Trial In Progress: A Phase 2 Study To Assess The Efficacy And Safety Of Reparixin In Breast Cancer Related Fatigue

Denise Yardley[1], Anne Blaes[2], Alessandra Fabi[3], Rebecca Pedersini[4], Lowell L. Hart[5], Elizabeth M. Gavioli[6], Francesco Sergio[7], Enrico M. Minnella[7], Flavio Mantelli[7], Marcello Allegretti[7]

1. Sarah Cannon Research Institute, TN, USA 2. University of Minnesota, MN, USA 3. IRCCS Regina Elena National Cancer Institute,Rome, Italy 4. ASST Spedali Civili, Brescia, Italy5. Florida-South (Sarah Cannon Network), FL, USA 6. . Dompé US, Boston, USA 7. Dompé Farmaceutici SpA, Milan, Italy

BACKGROUND

- Cancer-related fatigue (CRF) occurs in nearly all patients with breast cancer. The peak of CRF is typically during treatment with over 87% of patients with breast cancer who receive taxane-based chemotherapy reporting experiencing CRF.[1]
- Poor outcomes including lower quality of life, disruption of normal daily activities, and chemotherapy interruptions and dose delays have been associated with CRF.[2-5]
- Despite the significant impact of CRF, patients are often not provided treatment recommendations for their fatigue due to lack of documented diagnosis or limited availability of effective therapy.[3,4,6]
- IL-8 (CXCL8) is a proinflammatory chemokine expressed in immune, endothelial, and tumor cells that activates a signaling cascade after binding its receptors, CXCR1/ CXCR2.[7,8]
- Dysregulated signaling at the IL-8–CXCR1/CXCR2 axis has been associated with inflammatory diseases. Specifically, higher-than-normal IL-8 levels have been associated with severe fatigue during and after completion of chemotherapy in patients with breast cancer, as well as in people with chronic fatigue syndrome.[9,10]
- Additionally, taxane-based chemotherapy is the standard treatment for metastatic breast cancer; however, paclitaxel can lead to an increase in IL-8 in patients with breast cancer, potentially worsening fatigue symptoms.[11]
- Reparixin is an investigational, oral, noncompetitive allosteric inhibitor that can potentially reduce symptoms of CRF by binding the IL-8 receptors, CXCR1/CXCR2, to mitigate inflammatory signals.[12]
- fRida, a phase 2, randomized, double-blind study (NCT01861054) evaluated the safety and efficacy of reparixin plus paclitaxel (n= 62) versus placebo plus paclitaxel (n=61) in patients with metastatic stage IV TNBC over the course of 28-day cycles of the following reparixin 1200mg or placebo tablets three times daily, in addition to paclitaxel 80 mg/m^2.[13]
- The primary endpoint, prolonged progression-free survival with reparixin was not met. However, within a post-hoc analysis, treatment-emergent fatigue was significantly more frequent in the group of patients that received placebo plus paclitaxel versus reparixin plus paclitaxel (P = 0.003)
  - Asthenia (ie, weakness or lack of energy and strength), a fatigue-associated symptom, also occurred more frequently in the placebo group.[13]

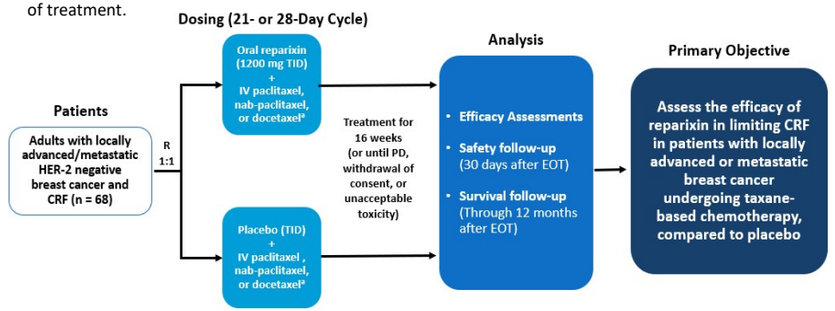
AEs in the Safety Population[a] of the fRida Study

Event, %	Reparixin plus paclitaxel (n = 61)	Placebo plus paclitaxel (n = 60)
Any TEAE	**98.4**	**95.0**
Serious TEAEs	**21.3**	**20.0**
TEAEs leading to discontinuation	**11.5**	**21.7**
Common ADRs:		
Nausea	24.6	26.7
Vomiting	13.1	3.3
Diarrhea	14.8	11.7
Fatigue	**11.5**	**28.3**
Asthenia	**11.5**	**20.0**
Alopecia	8.2	15.0
Headache	11.5	3.3
Anemia	11.5	1.7
Dysgeusia	9.8	3.3
Paresthesia	6.6	5.0
Neutopenia	8.2	3.3
Rash	11.5	5.0

