

Study protocol

Real-World Patient-Reported Outcomes After Initiation of Adjuvant Ribociclib Plus Endocrine Therapy in Early HR+/HER2– Breast Cancer: A Multicentre Prospective Observational Study in Croatia (PRO-QoL-Cro)

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Abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
CDK 4/6 inhibitors	cyclin-dependent kinases 4 and 6 inhibitors
CH	clinical hospital
CI	confidence interval
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	EuroQoL 5-dimension 5-level
EQ-VAS	EuroQol visual analogue scale
ET	endocrine therapy
GDPR	General data protection regulation
HER2	human epidermal growth factor receptor 2
HR+	hormone receptor - positive
HRQoL	health-related quality of life
M	month
MCID	minimal clinically important difference
MNAR	missing not at random
PRO	patient-reported outcome
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
UHC	university hospital centre
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

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SUMMARY

Study title	Real-World Patient-Reported Outcomes After Initiation of Adjuvant Ribociclib Plus Endocrine Therapy in Early HR+/HER2– Breast Cancer: A Multicentre Prospective Observational Study in Croatia (PRO-QoL-Cro)
Research question	In adults with non-metastatic HR+/HER2– breast cancer (stage II–III) in Croatia who initiate adjuvant ribociclib plus endocrine therapy in routine clinical practice, what is the within-patient change in EQ-5D-5L utility index from baseline (Month 0) to Month 6, and what is the trajectory of quality of life over Months 0, 1, 3, and 6?
Study design	Multicentre, prospective, non-interventional observational, single-arm cohort study (NIS PDC)
Timeline	Start of enrolment: 28 May 2026 End of enrolment: 28 October 2026 End of follow-up: 28 March 2027 Completion of study report: Q2 2027
Study centres	University Hospital Centre Split, University Hospital Centre Osijek, and Clinical Hospital Dubrava, Zagreb
Targeted population	Adult patients (women and men) with non-metastatic HR+/HER2– breast cancer (stage II–III) initiating adjuvant ribociclib plus endocrine therapy in routine clinical practice
Sample size	Planned enrolment of 76 participants to ensure 64 evaluable participants with both baseline (Month 0) and Month 6 EQ-5D-5L assessments, allowing for 15% missing Month 6 PRO data or non-evaluable participants.
Follow up	6 months of prospective follow-up per participant, with PRO assessments at Months 0, 1, 3, and 6. The 0–6-month window was selected to capture the early treatment experience after ribociclib initiation, including the acute phase, early treatment adaptation, and early maintenance phase. PRO changes will be interpreted in the context of adverse events and treatment modifications, recognising that adverse events and overall QoL deterioration are related but distinct constructs.
Primary endpoint	Within-participant change in EQ-5D-5L utility index, from baseline (Month 0) to Month 6. This primary endpoint is complemented by longitudinal analyses of PRO trajectories over Months 0, 1, 3, and 6, including breast cancer-specific quality of life, work productivity and activity impairment, and informal care needs.
Secondary endpoints	Within-participant changes in breast cancer-specific quality of life (EORTC QLQ-BR23), work productivity and activity impairment (WPAI:GH), and informal care needs (hours per week).
Data analysis	Primary and secondary endpoints will be analysed using mixed-effects models for repeated measures including all available

	assessments (Month 0, 1, 3, and 6). The primary estimand will be the model-based, covariate-adjusted mean change in EQ-5D-5L utility index from baseline (Month 0) to Month 6, reported with a two-sided 95 % confidence interval. Secondary and exploratory analyses will be interpreted primarily through the magnitude, direction, and precision of estimated effects. Supportive exploratory time-to-deterioration analyses may be performed to describe the timing and durability of clinically meaningful PRO deterioration over follow-up.
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1. INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide (and less commonly in men) and represents a major public health burden. In Croatia, breast cancer accounts for the highest incidence among female cancers. According to the Croatian National Cancer Registry, 2,869 women were newly diagnosed with breast cancer in 2020, corresponding to an age-standardized – using the standard European population – incidence rate of 98.6 per 100,000, while 722 women died from the disease in the same year, with an age-standardized mortality rate of 19.1 per 100,000 (1).

Owing to organised screening programmes, increased awareness, and advances in systemic therapy, breast cancer is increasingly diagnosed at earlier stages and treated with curative intent. In hormone receptor–positive (HR+), HER2-negative early breast cancer, adjuvant endocrine therapy has long represented the cornerstone of systemic treatment. More recently, the addition of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has further improved clinical outcomes in high-risk population (2,3).

Ribociclib is a CDK4/6 inhibitor that has demonstrated a significant reduction in the risk of recurrence when added to standard adjuvant endocrine therapy in patients with HR+/HER2– early breast cancer. The phase III NATALEE trial showed a clinically and statistically meaningful improvement in invasive disease-free survival with ribociclib plus endocrine therapy compared with endocrine therapy alone, supporting its use in the adjuvant setting (3). In parallel, extensive experience with ribociclib in advanced breast cancer has established a well-characterised safety profile, with adverse events occurring predominantly early during treatment and generally being manageable through dose modification and supportive care (4,5).

As survival outcomes improve, increasing attention is being directed towards patient-reported outcomes (PROs), including health-related quality of life (HRQoL), work productivity, and the need for informal care. These outcomes are particularly relevant in early breast cancer, where many patients are diagnosed during their working years and may remain on long-term systemic therapy. Returning to work is often viewed as a sign of recovery, yet antineoplastic treatments can substantially affect physical, emotional, and social well-being. Maintaining quality of life and functional ability has therefore become an important component of comprehensive cancer care.

Data from clinical trials suggest that ribociclib does not result in clinically meaningful deterioration in HRQoL and that patient-reported symptoms may remain stable or improve over time, including reductions in pain and other symptom domains (6,7). However, evidence from randomised trials may not fully capture the experience of patients treated in routine clinical practice, where patient characteristics, comorbidities, and treatment pathways are more heterogeneous.

Real-world data on patient-reported outcomes following initiation of adjuvant ribociclib remain limited, particularly in Central and Eastern European settings. The intent is to generate real-world evidence and provide context for future research. Understanding these aspects is essential for contextualising the overall burden of treatment and for informing patient-centred care.

The present study aims to characterise patient-reported outcomes during the first six months following initiation of adjuvant ribociclib in combination with endocrine therapy in patients with non-metastatic HR+/HER2– breast cancer treated in routine clinical practice in Croatia,

with emphasis on within-patient change from baseline and trajectories over Months 0, 1, 3, and 6.

2. RESEARCH QUESTION

In adults with non-metastatic HR+/HER2– breast cancer (stage II-III) in Croatia who initiate adjuvant ribociclib plus endocrine therapy in routine clinical practice, what is the within-patient change in EQ-5D-5L utility index from baseline (Month 0) to Month 6, and what is the trajectory of quality of life over Months 0, 1, 3, and 6?

3. OVERALL AIM

The overall aim of this study is to generate real-world evidence on patient-reported outcomes, including health-related quality of life, breast cancer-specific symptoms and functioning, work productivity, and informal care needs, during the first six months following initiation of adjuvant ribociclib plus endocrine therapy in early breast cancer. The study will estimate within-patient changes from baseline and describe trajectories over Months 0, 1, 3, and 6 in routine clinical practice in Croatia. The findings will improve understanding of the early patient experience during routine clinical use and will provide context for future research, including the planned longer-term extension.

4. OBJECTIVES AND ENDPOINTS

4.1. Primary objective

To estimate the within-patient change in health-related quality of life, as measured by the EQ-5D-5L utility index, from baseline (Month 0) to Month 6 after initiation of adjuvant ribociclib plus endocrine therapy in routine clinical practice.

