1. NAME OF THE MEDICINAL PRODUCT

TUKYSA 50 mg
TUKYSA 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TUKYSA 50 mg film-coated tablets
Each film-coated tablet contains 50 mg of tucatinib.

TUKYSA 150 mg film-coated tablets
Each film-coated tablet contains 150 mg of tucatinib.

Excipients with known effect
Each 150 mg film-coated tablet contains 27.64 mg of sodium and 30.29 mg of potassium.
A 300 mg dose of TUKYSA contains 55.3 mg of sodium and 60.6 mg of potassium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

TUKYSA 50 mg film-coated tablets

Round, yellow, film-coated tablet, debossed with “TUC” on one side and “50” on the other side. The 50 mg tablet has a diameter of approximately 8 mm.

TUKYSA 150 mg film-coated tablets

Oval-shaped, yellow, film-coated tablet, debossed with “TUC” on one side and “150” on the other side. The 150 mg tablet is approximately 17 mm in length and 7 mm in width.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.

4.2 Posology and method of administration

Treatment with TUKYSA should be initiated and supervised by a physician experienced in the administration of anti–cancer medicinal products.

Posology

The recommended dose is 300 mg tucatinib (two 150 mg tablets) taken twice daily continuously in combination with trastuzumab and capecitabine, at doses described in table 1. Refer to the summary of product characteristics (SmPC) for co-administered trastuzumab and capecitabine for additional information. The treatment components can be administered in any order.

Table 1: Recommended dosing

Treatment	Dose	Treatment days	Timing relative to food intake
Tucatinib	300 mg orally twice daily	Continuously	With or without a meal
Capecitabine	1000 mg/m^2 orally twice daily	Days 1 to 14 every 21 days	Within 30 minutes after a meal
Trastuzumab			
Intravenous dosing			
Initial dose	8 mg/kg intravenously	Day 1	
Subsequent doses	6 mg/kg intravenously	Every 21 days	Not applicable
OR			
Subcutaneous dosing	600 mg subcutaneously	Every 21 days	

Treatment with TUKYSA should be continued until disease progression or unacceptable toxicity.

Missed dose
In the case of a missed dose, the patient should take their next dose at the regularly scheduled time.

Dose modification
The recommended tucatinib dose modifications for patients with adverse reactions (see section 4.8) are provided in Tables 2 and 3. Refer to the SmPC for co-administered trastuzumab and capecitabine for dose modifications for toxicities suspected to be caused by those therapies.

Table 2: Recommended tucatinib dose reductions for adverse reactions

Dose level	Tucatinib dose
Recommended starting dose	300 mg twice daily
First dose reduction	250 mg twice daily
Second dose reduction	200 mg twice daily
Third dose reduction	150 mg twice daily[1]

1. TUKYSA should be permanently discontinued in patients unable to tolerate 150 mg orally twice daily.

Table 3: Recommended tucatinib dose modifications for adverse reactions

Adverse Reaction	**Severity**[1]	**Tucatinib dosage modification**
Diarrhoea	Grade 1 and 2	No dose modification is required.
	Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the same dose level.
	Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level.
	Grade 4	Permanently discontinue tucatinib.
Increased ALT, AST or bilirubin[2]	Grade 1 bilirubin (> ULN to 1.5 x ULN)	No dose modification is required.
	Grade 2 bilirubin (> 1.5 to 3 × ULN)	Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the same dose level.
	Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> 3 to 10 × ULN)	Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level.
	Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)	Permanently discontinue tucatinib.
	ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN	Permanently discontinue tucatinib.
Other adverse reactions	Grade 1 and 2	No dose modification is required.
	Grade 3	Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level.
	Grade 4	Permanently discontinue tucatinib.

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Co-administration with CYP2C8 inhibitors

Concomitant use with strong CYP2C8 inhibitors should be avoided. If coadministration with a strong CYP2C8 inhibitor cannot be avoided, the starting tucatinib dose should be reduced to 100 mg orally

twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, the tucatinib dose that was taken prior to initiating the inhibitor should be resumed (see section 4.4 and section 4.5). Monitoring for TUKYSA toxicity should be increased when administered with moderateCYP2C8 inhibitors.

Special populations

Elderly

No dose adjustment is required in patients aged ≥ 65 years (see section 5.2). Tucatinib has not been investigated in patients above the age of 80 years.

Renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment (seesection 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2).For patients with severe hepatic impairment (Child-Pugh C), a reduced starting dose of 200 mg orally twice daily is recommended.

Paediatric population

The safety and efficacy of TUKYSA in paediatric patients have not been established. No data are available.

Method of administration

TUKYSA is for oral use. The tablets should be swallowed whole.
No information is available regarding crushing, splitting, or chewing of tablets.
TUKYSA should be taken approximately 12 hours apart, at the same time every day, with or without a meal. TUKYSA may be taken at the same time with capecitabine.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Laboratory Tests

Increased ALT, AST, and bilirubin

Increased ALT, AST, and bilirubin have been reported during treatment with tucatinib (see section 4.8). ALT, AST, and bilirubin should be monitored every three weeks or as clinically indicated. Based on the severity of the adverse reaction, treatment with tucatinib should be interrupted,then dose reduced or permanently discontinued (see section 4.2).

Increased creatinine without impaired renal function

Increase in serum creatinine (30% mean increase) has been observed due to inhibition of renal tubulartransport of creatinine without affecting glomerular function (see section 4.8). Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

Diarrhoea

Diarrhoea, including severe events such as dehydration, hypotension, acute kidney injury and death, has been reported during treatment with tucatinib (see section 4.8). If diarrhoea occurs, antidiarrheals should be administered as clinically indicated. For Grade ≥3 diarrhoea, treatment with tucatinib should be interrupted, then dose reduced or permanently discontinued (see section 4.2). Diagnostic tests should be performed as clinically indicated to exclude infectious causes of Grade 3 or 4 diarrhoea or diarrhoea of any grade with complicating features (dehydration, fever, neutropenia).

Embryo-foetal toxicity

Based on findings from animal studies and its mechanism of action, tucatinib may cause harmful effects to the foetus when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rabbits during organogenesis caused foetal abnormalities in rabbits at maternal exposures similar to the clinical exposures at the recommended dose.
Pregnant women should be advised of the potential risk to a foetus. Women of childbearing potential should be advised to use effective contraception during and up to at least 1 week after the last dose of treatment (see section 4.6). Male patients with female partners of childbearing potential should also be advised to use an effective method of contraception during and up to at least 1 week after the last dose of treatment.

Sensitive CYP3A substrates

Tucatinib is a strong CYP3A inhibitor. Thus, tucatinib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased plasma concentrations of the other product (see section 4.5). When tucatinib is co-administered with other medicinal products, the SmPC for the other product should be consulted for the recommendations regarding co-administration with CYP3A inhibitors. Concomitant treatment of tucatinib with CYP3A substrates when minimal concentration changes may lead to serious or life–threatening adverse reactions should be avoided. If concomitant use is unavoidable, the CYP3A substrate dosage should be reduced in accordance with the concomitant medicinal product SmPC.

P-gp substrates

Concomitant use of tucatinib with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Dose reduction of P-gp substrates (including sensitive intestinal substrate such as dabigatran) should be considered in accordance with the concomitant medicine SmPC and P-gp substrates should be administered with caution when minimal concentration changes may lead to serious or life-threatening toxicities.

Strong CYP3A/moderate CYP2C8 inducers

Concomitant use of tucatinib with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib concentrations, which may reduce tucatinib activity. Concomitant use with a strong CYP3A inducer or moderate CYP2C8 inducer should be avoided.

Strong/moderate CYP2C8 inhibitors

Concomitant use of tucatinib with a strong CYP2C8 inhibitor increased tucatinib concentrations, which may increase the risk of tucatinib toxicity. Concomitant use with strong CYP2C8 inhibitors should be avoided (see section 4.2).
There are no clinical data on the impact of concomitant use of moderate CYP2C8 inhibitors on tucatinib concentrations. Monitoring for tucatinib toxicity should be increased with moderate CYP2C8 inhibitors.

Information about excipients

This medicinal product contains 55.3 mg sodium per 300 mg dose. This is equivalent to 2.75% of the recommended maximum daily dietary intake of sodium for an adult.

This medicinal product contains 60.6 mg potassium per 300 mg dose. This should be taken into consideration for patients who have impaired kidney function or are on a controlled potassium diet (diet with low potassium content).

