each treatment strategy to provide ROR-low score at surgery

Secondary Objectives

- To assess measures of clinical benefit of both arms.
- To evaluate the rate of breast conserving surgery (BCS) and transition to BCS of both arms.
- To explore the anti-proliferative effect of treatment arms as per molecular indicators.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)		
Name of Active Ingredient: Ribociclib		

- To assess the effect of investigational treatment and standard treatment on patient reported outcomes (PROs).
- To evaluate the safety and tolerability of investigational treatment and their corresponding standard treatment.
- To identify biomarkers of response or resistance to the study treatments.

METHODOLOGY:

This was a parallel, two-arm, randomized 1:1, stratified by tumor size and nodal involvement, open-label, multicenter, exploratory study in postmenopausal women with primary operable Hormone receptor positive (HR+)/HER2-negative Luminal B breast cancer according to PAM50 intrinsic subtype to evaluate the clinical benefit and biological effects of ribociclib combined with letrozole.

The primary trial objective was to evaluate the ability of each treatmet strategy to provide ROR-low score at surgery. The PAM50 ROR risk class integrated gene expression data, tumour size, and nodal status to define prognosis.

This study was exploratory and no formal comparison between both treatment arms was intended.

Patients underwent first a screening period, tumour measurement by breast Magnetic Resonance Imaging (MRI) for confirmation of baseline tumor measure ≥ 2cm and PAM50 analyses for evaluation of intrinsic subtype and confirmation of Luminal B subtype to be included.

Following confirmation of eligibility criteria, patients were randomly assigned (1:1) to receive either six 28-days cycles of ribociclib (oral 600 mg/day 3 weeks-on, 1 week-off) plus daily letrozole (oral 2.5 mg/day) or four cycles of doxorubicin (intravenous 60 mg/m2) and cyclophosphamide (intravenous 600 mg/m2) every 21 days followed by weekly paclitaxel (intravenous 80 mg/m2) for 12 weeks. Randomization was stratified by tumour size (T1–T2 vs T3) and nodal involvement.

Samples were prospectively collected at baseline (day 0), day-15 and at surgery.

After 12 weeks of treatment, and according to the standard of care, a breast Ultrasound (US) was performed to ensure that there is no progressive disease. A pre-surgery visit was performed at the end of the neoadjuvant treatment in order to assess the secondary endpoint tumor objective response by breast MRI. Breast surgery was carried 6 weeks after completion of neoadjuvant treatment. The

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

type of breast surgery and the management of the axilla followed local standard practices. Surgical specimens were collected for pathologic examination and other analyses. A post-surgery visit was performed within 28 days (±7 days) from surgery.

NUMBER OF PATIENTS (planned and analysed):

Planned: 94 patients to be recruited. Considering 10% drop-out rate, 104 patients was planned to be included.From July 27, 2017 to December 7, 2018, 198 patients were assessed for eligibility across 21 centres in Spain and 106 were finally recruited.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Inclusion Criteria:

1. Signed Informed Consent Form prior to any study-specific procedure.
2. Female patients.
3. Post-menopausal status and age ≥18 years. Post-menopausal status is defined as:

−Age ≥ 60 years*or*

−Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone (FSH) and plasma estradiol levels within post-menopausal range by locallaboratory assessment*or*

−Prior bilateral oophorectomy (≥7days prior to Day 1 of treatment).

4. Histologically confirmed invasive breast carcinoma, withallthe following characteristics:
   - −Primary tumor ≥ 2cm in largest diameter asmeasured by breast MRI
   - −Stage I to stage IIIA breast cancer
   - −No evidence of distant metastasis (M0)
5. Breast cancer eligible for primarysurgery.
6. Availablepre-treatment FFPE core (Tru-cut) biopsy evaluableforPAM50 orpossibility toobtain one. Minimal sample requirements are to have at least 2 tumor cylinders with a minimal tissue surface of 10mm^2tissue, containing at least 10% tumor cells and having enough tissue to do at least 2 cuts of 10 µm each.
7. Luminal B subtype as per PAM50 analysis of pre-treatment sample.
8. ER-positive and/or PgR-positive and HER2-negative tumor by ASCO/CAP guidelines assessed locally.
9. In the case of a multifocal tumor (defined as the presence of two or more foci of cancer within the same breast quadrant),the largest lesion must be ≥2cm and designated the“target” lesion

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

for all subsequent tumor evaluations and HR+/HER2-negative statusmust bedocumented in all the tumor foci.