4.2. Primary endpoint

The primary endpoint is the within-patient change in EQ-5D-5L utility index from baseline (Month 0) to Month 6. This primary endpoint is complemented by secondary and exploratory analyses describing PRO trajectories across Months 0, 1, 3, and 6.

EQ-5D-5L utility scoring will use a prespecified value set. In the absence of a Croatian EQ-5D-5L value set, the primary analysis will use the Hungarian value set. Sensitivity analyses will repeat scoring using the Italian value set.

4.3. Secondary objectives

1. To describe changes in EORTC QLQ-BR23 functioning and symptom domains over 6 months.
2. To evaluate changes in work productivity and activity impairment as measured by the WPAI:GH, over 6 months.
3. To evaluate changes in informal care needs, operationalised as informal care hours per week, over 6 months.
4. To explore associations between treatment-related side effects and changes in PROs over time.

5. To explore associations between sociodemographic characteristics and PRO trajectories over time.
6. To explore whether prior endocrine therapy duration (≤ 3 vs 4–12 months) is associated with PRO trajectories during the 6-months.

4.4. Secondary endpoints

Secondary endpoints will be assessed at Month 0, Month 1, Month 3, and Month 6 and will be summarised as change from baseline (Month 0) to Month 6 and modelled as trajectories over time. Additional exploratory contrasts from baseline to Month 1 and from baseline to Month 3 may be reported.

Secondary endpoints comprise within-patient change from baseline (Month 0) to Month 6 in pre-specified domains of:

- EORTC QLQ-BR23 functioning scales: body image, future perspective, sexual functioning,
- EORTC QLQ-BR23 symptom scales: systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss,
- WPAI:GH overall work impairment, absenteeism, presenteeism, activity impairment. Work-related domains will be analysed in the participants employed at baseline, and activity impairment in all participants.
- Informal care needs: informal care hours per week. Caregiver type will be summarized descriptively. Informal care will be collected as self-reported hours per week. Extreme values will be checked against source responses and summarised using robust methods where appropriate.

For interpretability, changes will be directionally harmonised across instruments. For the EQ-5D-5L utility index and EORTC QLQ-BR23 functioning scales, higher scores indicate better status, and positive change indicates improvement. For EORTC QLQ-BR23 symptom scales, higher scores indicate greater symptom burden, and negative change indicates improvement. For WPAI:GH domains, higher percentages indicate greater impairment, and negative change indicates improvement. For informal care hours per week, lower values indicate less need for support and negative change indicates improvement.

Supportive exploratory time-to-deterioration analyses may be conducted for selected PRO outcomes, primarily the EQ-5D-5L utility index, to describe the timing and durability of clinically meaningful deterioration over follow-up. These analyses will be descriptive and exploratory and will not redefine the primary endpoint, primary estimand, or sample size rationale.

5. METHODS

5.1. Study design

This is a multicentre, prospective, observational cohort study conducted in routine clinical practice. The study uses a single-arm longitudinal design in which outcomes are measured repeatedly within the same participants over time. Investigators do not assign or alter treatment; all therapies are prescribed as part of standard care.

Participants are followed from baseline, defined as the visit at which ribociclib is initiated (and at which the baseline PRO assessment is completed, ideally prior to the first dose), through predefined follow-up time points (months 1, 3 and 6).

The study will be registered in the HMA-EMA Catalogue of real-world data studies (Catalogue of RWD studies) before enrolment of the first participant, or as otherwise required by applicable national and institutional requirements. The study registration identifier will be added to the protocol and subsequent study reports once available.

5.2. Study treatment and drug handling

Ribociclib and endocrine therapy are prescribed, dispensed, stored, and administered entirely as part of routine clinical practice in accordance with local procedures and the approved product information. The protocol does not mandate dosing, dose modifications, storage conditions, or drug accountability processes; therefore, study-specific investigational product handling procedures are not applicable.

5.3. Study setting

The study will be conducted at three oncology centres in Croatia: University Hospital Centre Split, University Hospital Centre Osijek, and Clinical Hospital Dubrava, Zagreb.

5.4. Study duration / timeline

The total duration of the study includes a prospective follow-up period of six months for each participant, starting at baseline defined as initiation of adjuvant ribociclib in combination with endocrine therapy.

In addition, selected clinical data will be collected retrospectively from medical records for up to 12 months prior to baseline to characterise prior treatments and clinical context.

Recruitment and data collection will continue until the planned sample size is achieved.

Planned timeline

Start of enrolment: 28 May 2026

End of enrolment: 28 October 2026

End of follow-up: 28 April 2027

Completion of study report: Q2 2027

5.5. Study population

The study population consists of adult patients with non-metastatic breast cancer who are treated with adjuvant ribociclib in combination with endocrine therapy in routine clinical practice at participating centres.

Eligibility criteria are intended to identify a clinically relevant real-world population initiating adjuvant ribociclib in the early adjuvant setting, while maintaining sufficient homogeneity for interpretation of within-patient PRO change. The requirement that adjuvant endocrine therapy must have been initiated within 12 months prior to baseline was retained to focus the cohort on a relatively uniform early-treatment context and to limit heterogeneity related to prolonged pre-baseline endocrine therapy exposure.

Inclusion criteria:

- Women and men aged 18 years or older,

- Histologically confirmed hormone receptor–positive, HER2-negative breast cancer,
- Have an anatomical stage II or III of breast cancer according to AJCC 8th edition,
- Patients meet the following additional staging criteria:
 - Anatomic Stage Group III, or
 - Anatomic Stage Group IIB, or
 - Anatomic Stage Group IIA, that is either
 - N1, or
 - N0, with
 - Grade 3, or
 - Grade 2 with Ki-67 $\geq 20\%$ or Oncotype Recurrence Score ≥ 26 or MammaPrint categorized as high risk
- Initiation of adjuvant ribociclib in combination with endocrine therapy according to local product information (SmPC),
- Initiation of adjuvant endocrine therapy within 12 months prior to baseline,
- Ability to understand and complete the study questionnaires,
- Provision of written informed consent.

Exclusion criteria:

- Evidence of metastatic disease (stage IV according to AJCC 8th edition) or locoregional or distant recurrence prior to baseline,
- Prior treatment with a CDK4/6 inhibitor,
- Active second primary malignancy prior to ribociclib initiation
- Contraindications to ribociclib or endocrine therapy according to the SmPC,
- Severe cognitive impairment,
- Current participation in another interventional clinical study,
- Pregnancy or breastfeeding.

5.6. Sampling and recruitment

Eligible participants will be recruited using a consecutive recruitment approach at participating oncology centres. Patients scheduled for routine oncology consultations will be screened for eligibility by the treating physician or a designated member of the research team.

All patients who meet the inclusion criteria during the recruitment period will be invited to participate. After receiving verbal and written information about the study, patients who agree to participate will provide written informed consent prior to enrolment.

Recruitment will continue until the planned sample size is reached.

5.7. Sample size

As this is a single-arm cohort study, sample size was determined using an accuracy in parameter estimation (AIPE) approach for the primary endpoint, defined as the within-patient

change in EQ-5D-5L utility index from Month 0 (baseline) to Month 6. The objective is to estimate the mean within-patient change (that is, the mean of individual within-patient changes) with adequate precision, expressed as the full width of the two-sided 95% confidence interval (CI) for the mean change.

The target precision is defined as a two-sided 95% CI full-width of 0.08 utility units for the mean change. This corresponds to a half-width of 0.04 utility units. This precision target was selected to support clinically meaningful interpretation of the primary endpoint in a descriptive estimation framework.

The standard deviation (SD) of the within-patient change was assumed to be 0.16. This assumption is empirically informed by longitudinal breast cancer data reporting an SD 0.158 for the 6-month change in EQ-5D-5L utility, and was rounded up to 0.16 to remain conservative (8).