4.5 Interaction with other medicinal products and other forms of interaction

Tucatinib is primarily metabolised by CYP2C8. Tucatinib is a metabolism-based inactivator of CYP3A and inhibits renal transporters of metformin and creatinine. Tucatinib is a substrate of P–gp.

Effects of other medicinal products on tucatinib

CYP3A/CYP2C8 inducers
A clinical drug interaction study found that co-administration of a single dose of 300 mg tucatinib with rifampicin (a strong CYP3A and moderate CYP2C8 inducer) resulted in a reduction in tucatinib concentrations (0.6-fold C_{max} (90% CI: 0.5, 0.8) and 0.5-fold AUC (90% CI: 0.4, 0.6)).
Co-administration of tucatinib with strong CYP3A or moderate CYP2C8 inducers such as rifampicin, phenytoin, St. John's wort, or carbamazepine should be avoided as this may result in decreased activity of tucatinib (see section 4.4).

CYP2C8 inhibitors
A clinical drug interaction study found that co-administration of a single dose of 300 mg tucatinib with gemfibrozil (a strong CYP2C8 inhibitor) resulted in an increase in tucatinib concentrations (1.6-fold C_{max} (90% CI: 1.5, 1.8) and 3.0-fold AUC (90% CI: 2.7, 3.5)). Co-administration of tucatinib with strong CYP2C8 inhibitors such as gemfibrozil should be avoided as this may result in increased risk of tucatinib toxicity (see section 4.4).

CYP3A inhibitors
A clinical drug interaction study found that co-administration of a single dose of 300 mg tucatinib with itraconazole (a strong CYP3A inhibitor) resulted in an increase in tucatinib concentrations (1.3-fold C_{max} (90% CI: 1.2, 1.4) and 1.3-fold AUC (90% CI: 1.3, 1.4)). No dose adjustment is required.

Proton pump inhibitors
Based on clinical drug interaction studies conducted with tucatinib, no drug interactions were observed when tucatinib is combined with omeprazole (a proton pump inhibitor). No dose adjustment is required.

Effects of tucatinib on other medicinal products

CYP3A substrates
Tucatinib is a strong CYP3A inhibitor. A clinical drug interaction study found that co-administration of tucatinib with midazolam (a sensitive CYP3A substrate) resulted in an increase in midazolam concentrations (3.0-fold C_{max} (90% CI: 2.6, 3.4) and 5.7-fold AUC (90% CI: 5.0, 6.5)).
Co-administration of tucatinib with sensitive CYP3A substrates such as alfentanil, avanafil, buspirone, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, and vardenafil may increase their systemic exposures which may increase the toxicity associated with a CYP3A substrate. Concomitant use of tucatinib with CYP3A substrates, when minimal concentration changes may lead to serious or life-threatening toxicities, should be avoided. If concomitant use is unavoidable, the CYP3A substrate dosage should be decreased in accordance with the concomitant medicinal product SmPC.

P-gp substrates
A clinical drug interaction study found that co-administration of tucatinib with digoxin (a sensitive P-gp substrate) resulted in an increase in digoxin concentrations (2.4-fold C_{max} (90% CI: 1.9, 2.9) and 1.5-fold AUC (90% CI: 1.3, 1.7)). Concomitant use of tucatinib with a P-gp substrate may increase the plasma concentrations of the P-gp substrate, which may increase the toxicity associated with the P-gp substrate. Dose reduction of P-gp substrates (including sensitive intestinal substrate such as dabigatran) should be considered in accordance with the concomitant medicine SmPC and P-gp substrates should be administered with caution when minimal concentration changes may lead to serious or life-threatening toxicities (see section 4.4).

CYP2C8 substrates
A clinical drug interaction study found that co-administration of tucatinib with repaglinide (a CYP2C8 substrate) resulted in an increase in repaglinide concentrations (1.7-fold C_{max} (90% CI: 1.4, 2.1) and 1.7-fold AUC (90% CI: 1.5, 1.9)). No dose adjustment is required.