10. ECOG performance status of 0 or 1.
11. Adequate hematological, renal and hepatic function, as follows:

•Absolute neutrophil count (ANC) ≥1.5 x 10^9/L

•Platelets count≥100 x10^9/L

•Hemoglobin ≥10 g/dL

•Alkaline phosphatase (AP) ≤2.5x upper limit of normal (ULN)

•Total bilirubin < ULN. Patients with known Gilbert syndrome may be enrolled with total bilirubin≤3 xULNordirectbilirubin≤1.5 xULN.

•Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5x ULN

•Serum creatinine ≤1.5mg/dLorcalculatedcreatinineclearance≥60 mL/min

•Potassium, total calcium (correctedfor serum albumin), magnesium, sodium andphosphorus within institutional normal limits or corrected to within normal limits with supplements before first dose of study medication

12. Ability and willingness to comply with study visits, treatment, testing andto comply withtheprotocol.

<u>Exclusion criteria</u>

1. Any prior treatment for primary invasive breast cancer.
2. Inoperable locally advanced or inflammatory (i.e., inoperableStage III) breast cancer.
3. Metastatic (Stage IV) breast cancer.
4. Bilateral invasive breast cancer.
5. Multicentric breast cancer, defined as the presence of two or more foci of cancer in differentquadrants of the same breast.
6. Patients who have undergone sentinel lymph node biopsy prior to study treatment.
7. Inability or unwillingness to swallow pills.
8. Malabsorption syndrome or other condition that would interfere with enteric absorption of study drugs.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)		
Name of Active Ingredient: Ribociclib		

9. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer.
10. Patient with a Child-Pugh score B or C.
11. Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) or symptomatic pericarditis within 12 months prior to screening.
- History of documented congestive heart failure (New York Heart Association functional classification III-IV).
- Documented cardiomyopathy.
- Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO).
- Clinical significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
- Long QT Syndrome or family history of idiopathic sudden death or congenital long QT syndrome or any of the following:
    - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure or history of clinically significant/symptomatic bradycardia
    - QTc> 500 msec or conduction abnormality in the previous 12 months.
- On screening 12-lead ECG, any of the following cardiac parameters: bradycardia (resting heart rate < 50), tachycardia (resting heart rate > 90), PR interval > 220 msec, QRS interval >109 msec, or QTcF interval ≥450 msec (using Fridericia's correction).

12. Uncontrolled hypertension (Systolic blood pressure >160 mmHg or <90 mmHg and/or diastolic >100 mmHg).
13. Active infection requiring intravenous (IV) antibiotics.
14. Symptomatic hypercalcemia despite adequate management.
15. Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

16. Known human immunodeficiency virus (HIV) infection.
17. Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may compromise compliance with the protocol, that may affect the interpretation of the results, or renders the patients at high risk from treatment complications.
18. Significant traumatic injury within 3 weeks prior to initiation of study treatment.
19. Major surgical procedure (not including minor procedures such as lymph node biopsy, tumor core biopsy, fine needle aspiration or bilateral oophorectomy) within 4 weeks prior to initiation of study treatment or not fully recovered from any side effects of previous procedures.
20. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
21. History of other malignancy within 5 years prior to screening, except for appropriately treated basal or squamous cell carcinoma, carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer.
22. Estrogen replacement therapy stopped less than 2 weeks before treatment start.
23. Currently receiving or has received systemic corticosteroids until 2 weeks before treatment start or who have not fully recovered from side effects of such treatment. Following corticosteroid uses are permitted: single doses, topical applications (e.g. for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g. intra-articular)
24. Known hypersensitivity to any of the excipients of ribociclib, letrozole, doxorubicin, cyclophosphamide or paclitaxel.
25. Patients currently on following medications, which cannot be interrupted 7 days prior treatment start:

- Any prohibited medication as per letrozole, doxorubicin, cyclophosphamide, or paclitaxel label.
- Herbal preparations/medications, dietary supplements.
- Medications that have a known risk to prolong the QT interval or cause Torsades de Pointe.
- Medications with a narrow therapeutic window and predominantly metabolized through CYP3A4/5.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

- Strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, starfruit and Seville oranges.
- Warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin or fondaparinux is allowed.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

The study investigational treatment was Ribociclib (Kisqali ®). It was dministered as a flat-fixed dose of 600 mg daily (three 200-mg capsules), days 1 to 21 of a 28-days cycle.