Sample size calculations were performed using PASS 2021 (NCSS, LLC, Kaysville, UT, USA), using a two-sided interval approach with confidence level 0.95 and a target CI full width of 0.08 utility units. Under these assumptions, 64 evaluable participants with both Month 0 and Month 6 assessments are required. Allowing for 15 % non-evaluable participants or missing Month 6 PRO assessments, the planned enrolment is inflated to 76 participants.

For transparency, an illustrative table of expected 95% CI widths under several evaluable-sample scenarios is provided. This table is intended to describe the precision achieved under alternative missing-assessment scenarios and does not affect the planned enrolment target.

Table 1. Expected two-sided 95 % confidence-interval width for the mean within-patient change in EQ-5D-5L utility index under alternative evaluable sample sizes and assumed standard deviations of paired differences

Evaluable sample size (n)	95% CI	
	Half-width	Full width
With SD = 0.16		
50	0.045	0.091
60	0.041	0.083
64	0.040	0.080
70	0.038	0.076
80	0.036	0.071
90	0.034	0.067
100	0.032	0.063
With SD = 0.20		
50	0.057	0.114
60	0.052	0.103
64	0.050	0.100
70	0.048	0.095
80	0.045	0.089
90	0.042	0.084
100	0.040	0.079

Note: Values are based on two-sided 95% CI for the mean paired difference, assuming a standard deviation of paired differences of 0.16 or 0.20. Half-width denotes the distance from the estimated mean change to either confidence limit, and full width denotes the total width of the confidence interval. The formal sample size calculation was based on an assumed standard deviation of 0.16. Results shown for a standard deviation of 0.20 are illustrative only. Recruitment will continue until the prespecified evaluable sample size of 64 participants has been achieved.

6. VARIABLES

6.1. Primary outcome variable

The primary outcome variable is the mean within-patient change in generic health-related quality of life from baseline (Month 0) to Month 6, measured by the EQ-5D-5L utility index. Baseline (Month 0) is defined as the time of initiation of adjuvant ribociclib in combination with endocrine therapy with the baseline PRO assessment completed at the baseline visit, preferably prior to the first dose.

The EQ-5D-5L utility index will be calculated using a prespecified EQ-5D-5L value set. As a Croatian national EQ-5D-5L value set is not currently available, the primary analyses will use the Hungarian EQ-5D-5L value set. Sensitivity analyses will repeat scoring using the Italian EQ-5D-5L value set.

6.2. Secondary outcome variables

Secondary outcome variables are defined as within-participant changes from baseline (Month 0) to Month 6 in the following patient-reported measures:

1. Breast cancer–specific quality of life, measured using the EORTC QLQ-BR23 questionnaire, including prespecified functional and symptom domains,

2. Work productivity and activity impairment, measured using the Work Productivity and Activity Impairment questionnaire: General Health (WPAI:GH). Work-related domains (absenteeism, presenteeism, overall work impairment) will be evaluated among participants employed at baseline. Activity impairment will be assessed in all participants,
3. Informal care needs operationalised as self-reported informal care hours per week and the proportion of participants receiving any informal care. Caregiver type will be summarised descriptively.

All primary and secondary patient-reported outcomes will be collected at Month 0, Month 1, Month 3, and Month 6. Intermediate time points will support trajectory modelling within the repeated-measures framework and may be used for additional descriptive contrasts (Month 0 to Month 1 and Month 0 to Month 3). They will not define additional confirmatory hypotheses.

6.3. Covariates and descriptive variables

The following variables will be collected to describe the study population and to support exploratory and adjusted analyses:

- Age and gender,
- Disease stage (TNM classification and overall AJCC stage II–III),
- Tumour characteristics: tumour size (T), nodal status (N), histological type, tumour grade, Ki67, hormone receptor status, HER2 status, gene signature testing (if available),
- Prior treatments: surgery, chemotherapy, radiotherapy,
- Type and duration of prior endocrine therapy,
- Study centre,
- Comorbidities as recorded in the medical record,
- Baseline ECOG performance status,
- Baseline toxicity, as recorded in the medical record,
- Adverse events during follow-up, as recorded in the medical record,
- Treatment interruptions, dose reductions, and permanent discontinuation of ribociclib during follow-up,
- Changes in endocrine therapy backbone during follow-up,
- Post-discontinuation treatment context during follow-up, including subsequent systemic treatment where applicable,
- Intercurrent clinical events during follow-up, including hospitalisations and recurrence-related events,
- Concomitant and supportive treatments during follow-up where relevant to interpretation of PRO changes,
- Objective indicators of functional impact where available, including sick leave and analgesic use.

These variables are not primary outcomes. Baseline variables will be used to describe the study population and to support prespecified adjusted analysis, while follow-up variables will be summarised descriptively and may be used in supportive exploratory analyses to contextualise interpretations of PRO changes over time.

At baseline, a brief anchored recall item will be collected to characterise patient-reported QoL and productivity during the last 2-4 weeks prior to ribociclib initiation while receiving endocrine therapy alone. These data will be used for exploratory context only, will not replace baseline measurements and will not define formal pre–post contrasts

6.4. Data Sources:

- Clinical data: electronic medical records and the Hospital Information System,
- PRO and survey data: paper questionnaires completed in the clinic as source documents, then entered into the study database.

7. METHODS OF DATA COLLECTION

Data will be collected using a combination of patient-reported questionnaires and clinical information extracted from medical records.

7.1. Patient-reported data

Patient-reported outcomes will be collected at baseline (Month 0) and at Month 1, Month 3, and Month 6 using standardized questionnaires administered in the clinical setting. Questionnaires will be completed on paper as source documents and labelled with a study-specific participant ID. Paper questionnaires will not include direct personal identifiers. A participant identification log linking participant IDs to patient identifier will be stored separately at each site with restricted access.

To minimize bias, questionnaires will be administered prior to any clinical assessment or consultation related to the study visit. Participants will complete validated Croatian versions of the instruments independently. Assistance will be limited to procedural guidance where needed.

Data from paper questionnaires will be entered into an electronic database using EpiData with prespecified range checks and consistency checks. Data integrity will be supported through double data entry. Any discrepancies between entries will be resolved by reference to the original paper source documents, and corrections will be documented. Paper source documents will be stored securely at the study sites with access restricted to authorized personnel, in accordance with applicable data protection requirements.

7.2. Instruments and scoring

The following instruments will be used:

- EQ-5D-5L to assess generic health-related quality of life (9). The EQ-5D-5L utility index will be derived using the prespecified value set described in the analysis section.
- EORTC QLQ-BR23 to assess breast cancer–specific quality of life, The EORTC QLQ-BR23 will be scored according to the standard EORTC procedures and linearly transformed to a 0–100 scale. Higher functional scores indicating better functioning and higher symptom scores indicating greater symptom burden (10),

- WPAI:GH to assess work productivity and activity impairment (11). WPAI:GH outcomes will be calculated as percentages according to the standard scoring approach. Higher values indicating greater impairment (11). Work-related domains of the WPAI:GH will be completed only by participants who are employed at baseline, while the activity impairment domain will be completed by all participants.
- Informal care needs: self-reported informal care hours per week and caregiver type,
- Self-reported treatment-related symptoms and functional impact collected as supportive descriptive information, as specified in the case report materials.

These instruments capture distinct but complementary constructs and will therefore be analysed and interpreted independently; no direct numerical reconciliation or transformation across scales is planned.

7.2.1. Operational scoring rules and data checks

Scoring will follow instrument-specific manuals and prespecified study rules. For EORTC QLQ-BR23, item-level missingness will be handled strictly according to the EORTC scoring manual (including minimum item completion requirements for multi-item scales). For EQ-5D-5L, the utility index will be calculated only when all five dimensions are available; if one or more dimensions are missing, the utility score for that assessment will be set to missing. WPAI:GH responses will be checked using prespecified logical and range checks (including non-negative values and internal consistency of reported work hours); implausible values will be queried against source documents where possible, and unresolved implausible values will be set to missing for the affected derived score(s). Informal care hours will be checked for plausibility and transcription errors; values will not be automatically truncated in the primary analysis, and influential extreme values will be examined in prespecified sensitivity analyses.