MATE1/2K substrates
A clinical drug interaction study found that co-administration of tucatinib with metformin (a MATE1/2-K substrate) resulted in an increase in metformin concentrations (1.1-fold C_{max} (90% CI: 1.0, 1.2) and 1.4-fold AUC (90% CI: 1.2, 1.5)). Tucatinib reduced the renal clearance of metformin without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C. No dose adjustment is required.

CYP2C9 substrates
Based on clinical drug interaction studies conducted with tucatinib, no drug interactions were observed when tucatinib is combined with tolbutamide (a sensitive CYP2C9 substrate). No dose adjustment is required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on findings in animals, tucatinib may cause harmful pharmacological effects when administered to women during pregnancy and/or on the foetus/newborn child. Women of childbearing potential should be advised to avoid becoming pregnant and to use effective contraception during and up to at least 1 week after treatment. Male patients with female partners of childbearing potential should also be advised to use effective contraception during and up to at least 1 week after treatment (see section 4.4).

Please also refer to section 4.6 of the prescribing information for trastuzumab and capecitabine.

Pregnancy

There are no data from the use of tucatinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). TUKYSA should not be used during pregnancy unless the clinical condition of the woman requires treatment with tucatinib. The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with tucatinib. If the patient becomes pregnant during treatment, the potential hazard to the foetus/newborn child must be explained to the patient.

Breast-feeding

It is unknown whether tucatinib/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with TUKYSA. Breast-feeding may be resumed 1 week after treatment.

Fertility

No fertility studies in men or women have been conducted. Based on findings from animal studies, tucatinib may impair fertility in females of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

TUKYSA has no or negligible influence on the ability to drive and use machines. The clinical status of the patient should be considered when assessing the patient's ability to perform tasks that require judgment, motor, or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported Grade 3 and 4 adverse reactions (≥5%) during treatment are diarrhoea (13%), ALT increased (6%) and AST increased (5%).
Serious adverse reactions occurred in 29% of patients treated with tucatinib, and include diarrhoea (4%), vomiting (3%), and nausea (2%).
Adverse reactions leading to discontinuation of TUKYSA occurred in 6% of patients; the most common adverse reactions leading to discontinuation were diarrhoea (1%) and ALT increased (1%).
Adverse reactions leading to dose reduction of TUKYSA occurred in 23% of patients; the most common adverse reactions leading to dose reduction were diarrhoea (6%), ALT increased (5%), and AST increased (4%).

Tabulated list of adverse reactions

The data summarised in this section reflect exposure to TUKYSA in 431 patients with locally advanced unresectable or metastatic HER2-positive breast cancer who received TUKYSA in combination with trastuzumab and capecitabine across two studies, HER2CLIMB and ONT-380-005 (see section 5.1). The median duration of exposure to TUKYSA across these studies was 7.4 months (range, <0.1, 43.6).

The adverse reactions observed during treatment are listed in this section by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 4. Adverse reactions

System organ class	Frequency	Adverse reaction
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea, Nausea, Vomiting, Stomatitis[1]
Skin and subcutaneous tissue disorders	Very common	Rash[2]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
Investigations	Very common	AST increase, ALT increase, Blood bilirubin increased[3], weight decrease

1. Stomatitis includes stomatitis, oropharyngeal pain, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysaesthesia, tongue ulceration, aphthous ulcer
2. Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema and skin toxicity
3. Blood bilirubin increased also includes hyperbilirubinemia

Description of selected adverse reactions

Increased ALT, AST, or bilirubin
In HER2CLIMB, increased ALT, AST or bilirubin occurred in 41% of patients treated with tucatinib in combination with trastuzumab and capecitabine. Grade 3 and above events occurred in 9% of patients. Increased ALT, AST or bilirubin led to dose reduction in 9% of patients and treatment discontinuation in 1.5% of patients. The median time to onset of any grade increased ALT, AST, or bilirubin was 37 days; 84% of events resolved, with a median time to resolution of 22 days. Monitoring and dose modification (including discontinuation) should be considered (see section 4.4).

Diarrhoea
In HER2CLIMB, diarrhoea occurred in 82% of patients treated with tucatinib in combination with trastuzumab and capecitabine. Grade 3 and above diarrhoea events occurred in 13% of patients. Two patients who developed Grade 4 diarrhoea subsequently died, with diarrhoea as a contributor to death. Diarrhoea led to dose reduction in 6% of the patients and treatment discontinuation in 1% of the patients. The median time to onset of any grade diarrhoea was 12 days; 81% of diarrhoea events resolved, with a median time to resolution of 8 days. Prophylactic use of antidiarrheals was not required. Antidiarrheal medicinal products were used in less than half of the treatment cycles where diarrhoea events were reported. The median duration of antidiarrheal use was 3 days per cycle (see section 4.4).

