SUMMARY OF RESULTS

Name of Sponsor: Angelini Pharma S.p.A.	**(For National Authority Use only)**
Name of Finished Product: Trazodone hydrochloride 150-300 mg/once-a-day [redacted]	
Name of Active Ingredient: Trazodone hydrochloride	

TITLE OF STUDY:	Efficacy of Trazodone Once-a-Day for Treatment of Major Depressive Disorder in Patients with Breast Cancer EudraCT Number: 2021-005007-12
STUDY CENTRES:	Multicentre (Bulgaria)
STUDY PERIOD:	Date First Patient Screened: 15-Jun-2023 Date First Patient Enrolled: 29-Jun-2023 Date of Early Termination: 05-Oct-2023 Date Last Patient Completed: 10-Jan-2024
PHASE OF DEVELOPMENT:	Phase IV
BACKGROUND AND RATIONALE FOR THE STUDY	Cancer is a life-threatening and feared diagnosis and is a source of great distress to patients. Sadness and preoccupation may be a normal response to a cancer diagnosis; however, distress may result in more clinically significant states characterized by symptoms of anxiety or depressive disorders or other psychopathological conditions. Major depressive disorder (MDD) is a serious psychiatric condition affecting about 7% of the general population and with a prevalence in oncology of between 15% and 40% depending on several factors (e.g., type, stage of cancer, in/outpatient, on/off treatment, type of diagnostic tool for depression). Although depression is frequently observed in oncology, and there is evidence of its negative impact on patients' quality of life and physical condition as well as on disease outcomes, it remains frequently undetected and inadequately treated in clinical practice. Thus, there is a strong need to identify and treat depression in cancer patients in order to improve quality of life and reduce distress. Breast cancer is the most prevalent invasive cancer of women worldwide, constituting about one fifth of all cancer types. Its diagnosis and treatment, and the months following primary therapy are stressful times. Aside from the actual cancer threat, many women experience various degrees of depression, anxiety, sleep disturbances, issues with sexuality, and cognitive dysfunction. The aim of the present study was to assess the efficacy of trazodone once-a-day (OAD) monotherapy in improving depression symptoms, functional recovery including cognitive and behavioural responses, and quality of life in patients with breast cancer and co-morbid MDD. Treatment compliance and safety were also evaluated.
OBJECTIVES:	
Primary:	The primary objective was to assess the efficacy of trazodone OAD monotherapy in improving depression symptoms in patients with breast cancer and co-morbid MDD after an 8-week treatment period.

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Secondary:	Secondary objectives were to assess patients' evaluation of depressive symptoms, functional recovery including cognitive and behavioural responses, quality of life, compliance with antidepressant treatment, and safety over the 12-week study period.
METHODOLOGY:	This was a phase IV, open-label, single group multicentre study which planned to collect data on the efficacy of trazodone OAD monotherapy in improving depression symptoms in patients with breast cancer and co-morbid MDD after an 8-week treatment period. Patient evaluation of depressive symptoms, functional recovery including cognitive and behavioural responses, and quality of life was planned; compliance with antidepressant treatment and safety over the 12-week study period were also to be assessed. The study planned to enrol a total of 100 female patients (aged 18-64 years, limits included) and treat them with 150 mg and up to 300 mg trazodone OAD for a maximum of 84 (±3) consecutive days. Patient enrolment was competitive among clinical sites. At the Baseline Visit, all eligible patients were assigned to the following single treatment group: trazodone hydrochloride 150-300 mg/OAD for 84 (±3) consecutive days. The tablets were to be taken under fasting conditions with a glass of water, always once daily, in the evening or just before bedtime. Following the Baseline Visit, 4 visits were scheduled over the 84-day study period. Data were collected at study visits via a number of questionnaires: Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), Brief Symptom Inventory modified version (BSI18 MOD), Insomnia Severity Index (ISI), Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN), Mini-Mental Adjustment to Cancer Scale (MiniMAC), and EuroQuality of Life 5 dimensions – 5 level (EQ-5D-5L). Data were collected electronically via a real-time eSource Direct Data Capture platform. The investigator completed the MADRS, CGI, and BRIAN directly into the study eSource platform. In addition, the patient was responsible for completing the electronic patient-reported outcomes (BSI-18 MOD, ISI, Mini-MAC, and EQ-5D-5L) via a mobile app "Engage", accessible from their own, or a study provided, device.
NUMBER OF PATIENTS (Planned and Analyzed):	Planned 100 Screened 10 Enrolled 9 Discontinuations 1 Completed 8 Analyzed (Safety) 9 Analyzed (Efficacy: modified intent-to-treat population) 9 All patients were female and were enrolled at study sites located in Bulgaria.
REASON FOR EARLY STUDY TERMINATION	Due to low enrollment rate, this study was terminated early, after enrolling 9 out of the planned 100 patients.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:	To be eligible for this study, patients were to be female, of any ethnic origin, and between 18 and 64 years of age (limits included) who were outpatients with non-metastatic breast cancer under endocrine therapy. The primary diagnosis of breast cancer must have been confirmed by appropriate clinical and instrumental assessment. Patients had to have met the Diagnostic and Statistical Manual of Mental Disorders – 5th edition criteria for MDD diagnosis, experiencing a current major depressive episode