7.3. Schedule of assessments (summary)

Table 2. Schedule of assessments

Assessment	Baseline (Month 0)	Month 1	Month 3	Month 6
Informed consent	x			
EQ-5D-5L	x	x	x	x
EORTC QLQ-BR23	x	x	x	x
WPAI:GH (all participants: Activity impairment)	x	x	x	x
WPAI:GH (employed at baseline only: work domains)	x	x	x	x
Clinical data extraction (baseline characteristics, prior treatments)	x			
Informal caregiver type and care	x	x	x	x
Treatment modifications/discontinuation (medical record review)		x	x	x

Visit windows

- M1: 28 ±7 days
- M3: 90 ±14 days
- M6: 180 ±21 days

If more than one PRO assessment is available within the same visit window, the assessment closest to the target day (Month 1, Month 3, or Month 6 target) will be used for the primary time-point assignment. If two assessments are equally close to the target day, preference will be given to the assessment completed prior to the corresponding clinical consultation or treatment-related decision, where documented. Assessments outside the prespecified visit windows will be excluded from the primary time-point analysis but may be considered in descriptive summaries or supportive sensitivity analyses, as prespecified in the SAP.

Scoring direction

- EQ-5D-5L: higher = better
- BR23: higher functioning = better, higher symptoms = worse
- WPAI: higher % = worse
- Informal care hours: higher = greater care need

7.4. Justification for 6-Month PRO Follow-Up:

The 6-month PRO follow-up period is clinically and methodologically justified because:

1. The early treatment period is the most informative interval for short-term patient-reported change after ribociclib initiation. Treatment-related tolerability issues requiring clinical management, including dose modification or discontinuation, tend to occur early after treatment initiation. In the NATALEE safety update, adverse events generally occurred early, with a median time to AE-related dose reduction of 3.15 months and a median time to AE-related discontinuation of 4.17 months. The first 6 months therefore represent a clinically relevant window for capturing early treatment adaptation, dose modification, and short-term patient experience.
2. Adverse events and quality of life are related but distinct constructs. The occurrence of adverse events does not necessarily imply sustained deterioration in overall health-related quality of life. NATALEE HRQoL analyses and pooled MONALEESA PRO data suggest that overall HRQoL may be maintained over time despite treatment-related toxicity, while selected symptom domains may still vary during the early treatment period. The present study therefore aims to characterise PROs during the first 6 months and to interpret them in the context of safety and treatment modifications, rather than assuming a direct one-to-one correspondence between adverse events and overall QoL deterioration.
3. The 0–6-month window captures clinically interpretable phases of early treatment experience. Month 1 captures the acute or very early treatment phase. Month 3 captures the period in which dose adjustment, early adaptation, and initial stabilisation are expected. Month 6 captures an early maintenance phase, by which many patients are expected to be on an individualised and better-tolerated regimen. This design provides a clinically interpretable trajectory rather than a single post-baseline snapshot.
4. The selected instruments are suitable for repeated assessment over short to medium intervals. EQ-5D-5L, EORTC QLQ-BR23, and WPAI:GH are validated instruments appropriate for repeated use in oncology settings and suitable for detecting short-term changes in relevant patient-reported domains.
5. A 6-month duration supports feasibility in routine clinical practice. This follow-up window balances clinical relevance with feasibility by limiting respondent burden and reducing the risk of attrition and missing data in a real-world multicentre study.

6. Longer-term follow-up is outside the scope of the present protocol. The current protocol is focused on early PROs after treatment initiation. Longer-term PRO follow-up beyond Month 6 is planned, if implemented, within a separate extension study and corresponding protocol procedures.

7.5. Clinical data

Clinical and treatment-related data will be extracted from electronic medical records at baseline. These include demographic information, disease characteristics, prior treatments, and treatment timelines, ECOG performance status and toxicity, and objective indicators such as sick leave and analgesic use.

Information on treatment modifications, dose adjustments, and treatment discontinuation during the observation period will be collected from medical records and summarised descriptively.

8. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

A) Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A serious adverse event (SAE) is defined as an AE which:

- Results in death or is life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition as specified in the sections 6.3, 6.4 and 7. of the protocol.
 - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
 - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

Note: Transmission of infectious disease via medication is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. An ADR implies at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event.

The Novartis drug(s) of interest evaluated in this study is ribociclib.

B) AE collection

All AEs from all patients enrolled in the study must be collected and recorded in the study database, irrespective of seriousness or causal association.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Medical conditions/ diseases ongoing before starting treatment with a study drug are only considered AEs if they worsen after starting the study drug.

All AEs must be recorded on the AE case report form (CRF) with the following information:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a SAE

In addition, all reports of the following special scenarios, whether or not associated with AEs, are also collected and reported in the same manner as AEs:

- Drug-drug or drug-food interaction
- Drug use during lactation
- Lack of efficacy
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
- Drug dependence or addiction
- Withdrawal reaction/ syndrome or rebound symptoms
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

Note: Occupational or accidental exposure, for example of study personnel or family members of the patient should be to Novartis Patient Safety as a spontaneous report.

Any action taken with study drug or addition of treatment medication because of an AE should be recorded on the AE CRF. Some examples to be recorded are: no action taken (i.e., further observation only); study drug dosage adjusted/ temporarily interrupted; study drug permanently discontinued due to this AE.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common adverse effects already known about the study drug(s) can be found in the locally available labeling document (ema.europa.eu/hr/documents/product-information/kisqali-epar-product-information_hr.pdf) for the approved indication under evaluation in this study.

C) AE reporting

- Serious adverse events (SAE)

Information about all SAEs that occurred in patients exposed to the Novartis drug(s) of interest, irrespective of causality, must also be recorded in the Novartis safety database. The treating physician or other involved HCP must assess the relationship to the Novartis drug, complete the AE Report Form and send the completed, signed form by fax/ email within 24 hours to the local Novartis Patient Safety department.

The email address, telephone and telefax number of the contact persons in the local Patient Safety department, specific to the site, are listed in the treating physician/ HCP folder provided to each site and below:

Novartis Hrvatska d.o.o.

Radnička cesta 37 B, 10 000 Zagreb

e-mail: prijava.nuspojave@novartis.com

Fax number: +38516274258

Online via PVI: <https://www.report.novartis.com/>

The original copy of the AE Report Form and the fax confirmation sheet or the email must be kept with the CRF documentation at the study site.

- Exposure during pregnancy

Any occurrence of a pregnancy in a patient exposed to the Novartis drug(s) of interest must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed-up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Information about the pregnancy should be recorded on the Pregnancy Form and reported by the treating physician or other involved HCP to the local Novartis Patient Safety department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug should be reported.

Additionally, any SAE/ non-serious AE experienced during pregnancy must be collected on the respective CRF and reported to Novartis following the respective reporting routes described in this section.

- Non-serious AEs and events describing a special scenario (other than drug exposure during pregnancy)

Non-serious AEs as well as events describing a special scenario (other than drug exposure during pregnancy) that occurred in patients exposed to the Novartis drug(s) of interest must also be recorded in the Novartis safety database. In general, special scenarios with no associated clinical event will be considered as non-serious event. Where considered as serious, they should be reported following the SAE reporting route.

Information about all non-serious AEs, irrespective of causality, and events describing a special scenario that occurred in patients exposed to the Novartis drug(s) of interest must be recorded on the AE Report Form. The treating physician or other involved HCP must assess the relationship to the Novartis drug, complete the AE Report Form and send the completed, signed form by fax/ email within 10 calendar days to the local Patient Safety department.