Increased creatinine without impaired renal function
Increase in serum creatinine has been observed in patients treated with tucatinib due to inhibition of renal tubular transport of creatinine without affecting glomerular function. In clinical studies, increases in serum creatinine (30% mean increase) occurred within the first cycle of tucatinib, remained elevated but stable throughout treatment and were reversible upon treatment discontinuation.

Special populations

Elderly
In the HER2CLIMB study, 82 patients who received tucatinib were ≥65 years, of whom 8 patients were ≥75 years. The incidence of serious adverse reactions was 34% in patients ≥ 65 years compared to 28% in patients < 65 years. There were too few patients ≥75 years to assess differences in safety.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il

4.9 Overdose

There is no specific antidote, and the benefit of haemodialysis in the treatment of tucatinib overdose is unknown. In the event of an overdose, treatment with tucatinib should be withheld and general supportive measures should be applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EH03.

Mechanism of action

Tucatinib is a reversible, potent and selective tyrosine kinase inhibitor of HER2. In cellular signalling assays, tucatinib is >1000-fold more selective for HER2 compared to epidermal growth factor receptor. *In vitro*, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream cell signalling and cell proliferation, and induces death in HER2 driven tumour cells. *In vivo*, tucatinib inhibits the growth of HER2 driven tumours and the combination of tucatinib and trastuzumab showed enhanced anti-tumour activity *in vitro* and *in vivo* compared to either medicinal product alone.

Pharmacodynamic effects

Cardiac electrophysiology
Multiple doses of tucatinib 300 mg twice a day did not have an effect on the QTc interval in a TQT study in healthy subjects.

Clinical efficacy and safety

The efficacy of tucatinib in combination with trastuzumab and capecitabine was evaluated in a randomised, double-blind, placebo-controlled, active comparator, global study (HER2CLIMB). Patients enrolled had locally advanced unresectable or metastatic HER2-positive breast cancer, with or without brain metastases, and had prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. HER2 overexpression or amplification was confirmed by central laboratory analysis.
Patients with brain metastases, including those with untreated or progressing lesions, were eligible to enroll provided they were neurologically stable and did not require immediate brain radiation or surgery. Patients who required immediate local intervention could receive local therapy and be subsequently enrolled. The study included patients with untreated brain metastases and patients with treated brain metastases that were either stable or progressing since last brain radiation or surgery. Patients were excluded from the study if they received systemic corticosteroids (≥2 mg total daily of dexamethasone or equivalent) for control of symptoms of CNS metastases <28 days prior to the first dose of study treatment. The study also excluded patients with leptomeningeal disease. Patients who had previously been treated with HER2 tyrosine kinase inhibitors were excluded with the exception of patients who received lapatinib for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity. For patients with hormone receptor positive tumors, endocrine therapy was not permitted as concomitant therapy, with the exception of gonadotropin-releasing hormone agonists used for ovarian suppression in premenopausal women.

A total of 612 patients were randomised 2:1 to receive tucatinib in combination with trastuzumab and capecitabine (N=410) or placebo in combination with trastuzumab and capecitabine (N=202). Randomisation was stratified by the presence or history of brain metastases (yes *vs.* no), Eastern Cooperative Oncology Group (ECOG) performance status (0 *vs.* 1), and region (U.S., Canada, or rest of world).

Patient demographics were balanced between treatment arms. The median age was 54 years (range, 25 to 82); 116 (19%) patients were aged 65 years or older. 444 patients were white (73%) and 607 were female (99%). 314 patients (51%) had an ECOG performance status of 1 and 298 patients (49%) had an ECOG performance status of 0. Sixty percent had oestrogen and/or progesterone receptor-positive disease. Forty-eight percent of patients had a presence or history of brain metastases; of these, 23% had untreated brain metastases, 40% had treated but stable brain metastases, and 37% had treated but radiographically progressing brain metastases. Additionally, 49% of patients had lung metastases, 35% had liver metastases, and 14% had skin metastases. Patients had a median of 4 (range, 2 to 17) prior lines of systemic therapy and a median of 3 (range, 1 to 14) prior lines of systemic therapy in the metastatic setting. All patients received prior trastuzumab-based treatments and trastuzumab emtansine, while all but two patients had prior pertuzumab-based treatment.