Letrozole was administered orally, once per day, days 1 to 28 of a 28 days cycle, at 2.5 mg. Both ribociclib and letrozole were administered orally during 6 cycles and independently of the body surface area or body weight.

The ribociclib destined for use in the trial came from batches 1010010567 and WX027; and letrozole from batch SH083.

DURATION OF TREATMENT:

The total duration of the neoadjuvant treatment was 24 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

In chemotherapy arm: Doxorubicin and cyclophosphamide were administered on day 1 of a 21-days cycle during 4 cycles, followed by weekly (day 1 of a 7-day cycle) administration of Paclitaxel during 12 cycles. Doxorubicin was administered at 60 mg/m2, as a continuous IV perfusion according to local practice guidelines. Cyclophosphamide was administered at 600 mg/m2 in a 30 minutes IV infusion, instructing patients to hydrate abundantly to prevent vesical irritation. Emesis prophylaxis was mandatory, as per local practice. Paclitaxel was administered at 80 mg/m2, in one hour IV infusion. Patients should receive premedication with h1 and h2 antihistamines and corticosteroids.

CRITERIA FOR EVALUATION:

EFFICACY:

The primary endpoint was the Rate of ROR-low (at surgery) after neoadjuvant treatment, according to the Prosigna test.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

The secondary endpoints were: Tumor overall objective response rate (ORR), as per Investigator's assessments by breast MRI; ORR by physical examination, mammography and breast US, if available; pCR in the breast and pCR in the breast and axillary lymph nodes at surgery; Rate of residual cancer burden (RCB) score 0 or 1 (RCB0/1) after neoadjuvant treatment as per local and central assessments; Preoperative endocrine prognostic index (PEPI) score in the ribociclib plus letrozole treatment arm compared to historical values; Rate of breast conserving surgery (BCS); European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), version 3; Decrease in Ki67 from baseline to week 2, from baseline to surgery, from week 2 to surgery and from baseline to progression (in those patients who consent for early termination biopsy); rates of Luminal A disease (at surgery) in patients with residual disease in the breast at surgery; change to Luminal A from baseline to week 2, from baseline to surgery, from week 2 to surgery and from baseline to progression (in those patients who consent for early termination biopsy) and change to ROR low disease from baseline to week 2, from baseline to surgery, from week 2 to surgery and from baseline to progression (in those patients who consent for early termination biopsy).

SAFETY:

Incidence, duration and severity of Adverse Events (AEs) were assessed by the NCI Common Terminology for Classification of Adverse Events (CTCAE) version 4.03, including dose reductions, delays and treatment discontinuations.

STATISTICAL METHODS:

Sample Size Determination

Assuming that 20.0% to 25.0% of the subjects in each arm would achieve ROR-low disease, the study would require a sample size of 47 evaluable patients per arm for estimating the expected proportion with a 95% confidence interval of +/-11.5-12.4%. Assuming a proportion of patients of 10% dropping-out, a total of 104 patients was planned to be recruited. Both groups were analyzed independently without a formal comparison between both. The inclusion of a chemotherapy treatment arm was intended as an internal response control instead of an historical control.

Randomization: Patients were randomized (1:1) using a secure web-based system to ribociclib plus letrozole or multi-agent chemotherapy.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

Stratification: patients were stratified by tumour size (T1–T2 vs T3) and nodal involvement using permuted blocks and an internet-based tool.

Analysis Populations

Intent-to-Treat (ITT) population: included all patients entered into the study.

Modified intention to treat population (mITT), defined as all randomized patients who received study medication, and had a baseline efficacy measurement and at least one corresponding post-baseline efficacy measurement.