The email address, telephone and telefax number of the contact persons in the local Patient Safety department, specific to the site, are listed in the treating physician/ HCP folder provided to each site and below:

Novartis Hrvatska d.o.o.

Radnička cesta 37 B, 10 000 Zagreb

e-mail: prijava.nuspojave@novartis.com

Fax number: +38516274258

Online via PVI: <https://www.report.novartis.com/>

The original copy of the AE Report Form and the fax confirmation sheet or the email must be kept with the CRF documentation at the study site.

- Safety reporting for Novartis drugs other than the Novartis drug(s) of interest and for non-Novartis drugs

Adverse Drug Reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drug(s) of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report.

All adverse reactions identified for non-Novartis drugs should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

Follow-up information

Recurrent episodes, complications, or progression of the initial event must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within the same timelines as defined for initial information. Any event that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to the same contact person to whom the initial information was sent, stating, where an AE report form is used, that this is a follow-up to the previously reported event and providing the date of the original report. If known, the information missing from the initial report should be completed. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

In case an SAE is not previously documented in the labeling document for the study (ema.europa.eu/hr/documents/product-information/kisqali-epar-product-information_hr.pdf), a Novartis Patient Safety associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

In case an adverse event is considered to be of particular interest, a Novartis Patient Safety associate may seek additional information concerning the event. Corresponding

questionnaires will then be provided by Novartis Patient Safety to the treating physician or other involved health care professional on a case-by-case basis.

Safety reporting period

Every SAE, exposure during pregnancy, non-serious AE and special scenario, regardless of causality assessment, that occurred in patients exposed to the Novartis drug(s) of interest must be reported to Novartis:

- after the patient has provided informed consent
- until 30 calendar days after the patient discontinued the Novartis drug of interest during the study conduct or until 30 calendar days after the last patient last visit if the patient is still receiving the Novartis drug of interest.

Any SAEs, pregnancies, non-serious AEs and special scenarios experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the Novartis drug(s) of interest.

9. DATA MANAGEMENT

9.1. Overview

Study data will be managed using paper source documents and site-level electronic data entry. Patient-reported questionnaires will be completed on paper and retained at each study site as source documents. Clinical information will be extracted from routine medical records. Data from paper questionnaires and predefined clinical variables will be entered into an electronic study database using EpiData at each participating site.

9.2. Participant identification, pseudonymisation and confidentiality

Each participant will be assigned a study-specific participant ID. Paper questionnaires and all study datasets will be labelled using the participant ID only. Paper questionnaires and study datasets will not include names, initials, dates of birth, contact details, or other direct personal identifiers.

Direct personal identifiers will be used only for informed consent and administrative purposes. Signed informed consent forms and the re-identification key linking participant identity to the participant ID will be stored securely and separately from study data at the originating study site. Access to identifiable information will be restricted to authorised study personnel at each site.

9.3. Participant withdrawal

If a participant withdraws consent, no further study data will be collected from that participant. Data already collected up to the date of withdrawal will be retained in pseudonymised form and may be analysed to preserve the scientific integrity of the study, to the extent permitted by applicable law and the terms of the consent, recognising that erasure may not be feasible once data have been incorporated into analysis or required archives.

9.4. Data entry, validation and query management

Data entry will be performed in EpiData using a standardised database structure with predefined range checks and internal consistency rules. Patient-reported questionnaire data will be subject to double data entry in EpiData. Discrepancies between entries will be

resolved by reference to the original paper source documents. Corrections will be documented.

Clinical variables extracted from medical records will be entered according to a predefined data dictionary. Data completeness and plausibility checks will be performed at site level prior to data transfer. Each site will maintain a query log that records identified issues, the source used for resolution, the date of resolution, and the person making the change.

9.5. Data transfer and central consolidation

At predefined intervals, each site will export a pseudonymised EpiData dataset containing participant IDs only and will transmit it to the central data manager for consolidation. Encrypted transfers will use password-protected files with strong encryption, and passwords will be communicated via a separate channel.

Transferred files will follow a predefined file naming convention that includes the site code and export date to support version control. The central data manager will maintain a transfer log documenting the sending site, file name, export date, and receipt date.

Site datasets will be merged into a consolidated central database using the participant ID. After each merge cycle, central checks will be performed for completeness, internal consistency, outliers, and duplicates. Data queries arising from central checks will be returned to sites for resolution. Sites will resolve queries by reference to source documents and will return corrected datasets or documented clarifications, as applicable.

9.6. Data security and access control

Paper source documents will be stored securely at each study site with access restricted to authorised personnel. Electronic study data will be stored on access-controlled systems in accordance with institutional policies. Access permissions will follow the principle of least privilege. The consolidated central database and analysis datasets will be accessible only to authorised study personnel involved in data management and statistical analysis.

Routine back-up procedures will be applied in accordance with institutional policies. Any suspected data breach will be handled under institutional incident-management procedures and applicable data protection requirements.

9.7. Direct access, monitoring and auditing

Authorised representatives of the Collaboration Partner, ethics committees, or regulatory authorities may be granted direct access to source documents and study data for the purpose of verification, auditing, or inspection, in accordance with applicable laws and regulations and with full respect for participant confidentiality.

Given the non-interventional nature of the study, no intensive on-site monitoring is planned. Data quality will be supported through standardised data entry procedures, built-in validation checks in EpiData, double data entry for PROs, documented query resolution, and central review of completeness and internal consistency. Any audits or inspections will be facilitated as required. Direct access will be limited to what is necessary for verification and will be provided on-site where required, subject to applicable data protection rules and site procedures.

9.8. Archiving, retention and disposal

Paper source documents, signed informed consent forms, enrolment documentation, the re-identification key, the site-level EpiData datasets, the consolidated central database, and

analysis datasets will be retained for at least 10 years after the final study report or longer if required by applicable regulations, institutional archiving rules, or sponsor requirements.

Paper source documents will be retained securely at each study site until study completion. After study completion, paper source documents that do not contain direct personal identifiers may be transferred to University Hospital Centre Split for long-term archiving, subject to institutional procedures and documented chain of custody. Signed informed consent forms and re-identification keys will remain at the originating sites unless otherwise formally approved in accordance with institutional policies and applicable data protection requirements.

Disposal of study documentation after the retention period will be carried out only through the institutions' approved records management and destruction procedures, with appropriate documentation of what was destroyed and when.

9.9. Protocol deviations

Protocol deviations will be documented in a deviation log and classified as major or minor according to prespecified operational criteria.

Major deviations are those with potential to affect participant rights/safety, eligibility, primary endpoint interpretability, or data integrity (for example: enrolment not meeting key eligibility criteria, missing or invalid informed consent documentation, materially incorrect visit timing that prevents valid primary time-point assignment, or major source-data/identifier errors affecting dataset integrity). Minor deviations are deviations not expected to materially affect participant rights/safety or the interpretability of the primary analysis (for example: administrative delays, minor documentation omissions, or timing deviations that remain within prespecified visit windows).

All deviations will be reviewed and summarised before database lock. The primary analysis population (FAS) will be defined as prespecified in Section 11.1 and will not be modified post hoc on the basis of deviation review. Where appropriate, supportive sensitivity analyses may summarise results in subsets excluding selected major deviations, with full transparency regarding criteria and counts.

10. DATA ANALYSIS

Analyses will estimate within-patient changes in PRO during the first six months following initiation of adjuvant ribociclib plus endocrine therapy. This is a single-arm observational study that estimates within-patient change and describes trajectories over time. It is not designed to estimate a causal treatment effect versus a concurrent comparator. The primary endpoint will be reported as an estimated mean change from Month 0 to Month 6 with a two-sided 95% CI. Secondary and exploratory analyses will be interpreted primarily using effect sizes and 95% CIs.