Tucatinib or placebo, 300 mg orally twice per day, was administered until disease progression or unacceptable toxicity. Trastuzumab was administered intravenously as a loading dose of 8 mg/kg on Day 1 of Cycle 1, followed by a maintenance dose of 6 mg/kg on Day 1 of each subsequent 21-day cycle. An alternate dosing option for trastuzumab was a fixed dose of 600 mg administered subcutaneously on Day 1 of each 21-day cycle. Capecitabine, 1000 mg/m^2 orally twice per day, was administered on Days 1 through 14 of each 21-day cycle.

The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) in the first 480 randomized patients. In this population, the median duration of exposure to tucatinib was 7.3 months (range <0.1, 35.1) for patients on the tucatinib + trastuzumab + capecitabine arm compared to 4.4 months (range <0.1, 24.0) of placebo for patients on the placebo + trastuzumab + capecitabine arm. Similar differences in exposure to trastuzumab and capecitabine were observed. Secondary endpoints were evaluated in all randomized patients (N=612) and included overall survival (OS), PFS among patients with a history or presence of brain metastases ($PFS_{BrainMets}$) and confirmed objective response rate (ORR).

Efficacy results are summarized in Table 5 and Figures 1 to 3.

Primary and key secondary endpoint results were consistent across pre-specified subgroups: hormone receptor status, presence or history of brain metastases, ECOG status, and region. PFS as determined by the investigator was consistent with PFS as assessed by BICR.

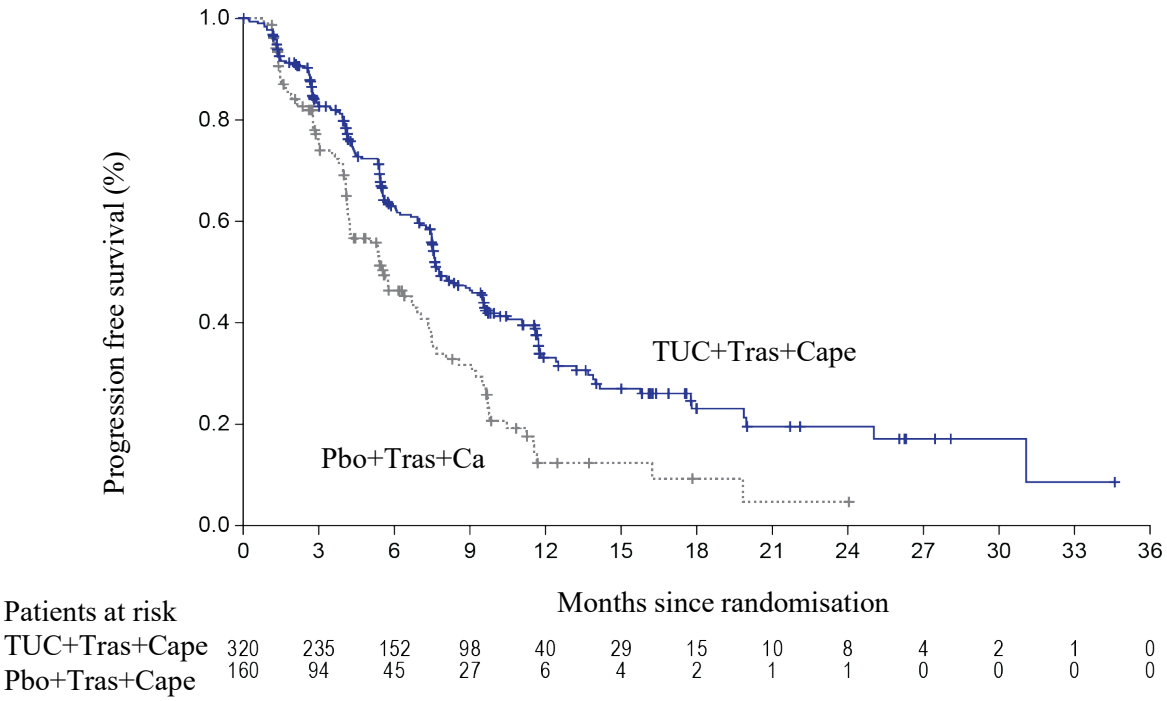
Table 5. Efficacy results from the HER2CLIMB study