Per protocol Population (PP): defined as all randomized subjects who met the inclusion criteria, received study medication, had a baseline efficacy measurement and at least one corresponding post-baseline efficacy measurement (for the main efficacy variable) and did not present major violations of the protocol.

Safety (SP) population: defined as all randomized subjects who took at least one dose of the study medication.

Primary and Secondary Analyses

Efficacy Variables

The main efficacy analysis was the estimation of proportion of patients with ROR-low at surgery described by means proportions and 95% confidence interval using the Clopper-Pearson method. Mixed linear effects models were applied to evaluate the changes of ROR Score between two time-periods, adjusting by tumour size and nodal involvement. All statistical analyses were performed with the R v3.5.1 software.

This method for estimation of results was performed for dichotomous variables related to response or progression, like overall objective response rate (ORR), defined as the sum of Partial Responses (PR) and Complete Responses (CR) according to modified RECIST v1.1.

The rest of variables were analyzed, if necessary, according to following strategy: the Fisher's exact test to compare categorical variables between-groups, for continuous or ordinal variables a non-parametrical Mann-Whitney U test will be calculate.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

QLQ-C30 and QLQ-B23 questionnaires were analyzed. A descriptive analysis was performed item by item and also statistical inference was made for global health status, functional scales and symptom scales using Mixed-Effect Model Repeated. Measure (MMRM) model.

Safety Variables

All safety analyses were performed on the Safety Population. All AEs were graded according to the NCI CTCAE v.4.03.

The number and percentage of patients who experienced one or more treatment-emergent AEs as well as the number of AE episodes have been tabulated by treatment group, system organ class, preferred term (according to MedDRA), seriousness, intensity and relationship to the study drug.

SUMMARY AND CONCLUSION(S):

EFFICACY RESULTS:

The primary endpoint was the Rate of ROR-low (at surgery) after neoadjuvant treatment, according to the Prosigna test. Following chemotherapy, the ROR-low group represented 24 (46.1%, 95% CI 32.9-61.5) of 52 patients. Following ribociclib and letrozole, the ROR-low group represented 23 (46.9%, 95% CI 32.5-61.7) of 49 patients. Consistent with the primary endpoint, intrinsic subtype conversion to luminal A occurred in 43 (82.7% [95% CI 69.7–91.8]) of 52 patients in the chemotherapy group and 43 (87.8% [75.3–95.4]) of 49 patients ribociclib plus letrozole group.

The overall response rate by breast MRI was 78.8% (95% CI 65.3-88.9) in patients treated with chemotherapy and 57.1% (95% CI 42.2-71.2) in patients treated with ribociclib plus endocrine therapy.

In the chemotherapy arm, the proportions of patients with a pCR, RCB 0/1 and PEPI 0 at surgery were 5.8% (95% CI 1.4-16.6), 11.8% (95% CI 4.5-27.8) and 17.3% (95% CI 8.6-31.4), respectively .In the ribociclib and letrozole arm, the proportions of patients with pCR, RCB 0/1 and PEPI 0 were 0%, 6.1% (95% CI 1.3-16.8) and 22.4% (95% CI 11.7-36.6), respectively.

The proportion of patients with breast conserving surgery was 72.2% (95% CI 58.4-83.5%) in the chemotherapy arm and 85.7% (95% CI 73.3-92.9%) in the ribociclib plus letrozole arm. No cases of progressive disease were observed.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

Considering quality of life evaluation by EORTC-QLQ-C30, in the chemotherapy group there were statistically significant differences in global status (p<0.001) , Physical functioning ,(<0.001), role functioning (p<0.001), social function (p=0.007), constipation (p=0.002), diarrohea (p=0.002), dyspnoea (p=0.011), fatigue (p=<.001) and finantial difficulties (p<0.001) In the ribociclib plus letrozole group there were statistically significant differences in functional scale (p=0.040), physical function (p=0.043), role function (p=0.034), constipation item (p=0.007), fatigue (p<0.001) and pain (p=0.042).

By QLQ-B23 in the chemotherapy group there were statistically significant differences in body image (p<0.001), sexual functioning (p=0.002), upset by hair loss (p=0.042); and in ribociclib plus letrozole group there were statistically significant differences only in upset by hair loss (p=0.003).