10.1. Analysis sets

The Full analysis set (FAS) will include all enrolled participants who initiate ribociclib plus endocrine therapy and have a baseline (Month 0) EQ-5D-5L assessment and at least one post-baseline EQ-5D-5L assessment. The FAS will be the primary analysis population for the primary endpoint. A Month 6 Completer Set will be defined as participants with both baseline (Month 0) and Month 6 EQ-5D-5L assessments and will be used for a prespecified sensitivity analysis.

10.2. Utility scoring for EQ-5D-5L

The EQ-5D-5L utility index will be derived using a prespecified EQ-5D-5L value set. As a Croatian national value set is not available, the primary analysis will use the Hungarian EQ-5D-5L value set. A sensitivity analysis will repeat scoring using the Italian EQ-5D-5L value set to assess robustness to the choice of tariff (13,14).

10.3. Primary analysis

The primary endpoint is the mean within-participant change in EQ-5D-5L utility index from baseline (Month 0) to Month 6, reported with a two-sided 95% CI. Higher values indicate better health status.

10.3.1. Primary estimand (prespecified)

The primary estimand is defined as follows:

- Population: the FAS, as defined in Section 10.1.
- Variable (outcome): EQ-5D-5L utility index scored using the prespecified Hungarian EQ-5D-5L value set (primary tariff), assessed at Months 0, 1, 3, and 6.
- Intercurrent events: treatment interruptions, dose reductions, permanent discontinuation of ribociclib, changes in endocrine therapy backbone, recurrence-related clinical events, hospitalisation, and other clinically relevant events occurring during follow-up will be recorded and summarised.
- Strategy for intercurrent events: a treatment-policy strategy will be used for treatment modifications/discontinuation and other on-study clinical events; participants will continue to contribute PRO data where available regardless of treatment changes.
- Summary measure: model-based estimated mean change from Month 0 to Month 6 (Month 6 minus Month 0) with a two-sided 95% CI.

10.3.2. Primary model

The primary analysis will use a mixed model for repeated measures (MMRM) with time modelled as a categorical fixed effect (Months 0, 1, 3, and 6) and participant-level repeated measurements modelled using an unstructured covariance matrix, where estimable. The primary estimand will be obtained as the model-based contrast for Month 6 versus Month 0.

A prespecified parsimonious covariate set will be included to improve precision (not for causal adjustment):

- study centre,
- age,
- months on endocrine therapy prior to ribociclib initiation,
- endocrine therapy backbone, and
- baseline ECOG performance status.

Recent chemotherapy and other collected baseline variables may be examined in exploratory adjusted analyses (Section 10.5) and/or sensitivity analyses if justified by data completeness and distribution.

If the unstructured covariance matrix is not estimable or model convergence is unsatisfactory, the covariance structure will be simplified according to the following prespecified hierarchy:

- 1) heterogeneous compound symmetry,
- 2) compound symmetry,
- 3) first-order autoregressive.

Degrees of freedom will be computed using a small-sample method appropriate for mixed models (Kenward-Roger or Satterthwaite). Model assumptions and fit will be assessed using residual diagnostics and influence checks. The primary result will be the model-based estimated mean change from Month 0 to Month 6 with its two-sided 95% CI.

10.3.3. Sensitivity analysis for the primary endpoint

The following prespecified sensitivity analyses will be conducted to evaluate the robustness of the primary analysis and of the estimated change in EQ-5D-5L utility index from Month 0 to Month 6:

- The primary model will be repeated without baseline covariates (time effect only, with the same repeated-measures covariance structure), and results will be compared with the primary analysis to assess sensitivity to covariate adjustment.
- Where the primary model uses a simplified covariance structure due to non-convergence of the unstructured model, results under alternative prespecified covariance structures (where estimable) will be summarised for comparison.
- Participants with both Month 0 and Month 6 EQ-5D-5L assessments (Month 6 Completer Set) will be analysed using an analogous repeated-measures model and compared with the primary FAS result.
- The primary model will be repeated using the Italian EQ-5D-5L value set, and estimates will be compared with the primary tariff analysis.
- A supportive sensitivity analysis will evaluate an alternative estimand strategy for permanent treatment discontinuation by restricting follow-up to assessments obtained up to permanent discontinuation (“on-treatment” analysis set for sensitivity only). This analysis will be interpreted as supportive and not as the primary estimand.

Sensitivity analyses addressing missing-data assumptions, including multiple imputation and MNAR-oriented analyses, are prespecified in Section 10.7.

10.4. Secondary analyses

Secondary outcomes will be analysed using analogous mixed-effects models, with outcome-appropriate distributional assumptions. Secondary results will be presented primarily as estimates of magnitude and precision, using estimated mean changes, 95% CIs, and, where appropriate, standardised effect sizes. Instruments will be analysed independently because they capture related but distinct constructs, and no direct numerical reconciliation across scales will be performed. Apparent differences in direction or magnitude across instruments will be interpreted descriptively and in clinical context.

EORTC QLQ-BR23 domain scores will be calculated and transformed according to EORTC scoring conventions. Changes from baseline will be summarised at each time point and modelled using mixed-effects models. Results will be reported as estimated mean changes with 95% CIs. Standardised effect sizes will also be reported, defined as the estimated mean

change divided by the baseline standard deviation, to support comparability across domains (15).

For WPAI:GH, work-related domains (absenteeism, presenteeism, overall work impairment) will be analysed in the subset of participants employed at baseline. Activity impairment will be analysed in all participants. Primary analyses will use mixed-effects models with results reported as estimated mean changes (percentage points) with 95% CIs for interpretability. Because WPAI outcomes are bounded percentages (0–100%) and may show floor/ceiling effects, prespecified sensitivity analyses will consider outcome-appropriate alternatives where indicated by diagnostics, including fractional-response models and/or transformed models for bounded data, with interpretation focused on consistency of direction and magnitude.

Supportive responder analyses at Month 6 will classify participants as improved, stable, or deteriorated using prespecified thresholds where available. For EQ-5D-5L utility, a supportive threshold of 0.03 utility units in either direction will be used. For EORTC QLQ-BR23 domains, supportive responder classification will use a 10-point threshold, with direction interpreted according to the domain scoring convention (higher functional scores = better; higher symptom scores = worse). Proportions and 95% CIs will be reported descriptively. These responder analyses are supportive only and will not define confirmatory conclusions.

Informal care hours per week will be summarised descriptively, including the proportion of participants reporting any informal care and the distribution of reported hours among those receiving care. Given the expected skewness and potential zero inflation, a prespecified two-part sensitivity analysis will be used where appropriate:

- 1) a model for any informal care (yes/no), and
- 2) a model for hours among participants reporting care, such as a log-transformed linear model or a generalised linear model with an appropriate distribution and link, depending on diagnostics.

As a supportive exploratory analysis, time to first clinically meaningful deterioration may be summarised for selected PRO outcomes, primarily the EQ-5D-5L utility index, using scheduled assessments at Months 1, 3, and 6. For EQ-5D-5L utility index, clinically meaningful deterioration will be defined as a decrease from baseline of at least 0.03 utility units. Time-to-deterioration analyses will be descriptive and will be interpreted alongside mean within-participant change and longitudinal trajectory analyses. They will not define the primary endpoint, primary estimand, or sample size rationale.

10.5. Exploratory association analyses

Exploratory analyses will examine associations between selected baseline sociodemographic, clinical and treatment-context characteristics and the magnitude of Month 0 to Month 6 changes in PROs, as well as, where appropriate, differences in PRO trajectories over Month 0, 1, 3, and 6. These analyses will be interpreted as associative and hypothesis-generating, and not as causal comparisons. Where appropriate, models will include the same prespecified covariates as the primary analysis. Time-varying follow-up factors, including treatment interruptions, dose reductions, permanent discontinuation, changes in endocrine therapy backbone, adverse events during follow-up, hospitalisations, and recurrence-related events, may be summarised descriptively and may be considered in supportive exploratory analyses where data completeness permits.