	Tucatinib + Trastuzumab + Capecitabine	Placebo + Trastuzumab + Capecitabine
PFS[1]	**N=320**	**N=160**
Number of events (%)	178 (56)	97 (61)
Hazard ratio (95% CI)[2]	0.54 (0.42, 0.71)	
P-value[3]	<0.00001	
Median (months) (95% CI)	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)
OS	**N=410**	**N=202**
Number of deaths, n (%)	130 (32)	85 (42)
Hazard ratio (95% CI)[2]	0.66 (0.50, 0.87)	
P-value[3]	0.00480	
Median OS, months (95% CI)	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)
$PFS_{BrainMets}$[4]	**N=198**	**N=93**
Number of events (%)	106 (53.5)	51 (54.8)
Hazard ratio (95% CI)[2]	0.48 (0.34, 0.69)	
P-value[3]	<0.00001	
Median (months) (95% CI)	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)
Confirmed ORR for Patients with Measurable Disease	**N=340**	**N=171**
ORR (95% CI)[5]	40.6 (35.3, 46.0)	22.8 (16.7, 29.8)
P-value[6]	0.00008	
CR (%)	3 (0.9)	2 (1.2)
PR (%)	135 (39.7)	37 (21.6)
DOR		
Median DOR in months (95% CI) [7]	8.3 (6.2, 9.7)	6.3 (5.8, 8.9)

BICR=blinded independent central review; CI=confidence interval; PFS=progression-free survival; OS=overall survival; ORR=objective response rate; CR=complete response; PR=partial response; DOR=duration of response.

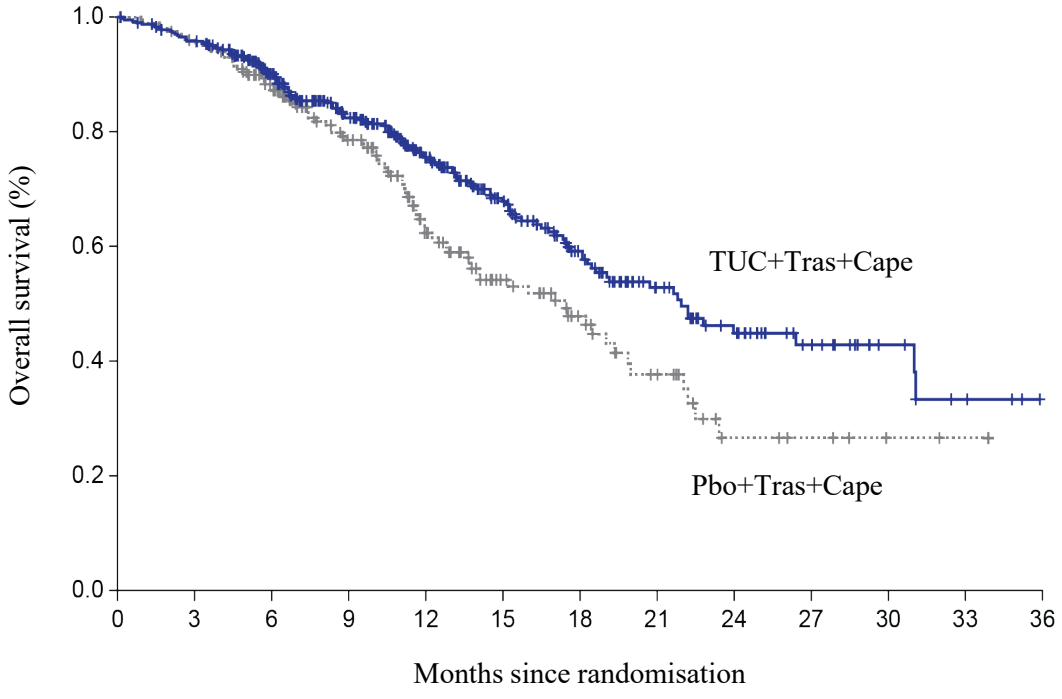
1. Primary PFS analysis conducted in first 480 randomized patients. PFS based on Kaplan-Meier analyses.
2. Hazard ratio and 95% confidence intervals are based on stratified Cox proportional hazards regression model controlling for stratification factors (presence or history of brain metastases, Eastern Cooperative Oncology Group (ECOG) status, and region of world)
3. Two-sided p-value based on re-randomization procedure controlling for stratification factors
4. Analysis includes patients with history or presence of parenchymal brain metastases at baseline, including target and non-target lesions. Does not include patients with dural lesions only.
5. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method
6. Cochran-Mantel-Haenszel test controlling for stratification factors (presence or history of brain metastases, Eastern Cooperative Oncology Group (ECOG) status, and region of world)
7. Calculated using the complementary log-log transformation method

