Study title: A Phase III Double-blind Randomised Study Assessing Efficacy and Safety of **Supersinib in Combination With Paclitaxel** in Patients With Advanced Triple Negative Breast Cancer.

Protocol number: SUPER-01

Study treatment:

- Drug: Supersinib/Placebo

200 mg (1 oral tablet) given once per day (QD). Study treatment will be continued until disease progression unless there is evidence of unacceptable toxicity, or if the patient requests to stop the study treatment.

- Drug: Paclitaxel

80 mg/m2 concentrate for solution for infusion, 3 consecutive weekly infusions of 80 mg/m2 (given on Day 1 of Weeks 1, 2, and 3), followed by 1 week off-treatment within each 28-day treatment cycle. Paclitaxel treatment will be continued unless the patient experiences unacceptable toxicity that is attributed directly to treatment with paclitaxel.

Main inclusion criteria:

1. Histologically confirmed triple negative breast cancer
2. Metastatic or locally recurrent disease; locally recurrent disease most not be amenable to resection with curative intent (patient who are considered suitable for surgical or ablative techniques following potential down-staging with study treatment are not eligible)
3. ECOG PS: 0-1
4. Measurable disease according to RECIST 1.1
5. Laboratory values

    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, Platelets (PLT) $\geq 100 \times 10^9$/L Hemoglobin ≥ 10.0 g/dL
    - International Normalized Ratio (INR) ≤ 1.5
    - Creatinine Clearance ≥ 35 mL/min using Cockcroft-Gault formula
    - Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) $< 3 \times$ Upper limit of normal (ULN). If the patient has

liver metastases, ALT and AST ≤ 5 × ULN is acceptable. Total bilirubin < 1.5 x ULN

- Fasting plasma glucose (FPG) ≤ 7.7 mmol/L and Glycosylated Hemoglobin (HbA1c) ≤ 7%
- Fasting Serum amylase ≤ 2 × ULN, Fasting Serum lipase ≤ 2x ULN

Main exclusion criteria:

1. Prior Chemotherapy in the neoadjuvant or adjuvant setting within 6 months from the end of chemotherapy to the date of randomization; taxane chemotherapy in the neoadjuvant or adjuvant setting within 12 months from the end of chemotherapy to the start of randomization
2. Prior systematic therapy for inoperable locally advanced or metastatic disease
3. Pre-existing sensory or motor polyneuropathy more than grade 1
4. Participant has not recovered from all toxicities related to prior anticancer therapies to Grade ≤1; with the exception of alopecia
3. Any of the following cardiac criteria at screening:
    - Any clinically important cardiac arrythmias, high-grade AV block in place
    - Corrected QT interval by Fridericia (QTcF) >460 msec
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for Torsades de Pointes, congenital long QT syndrome, family history of long QT syndrome or any concomitant medication known to prolong the QT interval
    - Any of the following in the last 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure New York Heart Association (NYHA) grade ≥2
    - Uncontrolled hypotension - SBP <90 mmHg and/or DBP <50 mmHg and Uncontrolled hypertension –SBP ≥ 160 mmHg and/or DBP ≥ 100 mm Hg

4. Cardiac ejection more than <55% measured by ECHO or MUGA scan

5. Patients with diabetes mellitus type I or diabetes mellitus type II requiring insulin treatment

6. Participant has a history of acute pancreatitis within 1 year prior to screening or past medical history of chronic pancreatitis

7. Potent inhibitors or inducers of CYP3A4 within 2 weeks prior to the first dose of study treatment (3 weeks for St John's wort), or drugs that are sensitive to CYP3A4 inhibition within 1 week prior to the first dose of study treatment.

8. Participant is currently receiving or has received systemic corticosteroids, toppical and inhalation corticosteroids are allowed

9. Any other medical condition than will interfere with participation patient in the study

10. Currently pregnant (confirmed with positive pregnancy test) or breast-feeding patients

Patient A-A, DOB 2.2.1952

Anamnesis: Patient palpated lump in left breast in february 2018. Tru cut biopsy from 25.2.2018 confirmed invasive breast cancer. On 12.3.2018 patient underwent quadrentectomy and exenteration of axilla- left. Histology : ER 50%, PR 0%, HER-2 IHC 3+, grade 2, tumor 22 mm (T2), 17 lymph nodes were exenterated, 12 were positive (N3). Bone scan 1.3.2018 negative, CT chest, abdomen and pelvis from 6.3.2018 no distant metastasis were present (M0), stage IIIA. Patient received adjuvat chemotherapy TAC (paclitaxel adriamycin, cyclophosphamide) from 21.3.2018-2.7.2018, radiotherapy for left breast and left axillae 50 Gy 21.7.-21.8.2021, letrozole from 5.8.2018.

On 25.9.2022 CA-125 increased, so **CT** was performed on 21.12.2022-metastasis in liver, lung and mediastinal lymph nodes. Liver lymph nodes were multiple with max 9x9 mm, lung lymph nodes multiple 8x9 mm, mediastinal lymph nodes 16x11 mm, 13x10 mm.

Bone scan from 3.10.2022 negative

Gynecology anamnesis: menstruation from 1966, 3x delivery, healthy children, menopause as 52 years old

Medical history: hypertension gr 1 from from 2017, no tretment, anxiety and depression gr 2 from october 2022 (Tritico 150mg po QD) from 18 .2.2021, tumour related pain gr 2 from aug 2022 (Novalgin po 500 mg PRN), hypothyreoidism gr 2 from 1998 (Euthyrox p.o. 50 ug QD), polyneuropathy sensory from paclitaxel gr 1 6/2018-10/2021, anopyrin-prophylaxis thrombosis 100 mg po from 2017, Diabettes mellitus II from 5/2018 (Metformin XR po 1g QD)

Drug anamnesis:

Labs from 5.1.2022-Hgb 98 g/L, PLT 120 10^9/L, ANC 1,9, 10^9/L, hemocoagulation within normal limits, ALT 0,72 ukat/L (ULN 0,18 ukat/L), AST 2,3 ukat/L (ULN 0,57 ukat/L) Bilirubin 34,1 umol/L (ULN 31 umol/L), amylase 0,8 ukat/L ULN (1,97 ukat/L), lipase 0,6 ukat/L (ULN0,88 ukat/L), glucose 8,2 mmol/L, HbA1c 7 %, Creatinine clearance 50 ml/min,

Physical exam: NCS

Vital signs: 120/75, HR 82, 36,3 **C, respiration 16/min**

Weight: 80 kg, **Height:** 173 cm

ECG: QtCF 475 msec, HR 82, withoout ischemic changes, sinus rhytm

ECHO: EF 65%, NCS