10.6. Measurement properties of PRO (supportive analysis)

Supportive analyses will be undertaken to characterise the measurement performance of the PRO instruments in this study sample and to support interpretation of longitudinal change. These analyses will be descriptive and supportive in nature and will not redefine the primary endpoint, the primary estimand, or the prespecified scoring algorithms (12).

10.6.1. Data completeness and distributional characteristics

For each instrument and time point, item-level missingness and scale-level missingness will be summarised descriptively. Floor and ceiling effects will be reported as the proportion of participants achieving the minimum or maximum possible score for each domain, using commonly applied descriptive thresholds as supportive context.

10.6.2. Internal consistency (multi-item domains)

For multi-item EORTC QLQ-BR23 scales, internal consistency will be assessed at baseline and at each follow-up time point using McDonald's omega, with Cronbach's alpha reported as a supplementary index. Values of ≥ 0.70 will be interpreted as indicating acceptable internal consistency for group-level comparisons, while recognising the limitations of internal consistency metrics for short scales.

10.6.3. Structural validity and longitudinal measurement invariance (EORTC QLQ-BR23)

Supportive psychometric analyses of structural validity and longitudinal measurement invariance will be undertaken only if the available sample size, item-level completeness, and model convergence support stable estimation. These analyses are intended to provide contextual information and will not redefine prespecified scoring algorithms, endpoints, or estimands.

If feasible, confirmatory factor analysis (CFA) will be conducted for EORTC QLQ-BR23 at baseline to assess consistency with the expected domain structure. If feasible and estimable, longitudinal measurement invariance across the four assessments (Months 0, 1, 3, and 6) will be evaluated sequentially (configural, metric, and scalar invariance) using standard fit indices and changes in fit indices.

Where model convergence is not achieved, estimation is unstable, or sample support is insufficient for reliable longitudinal CFA, these analyses will not be forced. In that case, supportive psychometric evaluation will rely on the prespecified descriptive analyses, including data completeness, distributional characteristics, floor/ceiling effects, and internal consistency, and interpretation of longitudinal change will be qualified accordingly.

Where invariance is partially supported, partial invariance approaches may be considered as supportive analyses, with transparent reporting of released constraints and cautious interpretation.

10.6.4. Implications for interpretation

Findings from these supportive psychometric analyses will be used to contextualise the interpretation of domain-level change over time. They will not replace the prespecified scoring algorithms or the primary model-based estimand.

10.7. Missing data

Missingness will be summarised at both item level and scale/score level by instrument and time point, including the frequency and proportion of missing values at Months 0, 1, 3, and 6.

Patterns of missingness (intermittent versus monotone dropout) will be described. Where available, reasons for missing PRO assessments (e.g. missed visit, administrative reasons, participant refusal, illness, treatment discontinuation) will be summarised descriptively.

10.7.1. Primary analysis assumption

The primary repeated-measures analysis uses likelihood-based estimation under a Missing At Random (MAR) assumption, conditional on observed outcomes and included covariates. Under this approach, participants with incomplete follow-up contribute all available observed data.

10.7.2. Assessment of MAR plausibility

To assess the plausibility of MAR, baseline characteristics and prior observed outcomes will be compared between participants with complete versus incomplete follow-up. Associations between missingness at each follow-up time point and prior observed PRO values, treatment modification/discontinuation, and selected baseline covariates will be explored descriptively (and, where informative, using logistic regression models for missingness indicators).

10.7.3. Instrument-level scoring and item-level missingness

Instrument scoring will follow prespecified instrument-specific rules (Section 8.2). No ad hoc item-level imputation will be applied prior to scale scoring except where explicitly permitted by the instrument scoring manual.

10.7.4. Multiple imputation sensitivity analysis (MAR-based)

As a prespecified sensitivity analysis, multiple imputation by chained equations (MICE) will be used to assess robustness to alternative imputation models under MAR. The imputation model will include, at minimum:

- all repeated PRO measurements (EQ-5D-5L utility, EORTC QLQ-BR23 domains, WPAI:GH outcomes, and informal care variables, as applicable),
- baseline covariates prespecified for adjusted analyses (including study centre, age, months on endocrine therapy prior to ribociclib initiation, endocrine therapy backbone, and baseline ECOG performance status),
- indicators of treatment modification/interruption/discontinuation,
- visit attendance indicators and missingness indicators,
- reasons for missingness where available, and
- relevant auxiliary variables recorded in the study (e.g. selected clinical status or functional-impact indicators), where available and sufficiently complete.

Imputation methods appropriate to variable type will be used (e.g. predictive mean matching for continuous or bounded outcomes where appropriate; logistic/multinomial models for categorical variables). A sufficient number of imputations will be generated (at least 50 imputations, and more if warranted by the fraction of incomplete cases). Estimates will be combined using Rubin's rules.

10.7.5. MNAR-oriented sensitivity analyses

At least one prespecified sensitivity analysis addressing potential Missing Not At Random (MNAR) mechanisms will be conducted using a pragmatic pattern-mixture / delta-adjustment

approach, focusing on the primary endpoint. In participants with missing Month 6 EQ-5D-5L utility (and/or after permanent treatment discontinuation), imputed Month 6 values will be shifted by prespecified negative deltas to represent less favourable outcomes than predicted under MAR. The primary planned delta grid for EQ-5D-5L utility will be: -0.01, -0.02, -0.03, and -0.05 utility units.

The impact of these assumptions on estimated Month 0 to Month 6 change in EQ-5D-5L utility and its two-sided 95% CI will be summarised. Where feasible, a tipping-point summary or figure will be presented to show the range of MNAR departures under which the estimated magnitude and direction of change materially differ from the primary MAR-based analysis.

10.7.6. Deaths during follow-up

Participants who die during follow-up will contribute observed data up to death. Deaths will be summarised descriptively. A supportive composite sensitivity analysis for the primary endpoint may assign EQ-5D-5L utility = 0 at subsequent scheduled time points after death, with results reported separately and interpreted cautiously.

10.8. Multiplicity

Multiplicity is limited by design because the study has a single prespecified primary endpoint evaluated at a single primary time point (Month 6). The primary analysis and all secondary or exploratory analyses will be interpreted primarily through the magnitude, direction, and precision of estimated effects, using 95% CIs as the main inferential measure.

No formal multiplicity adjustment is planned. Where families of related secondary outcomes are reported, such as multiple EORTC QLQ-BR23 domains, results will be presented transparently as a family.

If p-values are reported for families of related secondary outcomes, a supportive false discovery rate (FDR) adjustment using Benjamini-Hochberg method may be added as a supplementary analysis to aid interpretation.

10.9. Statistical software

Statistical analyses will be conducted using Stata 19 (StataCorp LLC, College Station, TX, USA). A detailed Statistical Analysis Plan (SAP) will be finalised, version-controlled, and dated before final database lock and before execution of the primary analysis. The SAP will prespecify derivation rules, scoring conventions, analysis datasets, model specifications (including covariance-structure fallback hierarchy), diagnostic procedures, and sensitivity analyses. Any deviations from the SAP or protocol-defined analyses made after database lock will be documented, justified, and clearly labelled as post hoc in study outputs.

10.10. Clinical relevance and MCID justification

Interpretation of study findings will consider both statistical significance and clinical relevance. Where available, anchor-based minimal clinically important differences (MCIDs) will be prioritised. In the absence of robust anchor-based thresholds in oncology populations, distribution-based benchmarks will be used as supportive criteria, in line with established methodological guidance (12,16).