[a]Patients who received at least one dose of study drug
TEAE: treatment-emergent adverse event

STUDY DESIGN

- A phase 2, multicenter, double-blind, placebo-controlled trial is ongoing to investigate the efficacy and safety of reparixin in limiting CRF in adult patients with locally advanced or metastatic breast cancer at 23 sites in the United States, Germany, and Italy. Patients will be randomized to oral reparixin 1200 mg three times a day or placebo, in addition to taxane therapy, for 16 weeks.
- An interim analysis will be conducted when half of the patients are evaluable. The planned total enrollment is 76 patients, with evaluation of at least 68 of those enrolled to provide 80% power to detect a ≥5 point difference in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score after 16 weeks of treatment.



[a]Paclitaxel or docetaxel will be administered once every 21 days, or weekly on days 1, 8, 15, and 28.
CRF, cancer-related fatigue; EOT, end of treatment; IV, intravenous; PD, progressive disease; R, randomized; TID, three times a day

Inclusion criteria	Exclusion criteria
Men or women aged ≥18 years of age	> 1 prior systemic chemotherapy for advanced disease (excluding hormonal or biological therapy either alone or in combination)
Pathologically documented locally advanced (not amenable to surgical resection) or metastatic HER2-negative breast cancer	Brain metastases that are untreated or symptomatic, or require therapy to control symptoms
Able to receive single-agent taxane-based chemotherapy (paclitaxel, nab-paclitaxel, or docetaxel) at cycle 1 of study treatment	Concomitant use of ibuprofen or CYP2C9 inhibitors/inducers or non-steroidal anti-inflammatory drugs (NSAIDs) and inability to pause during the study
Cancer-related fatigue score of 1-6 on a numerical rating scale of 0 (no fatigue) to 10 (worst fatigue) within the previous 24 hours and lasting ≥4 days	Concomitant use of medications/dietary supplements for fatigue; or use of cannabidiol (CBD) or tetrahydrocannabinol (THC)
Eastern Cooperative Oncology Group Performance Status of 0-2	Malabsorption syndrome or disease significantly affecting gastrointestinal function
Adequate organ function	Other causes of fatigue[€]
Life expectancy ≥6 months	History or evidence of neurological/psychiatric disorder
Able to swallow oral tablet	Oral morphine treatment >60 mg/day (or equivalent)
No known infection from hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)	Other invasive malignancy <5 years from study start (other than curatively treated basal or squamous cell skin cancer)
Not pregnant or lactating and follow protocol-defined contraception guidance	Contraindication to NSAIDs and/or history of GI bleeding or perforation related to prior NSAID therapy, or active/historical recurrent peptic ulcer or hemorrhage or coagulation disturbances

[€]Including, but not limited to: untreated hypothyroidism, pituitary disorder, insomnia, alcohol abuse, uncontrolled pain, chronic anemia (>grade 2), uncontrolled cardiac disease/disorder, acute infection, major depressive disorder, uncontrolled neurological disorder.
CRF, cancer-related fatigue; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; NRS, numerical rating scale

STUDY ENDPOINTS

Primary Endpoint: Change from baseline FACIT-Fatigue score at week 16

Secondary Endpoints

Quality of life assessments (measured day 1 of each cycle until EOT)
- EQ-5D-5L score
- Patient Global Impression of Severity (PGI-S) score
- Patient Global Impression of Change (PGI-C) score

Proportion of patients delaying next dose of chemotherapy due to CRF

Proportion of patients discontinuing chemotherapy due to CRF

Change in ECOG PS from baseline to day 1 of each cycle

Tumor response and survival assessments
- Overall response rate through study treatment
- Progression-free survival up to 12 months post treatment
- Overall Survival up to 12 months post treatment

Safety: Incidence of AEs and serious AEs

Pharmacokinetics

Plasma level measurements (each cycle) of reparixin, unbound reparixin, metabolites of reparixin (DF2243Y, DF2188Y, ibuprofen), and Taxanes (paclitaxel, nab-paclitaxel, docetaxel)

AE, adverse event; CRF, cancer-related fatigue; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; FACIT, Functional Assessment of Chronic Illness Therapy

STUDY INFORMATION

ClinicalTrials.gov Identifier: NCT05212701

Status: Recruiting:

Lead Investigator: Denise Yardley, MD, Sarah Cannon Research Institute

Funding: Dompé Farmaceutici SpA.

Contact usmedinfo@dompe.com for any questions or for information related to clinical trial sites.

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DISCLOSURES

EMG, FS, EMM, FM, and MA are Dompé employees.