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	of at least moderate severity, defined by a MADRS total score ≥20 at the Baseline Visit. Patients must have been eligible to start treatment with trazodone OAD monotherapy at the Baseline Visit. Women of childbearing potential and women with no menses for a period <12 months were to have a negative pregnancy test at the Baseline Visit and agree not to start a pregnancy and use an appropriate birth control method from the signature of the informed consent form up to the final visit. Patients had to be legally capable of giving their written consent to participate in the study (including personal data processing) and willing to comply with all study procedures. Patients who met any of the contraindications to the administration of trazodone OAD according to the approved Summary of Product Characteristics or had known hypersensitivity or allergy to the active ingredient and/or to any component of the study treatment were excluded from the study. Patients with locally advanced or metastatic breast cancer, those receiving adjuvant chemotherapy, or concomitant treatment with other antidepressant drugs and/or proved resistance to the trazodone OAD monotherapy were also excluded. In addition, patients with previous or current diagnosis of bipolar disorder, schizophrenia or other psychotic disorder, severe personality disorder, mental retardation, organic mental disorders or mental disorders due to a general medical condition, previous or current history of a clinically significant neurological disorder, or any neurodegenerative disease, or other relevant condition that, in the opinion of the investigator, could have compromised participation in the study, or who were at risk of suicide defined by a score ≥4 in MADRS item #10 at the Baseline Visit were excluded. Patients were not eligible for the study if they were pregnant or lactating, had clinically significant abnormalities on physical examination, vital signs, and/or laboratory values at the Baseline Visit, with known cardiovascular disease associated to the prolongation of the QT interval.
TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:	Patients were assigned to treatment with trazodone hydrochloride 150-300 mg/OAD. Tablets were to be swallowed once daily under fasting conditions with a glass of water, in the evening or just before bedtime. • [redacted] Each tablet contained 150 mg trazodone hydrochloride, corresponding to 136.6 mg trazodone (batch number: 0128) • [redacted] Each tablet contained 300 mg trazodone hydrochloride, corresponding to 273.2 mg trazodone (batch number: 1229)
DURATION OF TREATMENT:	Patients were assigned to treatment with trazodone hydrochloride 150-300 mg/OAD for 84 (±3) consecutive days. Participation in the study was expected to last for a maximum of 87 days.
ENDPOINTS:	
Efficacy:	Primary Efficacy Endpoint • The primary efficacy endpoint of this study was the mean change in MADRS score from the Baseline Visit to Visit 3 Secondary Efficacy Endpoints • Mean changes in MADRS score from the Baseline Visit to Visits 1, 2, and 4

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	• Changes in the distribution of CGI from the Baseline Visit to Visits 1, 2, 3, and 4 • Mean changes in BSI-18 MOD total score from the Baseline Visit to Visits 1, 2, 3, and 4 • Changes in the distribution of ISI from the Baseline Visit to Visits 1, 2, 3, and 4 • Mean changes in BRIAN total score from the Baseline Visit to Visit 4 • Mean changes in Mini-MAC total score from the Baseline Visit to Visits 3 and 4 • Changes in EQ-5D-5L and mean changes in the visual analogue scale (VAS) from the Baseline Visit to Visits 3 and 4 • Comparison between MADRS, BSI-18 MOD, Mini-MAC, and VAS of EQ-5D-5L at the Baseline Visit, Visit 3 and Visit 4
Safety:	Secondary Safety Endpoints • Compliance to antidepressant treatment (calculated from the number of trazodone OAD tablets taken by patient since enrolment until the last day of medication) • Changes in concomitant medications for treatment of depression over the 12-week study period • Safety and tolerability were assessed by monitoring the frequency of adverse events (AEs). In addition, changes from baseline in vital signs and physical examination were assessed
STATISTICAL METHODS:	The study was essentially descriptive and did not include any hypothesis to be tested. Accordingly, the statistical analysis was descriptive, and all variables were analyzed with appropriate statistical methods. Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations primarily used SAS (release 9.4 or higher). All formal statistical comparisons were based on adjusted means in a mixed model for repeated measures. Statistical tests were interpreted in an exploratory sense only and were not considered formal hypothesis tests. The following populations were defined for statistical analysis: • Safety: all patients who took at least 1 dose of the study treatment. • Modified intent-to-treat (mITT): all patients who took at least 1 dose of the study treatment and had the MADRS evaluation at baseline and at least 1 post-baseline visit. • Per protocol (PP): all patients who took at least 1 dose of the study treatment and had all MADRS evaluations, with no major protocol violations.
SUMMARY OF RESULTS AND CONCLUSIONS	