10.10.1. EQ-5D-5L

Minimally clinically important within-patient change for the EQ-5D-5L utility index is heterogeneous and depends on baseline health status, anchors, and the applied value set (17). In

a large longitudinal cohort of patients with cancer, anchor-based analysis suggested a weighted MCID of approximately 0.03 for EQ-5D-5L utility index for both improvement and deterioration (18). In this study, this value will be used as a supportive benchmark for clinical interpretation of within-patient change. Accordingly, within-patient changes of at least 0.03 utility units in either direction will be considered potentially clinically meaningful, alongside the estimated magnitude of change, its 95% CI, and the overall pattern of results across time points. No formal decision rule based on an MCID threshold will be used for the primary analysis.

10.10.2. EORTC QLQ-BR23

Interpretation of changes in EORTC QLQ-BR23 domain scores will be guided by widely used thresholds for interpreting change in EORTC scores, applied as pragmatic benchmarks in the absence of robust module-specific MCIDs (15).

According to these guidelines:

- a change of ≥ 10 points represent a clinically meaningful change,
- changes of 5–10 points indicate a small change,
- changes of ≥ 20 points indicate a large change.

These thresholds will guide supportive interpretation of both functional and symptom domains of the QLQ-BR23. For functional scales, negative changes indicate worsening, whereas for symptom scales, positive changes indicate worsening. Results will therefore be presented consistently as changes from baseline, with direction of clinical worsening clearly indicated for each domain. In addition to estimated mean changes and 95% CIs, the proportion of participants experiencing clinically meaningful deterioration or improvement will be summarised descriptively using prespecified thresholds.

10.10.3. WPAI:GH

There are no anchor-based MCIDs for WPAI outcomes specifically validated in oncology populations (19). Evidence from chronic disease populations suggests that changes of approximately 7–20 percentage points may represent clinically relevant differences in work productivity and activity impairment (20,21).

In this study, a 10-percentage-point change in WPAI:GH domains (overall work impairment, absenteeism, presenteeism, or activity impairment) will be used as a pragmatic benchmark to support interpretation of clinical relevance, alongside effect sizes and 95% CIs, and the overall pattern of change over time. This threshold will be used for supportive interpretation only.

10.10.4. Informal care needs

No validated anchor-based MCIDs have been established for changes in informal care hours in oncology populations. Changes in weekly informal care hours will therefore be interpreted descriptively and in relation to distribution-based benchmarks, including half a standard deviation (0.5 SD) of the baseline informal care hours as a supportive reference, together with the overall pattern of change over time and 95% CIs. This benchmark has been shown to approximate a MCID across a wide range of health measures and is commonly used as a distribution-based criterion when anchor-based estimates are unavailable (22,23).

11. LIMITATIONS

This study has several limitations that should be considered when interpreting the findings.

First, as a single-arm observational study without a concurrent control group, the analyses are limited to estimation of within-patient changes over time and exploratory associations. The study is not designed to support causal inference, and observed changes may be influenced by factors unrelated to treatment.

Second, although the study includes repeated measurements, the primary analysis focuses on the change from baseline (Month 0) to Month 6. Intermediate assessments at Month 1 and Month 3 are included to support longitudinal modelling, interpretation of temporal patterns, and data completeness, but they do not define separate primary endpoints.

Third, patient-reported outcomes are subject to response bias and reporting variability, which may be influenced by expectations, symptom perception, or adaptation over time, or changing reference standards. To mitigate this, validated instruments are used and data collection is standardised across centres.

Fourth, missing data may occur due to missed visits or treatment discontinuation. Although the primary analytical approach accommodates missing data under standard assumptions and sensitivity analyses are planned, residual bias due to non-random missingness cannot be completely excluded.

Fifth, regression to the mean may contribute to apparent changes in PROs over time, particularly if baseline assessments occur during periods of heightened symptoms or heightened treatment-related concern around therapy initiation.

Sixth, outcomes may be influenced by intercurrent events and time-varying factors during follow-up, including dose interruptions or reductions, treatment discontinuation, intercurrent illnesses, changes in concomitant medications, adverse events during follow-up, hospitalisations, recurrence-related events, or additional supportive interventions. These factors may complicate interpretation of within-participant change and may not be fully captured or modelled.

Seventh, EQ-5D-5L utility estimation relies on an external value set, as a Croatian national EQ-5D-5L value set is not available. Although sensitivity analysis will assess robustness of results to the choice of tariff, some uncertainty related to cross-country valuation differences may remain.

Finally, the study is conducted in a limited number of centres within a single country, which may affect the generalisability of the findings to other healthcare settings. The multicentre routine-practice design supports relevance to the participating centres and to broadly similar clinical contexts, but extrapolation beyond these settings should be made with caution.

12. BENEFIT RISK ASSESSMENT

This is a non-interventional observational study in which all treatments and clinical procedures are provided as part of routine care. The study does not require any additional diagnostic or therapeutic interventions beyond standard clinical practice.

The anticipated risks for participants are minimal. They relate primarily to the time required to complete patient-reported outcome questionnaires and potential discomfort when answering health-related questions. There is also a small risk related to confidentiality and data protection associated with collection and processing of questionnaire and clinical data.

This risk will be mitigated through pseudonymisation, separation of identifiable information from study data, restricted access to study materials, and secure storage and transfer procedures as described in the Data management section. No study-specific medical risks are expected.

Potential benefits are indirect and include generating real-world evidence on health-related quality of life, work productivity, and informal care needs during adjuvant ribociclib plus endocrine therapy. This may inform patient-centred care and future research, and may contribute to evidence generation relevant to clinical practice and health policy.

13. ETHICAL CONSIDERATIONS

This study is a non-interventional observational study conducted in accordance with the principles of the Declaration of Helsinki and applicable national regulations. The study will also be conducted in compliance with applicable data protection legislation, including the General Data Protection Regulation (GDPR).

Prior to initiation, the study protocol and relevant study documents will be submitted for review and approval by the National Ethics Committee.

All eligible patients will receive clear verbal and written information about the study objectives, procedures, potential risks, and data handling. Written informed consent will be obtained from all participants before enrolment. Participation is voluntary, and participants may withdraw from the study at any time without any impact on their standard medical care.

The study does not involve any additional diagnostic or therapeutic procedures beyond routine clinical practice. Data collection is limited to patient-reported questionnaires and clinical information obtained from medical records.

Participant confidentiality will be strictly maintained. Personal identifiers will be used only for consent and administrative purposes and will be stored separately from analytical data. Study data will be pseudonymised using study-specific identification codes, and access to identifiable information will be restricted to authorised study personnel.

Roles and responsibilities for data controllership and data processing will be defined in accordance with applicable requirements. All study data will be stored securely and handled in compliance with applicable data protection regulations.

14. FUNDING

This study is financially supported by Novartis Hrvatska d.o.o.

The regulatory sponsor of the study is Hrvatsko društvo za promicanje kliničkih istraživanja u onkologiji (the Croatian Cooperative Group for Clinical Research in Oncology (CCG CRO)). The sponsor and investigators are responsible for study conduct, data collection, data management, statistical analysis, interpretation of results, and preparation of the final study report. Novartis Oncology may review study documents and outputs for factual accuracy and confidentiality considerations, but does not have sole control over data interpretation or the decision to publish.

15. PUBLICATION

The results of this study will be submitted for publication in a peer-reviewed, international English-language journal of appropriate scope and/or presented at a scientific conference. The coordinating investigator, together with the study statistician, will consult the co-investigators and agree the scope of the manuscript(s), the writing plan, and responsibilities for drafting and review. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) criteria.

Investigators at individual study sites may propose additional analyses addressing scientific questions not prespecified in this protocol, using study data. Such analyses and any related publications will require consultation with the study sponsor to ensure appropriate governance, consistency with data use agreements, protection of participant confidentiality, and avoidance of overlapping or duplicative publications. Site-specific analyses will not compromise the integrity of the primary study analyses and publications.

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