Non-Interventional Study Protocol

Protocol No: A5481145

Treatment Patterns and Clinical Outcomes Among Indian Patients Receiving Palbociclib Combinations for HR+/HER2- Advanced/Metastatic Breast Cancer in Real World Settings.

Statistical Analysis Plan (SAP)

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not Applicable

2 INTRODUCTION

This is a retrospective physician based medical record review study. will collect data from the medical records of patients, who have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy will be reviewed. Data will be collected retrospectively at a single point in time from patient medical records.

This statistical analysis plan (SAP) will be the guiding document for the analyses that will be conducted in the study. This study intend to describe the demographics, clinical characteristics, treatment patterns, and clinical outcomes of adult female patients who have received palbociclib combination treatments for HR+/HER2- ABC/MBC in real world settings in India. SAP describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 1.0 dated 19th October 2020 and case report form (CRF) version 0.09, 20th May 2021.

2.1 STUDY DESIGN

This is a post marketing, retrospective, non-interventional study (NIS). The study will be conducted as a retrospective medical record review of patients who have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy. It will comprise of an initial screening and eligibility assessment of patients followed by data collection from eligible patient records.

Data collection will be conducted using a predesigned electronic case report form (eCRF). Eligible physicians will be invited to complete the eCRF of patients that meet the study criteria. Patient eligibility will be confirmed by treating physicians. In order to allow for a sufficiently long observational window, treating physicians will be asked to go back to a specific point in time, the index date, and sequentially select the medical records of the next ‘n’ patients who meet the inclusion criteria.

Study population

Female cancer patients who have received palbociclib combination treatments for HR+/HER2- ABC/MBC in real world clinical practice setting.

Data source

Data will be collected from the Indian routine clinical practice settings. Approximately 10 oncologists will be included based on predefined egilbility criteria. Each selected physician will complete at least 10-15 electronic case report forms (eCRFs).

To be eligible, physicians must have treated or be treating 10 or more HR+/HER2- ABC/MBC patients who meet the eligibility criteria for the study. This will ensure that recruited physicians will be able to complete the minimum number of eCRFs required to participate in the study. In addition, during physician recruitment a representative geographical split and private/public practice split will be sought where possible to ensure a representative sample.

Inclusion Criteria

Physician inclusion criteria

- Oncologist.
- Responsible for treating ≥ 10ABC/MBC patients who meet the eligibility criteria.
- Agrees to participate in the study and complete the eCRFs within the data collection period

Patients Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- ≥18 years old females.
- HR+/HER2- breast cancer diagnosis with confirmed metastatic or advanced disease.
- Received palbociclib with aromatase inhibitor (as prescribed by the Physician) as initial endocrine therapy in postmenopausal MBC patients or with fulvestrant in patients who have progressed on prior endocrine therapy.
- Patients on LHRH agonists for ovarian function suppression in pre- or perimenopausal stage only if prescribed palbociclib with fulvestrant.
- No prior or current enrolment in an interventional clinical trial for ABC/MBC.
- Minimum of 3 months of follow up data since palbociclib with fulvestrant initiation, or minimum of 6 months of follow up data since palbociclib with aromatase inhibitor initiation

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- Cancers other than breast cancer
- Male breast cancer
- Indications other than mentioned in the protocol
- Visceral crisis

Treatment/cohort labels

Palbociclib

2.2 STUDY OBJECTIVES

Primary Objectives:

1. To describe the demographics and clinical characteristics of patients who have received palbociclib combination with aromatase inhibitor (as prescribed by the Physician) in menopausal state as initial endocrine therapy in MBC or with fulvestrant after progression on prior endocrine therapy.
2. To summarize adjuvant therapies received for the treatment of early or locally advanced breast cancer (Stages 0-IIIa).
3. To describe treatments received in the advanced/metastatic setting, before and after palbociclib combination use.
4. To describe dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib use in clinical practice.
5. To describe supportive therapies received by patients while receiving palbociclib combination treatments.
6. To determine in overall population and defined subgroups, clinical outcomes including (but not limited to):
   - Proportion of patients who are progression free at specific intervals (eg, 6, 12, 18 months).
   - Objective response rate (ORR) - depending on availability of follow-up data.
   - Proportion of alive patients 1 and 2 years post palbociclib combination initiation -depending on availability of follow-up data (sample size permitting).

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3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

Not Applicable

3.2 STATISTICAL DECISION RULES

Not Applicable

4 ANALYSIS SETS/POPULATIONS

4.1 ALL SUBJECTS SET

All available data of 150 patients received palbociclib with aromatase inhibitor (as prescribed by the Physician) will be used for summary/analysis purpose.

4.2 SAFETY ANALYSIS SET
The safety analysis set is the same as the all subjects set.

4.3 OTHER ANALYSIS SET
Not Applicable

4.4 SUBGROUPS
Not Applicable

5 ENDPOINTS AND COVARIATES

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)
- Treatment success of the patients treated with palbociclib with aromatase inhibitor (as prescribed by the Physician) will be progression free i.e. complete response, partial response or stable disease at the end of regimen.