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Patient Disposition:	A total of 10 patients were screened for the study, and 9 patients, of the planned 100, were enrolled. Eight patients completed the study; 1 patient withdrew consent and did not complete the study.
Demography and Baseline Characteristics:	All enrolled patients were post-menopausal females, White, not Hispanic or Latino, and with a mean (SD) age of 57.1 (7.72) years. Per protocol, all 9 patients (100.0%) reported a medical history in the system organ class neoplasms benign, malignant and unspecified (incl cysts and polyps), with 8 patients (88.9%) reporting breast cancer and 1 patient (11.1%) reporting breast neoplasm.
Efficacy Results:	• For the primary efficacy endpoint, the mean (SD) change in MADRS score from the Baseline Visit to Visit 3 was -12.8 (5.85) in the mITT population. The mean (SD) MADRS score was 26.6 (4.50) at the Baseline Visit, which reduced to 13.8 (9.00) at Visit 3. A reduction in MADRS score was seen for all patients, and ranged from -2 to -22. • A reduction from the Baseline Visit in mean (SD) MADRS scores was also reported at Visit 1 (-3.2 [2.49]), Visit 2 (-6.2 [2.91]), and Visit 4 (-17.2 [6.57]). • Over time, all patients showed improvements in CGI-S and CGI-I scores. • Mean BSI-18 MOD, BSI-18, and Cancer Irritability Scale scores decreased over time. • Following reports of insomnia in all patients at the Baseline Visit in the ISI, all patients from whom data were collected reported an absence of insomnia at Visits 3 and 4. • Reductions in BRIAN and Mini-MAC total scores were recorded from the Baseline Visit to Visit 4. • In the EQ-5D-5L, scores in the dimensions of mobility, self-care, and pain/discomfort indicated no or slight problems or issues, which remained consistent throughout the study. The dimensions of usual activities and anxiety/depression showed an improvement over time. At the Baseline Visit, 5 patients reported having moderate or slight problems performing their usual activities and 3 patients reported having no problems; at Visit 4, 8 patients reported no problems performing their usual activities. At the Baseline Visit, 8 patients described feeling either slightly, moderately, or severely anxious or depressed; at Visit 4, 7 patients reported no feelings of anxiousness or depression, 1 patient reported feeling slightly anxious or depressed. • An increase, indicating an improved outcome, in the EQ VAS was recorded over time, with a mean (SD) change from the Baseline Visit of 28.3 (12.78) at Visit 3 and 37.6 (11.30) at Visit 4. • No clear patterns were identified in the correlations between scales over time.
Safety Results:	No deaths, serious adverse events, ADRs, or other significant AEs occurred during this study. No patients were withdrawn from the study due to an AE, and no concomitant medication, other than trazodone OAD, was necessary to treat depression in any of the patients. All patients were 100.0% compliant with the study treatment.

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The evaluation of AEs, physical examinations, and measurement of vital signs (blood pressure and pulse rate) revealed no safety concerns and confirmed the well-known safety profile of trazodone OAD in patients with breast cancer and co-morbid MDD.

CONCLUSIONS:

Results of this study indicate how breast cancer patients with MDD could benefit from an antidepressant treatment, but at the same time, highlight an important cultural issue in the management of these patients. Indeed, the low number of enrolled patients suggest that the mental health issues faced by breast cancer patients are often underestimated and minimized, despite increasing data demonstrating how a holistic approach to these patients could offer effective management interventions (Fabi A, Rossi A, Mocini E, et al. An integrated care approach to improve well-being in breast cancer patients. *Current Oncology Reports*. 2024;26(4):346-358). A more interdisciplinary approach should, therefore, be considered in the management of breast cancer patients focusing particular attention on brain health.

Following 12 weeks of treatment trazodone OAD monotherapy in patients with breast cancer and co-morbid MDD, improvements were recorded in all outcomes measuring depression symptoms: the overall severity of core mood symptoms of depression; the severity of psychopathology and the global improvement; psychological distress; insomnia; circadian rhythm disturbance; maladaptive cognitive and behavioural responses to cancer; and health outcomes.

No safety concerns were noted, consistent with the well-established safety profile of trazodone OAD.

Despite the limited number of patients enrolled in this clinical study, results showed improvements in outcomes measuring symptoms of depression following 12 weeks of treatment with trazodone OAD monotherapy. This, together with a favourable safety profile, indicates that trazodone OAD monotherapy could be a suitable treatment for MDD in patients with breast cancer.