ROR score at day-15 was successfully identified in 97 (91.5%) of 106 patients. Nineteen (40.4%) and 48 (96.0%) of patients had switched to Luminal A subtype by day-15 in the chemotherapy and ribociclib plus letrozole arms, respectively. Similar results were obtained when individual changes in ROR score were evaluated in each arm. The results revealed a decrease in ROR score at day-15 in most of patients in both treatment arms, being more pronounced in the ribociclib arm.

SAFETY RESULTS:

A total of 102 patients (99.0%) had at least one adverse event in the SP. Regarding severity 676 of the AEs were grade 1, 300 were grade 2, 95 were grade 3 and 38 were grade 4.

Fourty-three (82.7%) of patients in the chemotherapy arm and 30 (58.58%) in the ribociclib plus letrozole arm had the dosage adjusted/temporarily interrupted. The dosage was permanently discontinued, due to an AE respectively in 10 (19.2%) and 8 (15.7%) of patients in the chemotherapy and robociclib arms, respectively. No deaths were observed due to AEs.

Most adverse events were grade 1-2, with the most frequent ones being alopecia (n= 52; 100%), neutropenia (n= 36; 69%) and asthenia (n=28; 54%) in the chemotherapy arm and neutropenia (n=29;57%) of 51 patients, increased alanine aminotransferase (n=13; 26%) and asthenia (n=13; 26%) in the ribociclib and letrozole arm. Nearly all of the most frequent adverse events were deemed possibly related to study treatment. Grade 3-4 toxicities were observed in 29 (56.9%) of 51 patients in the ribociclib arm and 36 (69.2%) of 52 patients in the chemotherapy arm.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)	**Volume:** **Page:**	
Name of Active Ingredient: Ribociclib		

The most common grade 3-4 adverse events in the ribociclib and letrozole arm were neutropenia (n=22; 43%) of 51 patients and elevated alanine transaminase concentrations (n=10; 20%). In this arm, grade 1-3 QTc prolongation was observed in 2 (4%) of 51 patients and 8 (16%) of 51 patients discontinued study treatment because of grade 3-4 increased transaminases. The mean of treatment completion in patients who stopped ribociclib early was 55.0%. Four (8%) of 52 patients required a dose reduction of ribociclib.

The most common grade 3-4 adverse events in the chemotherapy arm were neutropenia (n=31;60%) of 52 patients and febrile neutropenia (n=7;13%). In this arm, 10 (19%) of 52 patients discontinued study treatment because of grade 3-4 peripheral neuropathy and colitis, both during paclitaxel treatment. The mean of treatment completion in patients who stopped paclitaxel early was 80.2%. Sixteen (31%) of 52 patients required a dose reduction. 13 serious adverse events have been reported in ten patients, two (4%) of 51 patients in the ribociclib plus letrozole group`and eight (15%) of 52 patients in the chemotherapy group. The most reported serious adverse event in the chemotherapy group was febrile neutropenia, in four patients. No deaths were observed during the study in either group.

CONCLUSION(S):

At baseline, 86.8% of patients had ROR-high disease and 13.2% had ROR-intermediate disease.

At surgery, proportion of patients with ROR-low disease in the chemotherapy and ribociclib arms were 46.1% (95% CI 32.9-61.5) and 46.9% (95% CI 32.5-61.7), respectively. Grade 3-4 toxicities were observed in 29 patients (56.9%) treated with ribociclib and letrozole and in 36 patients (69.2%) treated with chemotherapy. The most common grade 3-4 adverse events in the ribociclib and letrozole arm were neutropenia and elevated alanine transaminase. The most common grade 3-4 adverse events in the chemotherapy arm were neutropenia and febrile neutropenia. No deaths were observed during the study.

The results from the CORALLEEN study suggest that a high proportion of patients achieve a molecular downstaging in clinically high-risk luminal B breast

cancer treated with neoadjuvant ribociclib plus letrozole.

Name of the Sponsor/Company: SOLTI	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Ribociclib (Kisqali®)		
Name of Active Ingredient: Ribociclib		
Despite the non-comparative nature of this trial, our results suggest that selected patients with high-risk early-stage HR+/HER2-negative breast cancer might not need chemotherapy if treated with a CDK4/6 inhibitor and endocrine therapy.		