5.2 OTHER ENDPOINTS
Not Applicable

5.3 COVARIATES
Not Applicable

6 HANDLING OF MISSING VALUES
No imputation for missing values will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS
Analysis of the data will be performed by the Biostatistics and Statistical Programming team. All statistical analyses will be performed using STATA 13.0 Version or higher. The SAP will be finalized before database lock.

The following standard descriptive summaries will be presented:

Descriptive statistics for continuous data:
The continuous data will be summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max).

The number of observations (n) will be presented with no decimal place, mean and median will be presented up to one decimal place from the original value, SD up to two decimal places from the original value and (min, max) as an original value.

Descriptive statistics for categorical data:

The categorical variables will be summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies will be presented up to 0 decimal places, percentage up to 1 decimal place.

All the analysed variable will be presented by the line of treatment (1st line of treatment and 2nd and later line). If data are not available, a missing category will be presented. Statistical tests, if any, will be performed at 5% level of significance. The denominator for percentages will be based on the number of patients appropriate for the purpose of the analysis.

7.2 STATISTICAL ANALYSES

- **Demographic Characteristics**
  The demographic and baseline characteristics will be summarized by using descriptive statistics. Continuous variables such as age will be summarized by number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max) and Categorical variables such as menopausal status, induced menopause, family history of breast cancer and patient deceased will be presented by frequency (n) and percentage (%).

- **Initial and advance breast cancer diagnosis**
  For all the patients initial diagnosis of breast cancer stages (stage 0 to stage IV) will be presented in frequency counts (n) and percentage (%). For the advance stages (stage IIIb, IIIc or IV) of breast cancer patients again locoregionally advanced or metastatic frequency counts (n) and percentage (%) will be given. For the metastatic disease, sites of metastases such as Bone, Liver, Brain, Lung, Lymph nodes and others with further segregation like single or multiple locations will be presented in frequency (n) and percentage (%).

- **Prior Therapy**
  For all patient's prior therapy type (Targeted, Endocrine and Chemotherapy) will be presented by frequency count and percentage

- **Performance status**
  Performance status using ECOG scale at the initiation of palbociclib treatment. Status is measured using 4 point scale from fully active to completely disable and will be summarized by frequency (n) and percentage (%).

- **Early Breast Cancer Treatment History**
  Following early breast cancer diagnosis treatments received such as surgery, radiotherapy, neoadjuvant treatment, adjuvant chemotherapy, adjuvant endocrine therapy by patients will be summarized by frequency (n) and percentage (%).

- **Palbociclib Treatment**

For all the patients initial dose prescribed of palbociclib, any dose adjustments made to palbociclib and for each dose adjustment if dose reduced or increased, palbociclib was temporarily interrupted, cycle delay and reason for dose change will be summarized by frequency (n) and percentage (%). Moreover, complete summary (frequency and percentage) of all supportive therapies that patients received will be presented.

- **Advance Breast Cancer Treatment History**
  For all the patients' line of treatment for Palbociclib combination started will be given in frequency and percentage, time (months) from diagnosis of breast cancer to start of Palbociclib combination will be presented as mean, median, standard deviation and range value (minimum and maximum). CCI

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- **Clinical Outcome**
  For all the patients initially recorded responses like complete positive response to the disease, partial positive response to the disease, stable disease and progressive disease, will be summarized with frequency counts (n) and percentages (%). Moreover, based on initial response, objective response rate (ORR) and clinical benefit rate (CBR) will be calculated and presented as percentage.

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8 LIST OF TABLES

9 REFERENCES

1. A5481145,Version 1.0, October 19, 2020
2. A5481145, CRF Version , May 20, 2021

10 APPENDICES

10.1 APPENDIX 1: MOCK SHELLS FOR TABLES

Table 1 Demographic Characteristics – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Age of the patients	n	xx
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
Age group >65 yrs vs <65 yrs	n (%)	
Menopause Status		
Induced	n (%)	xx (xx.x)
Natural	n (%)	xx (xx.x)
Type of Induced Menopause		
LHRH suppression	n (%)	xx (xx.x)
Radioablation	n (%)	xx (xx.x)
Surgical	n (%)	xx (xx.x)
Patient deceased		
No	n (%)	xx (xx.x)
Yes	n (%)	xx (xx.x)
Family History of Breast Cancer		
No	n (%)	xx (xx.x)
Yes	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category; LHRH = Luteinizing Hormone Releasing Hormone Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 1.1 Demographic Characteristics by line of treatment (first line vs. second and later line)		

Table 2 Initial and Advance Breast Cancer Diagnosis– All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Stage of Breast Cancer at diagnosis		
Stage I	n (%)	xx (xx.x)
Stage II	n (%)	xx (xx.x)
Stage IIIa	n (%)	xx (xx.x)
Stage IIIb	n (%)	xx (xx.x)
Stage IIIc	n (%)	xx (xx.x)
Stage IV	n (%)	xx (xx.x)
Type of breast cancer (Metastatic/ locally advanced)		
Locoregionally advanced	n (%)	xx (xx.x)
Metastatic	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 2.1 Initial and Advance Breast Cancer Diagnosis by line of treatment (first line vs. second and later line)		

Table 3 Advance Breast Cancer Diagnosis – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Sites of Metastases		
Bone	n (%)	xx (xx.x)
Lung	n (%)	xx (xx.x)
Liver	n (%)	xx (xx.x)
Lymph nodes	n (%)	xx (xx.x)
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Bone		
Single site	n (%)	xx (xx.x)
Multiple sites	n (%)	xx (xx.x)
Liver		
Single site	n (%)	xx (xx.x)
Multiple sites	n (%)	xx (xx.x)
Lung		
Single lung	n (%)	xx (xx.x)
Bilateral	n (%)	xx (xx.x)
Pleural effusion	n (%)	xx (xx.x)
Lymph Nodes		
Regional	n (%)	xx (xx.x)
Distal	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 3.1 Advance Breast Cancer Diagnosis by line of treatment (first line vs. second and later line)		

Table 4 Prior Therapy– All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Prior Therapy		
Targeted	n (%)	xx (xx.x)
Endocrine	n (%)	xx (xx.x)
Chemotherapy	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 4.1 Prior Therapy by line of treatment (first line vs. second and later line)		

Table 5 Performance Status– All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Performance Status on ECOG Scale at Palbociclib initiation		
0	n (%)	xx (xx.x)
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
3	n (%)	xx (xx.x)
4	n (%)	xx (xx.x)
5	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category; ECOG = Eastern Cooperative Oncology Group Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 5.1 Performance Status by line of treatment (first line vs. second and later line)		

Table 6 Early Breast Cancer Treatment History – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Neo/Adjuvant Therapy Received by Patient		
Adjuvant chemotherapy	n (%)	xx (xx.x)
Adjuvant endocrine therapy	n (%)	xx (xx.x)
Neoadjuvant treatment	n (%)	xx (xx.x)
Radiotherapy	n (%)	xx (xx.x)
Surgery	n (%)	xx (xx.x)
Don't Know	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 6.1 Early Breast Cancer Treatment History by line of treatment (first line vs. second and later line)		

Table 7 Palbociclib Treatment – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Initial Dose Prescribed		
125 mg/day	n (%)	xx (xx.x)
100 mg/day	n (%)	xx (xx.x)
75 mg/day	n (%)	xx (xx.x)
Dose Adjustment		
No	n (%)	xx (xx.x)
Yes	n (%)	xx (xx.x)
Reason for Dose Adjustment		
Side effects/toxicity	n (%)	xx (xx.x)
Lack of response	n (%)	xx (xx.x)
Patient request	n (%)	xx (xx.x)
Other reasons	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 7.1 Palbociclib Treatment by line of treatment (first line vs. second and later line)		

Table 8 Dose Adjustment – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Dose Reduced		
Yes	n (%)	xx (xx.x)
Dose Resumed following interruption or cycle delay		
Yes	n (%)	xx (xx.x)
Dose Interrupted (temporarily stopped during a dose cycle)		
Yes	n (%)	xx (xx.x)
Cycle delay (the next cycle is pushed back)		
Yes	n (%)	xx (xx.x)
Combination partner therapy continued		
Yes	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 8.1 Dose Adjustment by line of treatment (first line vs. second and later line)		

Table 9 Palbociclib Treatment- Supportive Therapies – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Supportive therapies		
Nutritional Support	n (%)	xx (xx.x)
Bisphosphonates	n (%)	xx (xx.x)
Antibiotics	n (%)	xx (xx.x)
Anti-anxiety drugs	n (%)	xx (xx.x)
Opioid extended release	n (%)	xx (xx.x)
NSAIDs	n (%)	xx (xx.x)
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Don’t Know	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 9.1 Palbociclib Treatment- Supportive Therapies by line of treatment (first line vs. second and later line)		

Table 10 Advance Breast Cancer Treatment History – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Time duration from Diagnosis to initiation of Palbociclib	n	xx
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
Line of treatment		
1st line	n (%)	xx (xx.x)
2nd line	n (%)	xx (xx.x)
3rd line	n (%)	xx (xx.x)
4th or later line	n (%)	xx (xx.x)
Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category Note 1: Percentages are based on the number of subjects in the Palbociclib group.		
Table 10.1 Advance Breast Cancer Treatment History by line of treatment (first line vs. second and later line)		

Table 11 Clinical Outcome – All Subjects

Characteristic (Unit)	Statistics	Palbociclib (N=xx)
Complete response		
Yes	n (%)	xx (xx.x)
Partial response		
Yes	n (%)	xx (xx.x)
Stable disease		
Yes	n (%)	xx (xx.x)
Progressive disease		
Yes	n (%)	xx (xx.x)
Objective Response Rate (ORR)		
Yes	n (%)	xx (xx.x)
Clinical Benefit Rate (CBR)		
Yes	n (%)	xx (xx.x)
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Abbreviations: N = number of subjects in Palbociclib group; n = number of subjects in specified category
Note 1: Percentages are based on the number of subjects in the Palbociclib group.

Table 11.1 Clinical Outcome by line of treatment (first line vs. second and later line)

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