Figure 1. Kaplan-Meier curves of progression-free survival (per BICR)



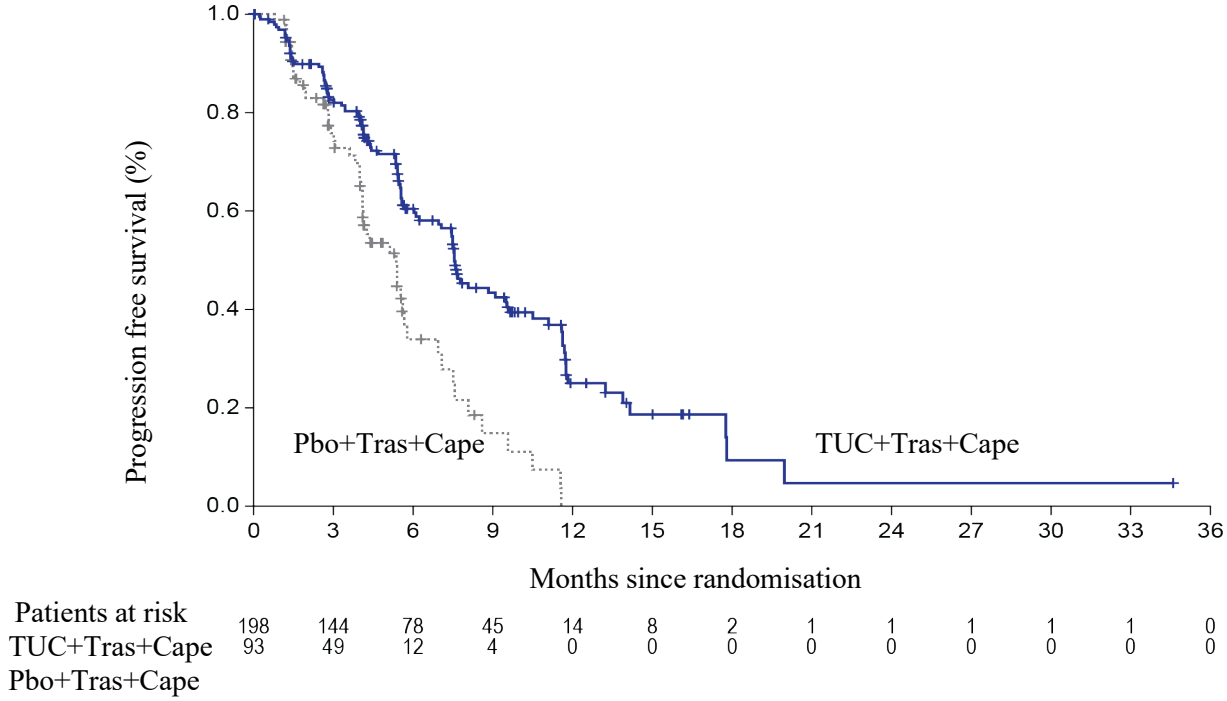
Patients at risk													
TUC+Tras+Cape	320	235	152	98	40	29	15	10	8	4	2	1	0
Pbo+Tras+Cape	160	94	45	27	6	4	2	1	1	0	0	0	0

Figure 2. Kaplan-Meier curves of overall survival



Patients at risk													
TUC+Tras+Cape	410	388	322	245	178	123	80	51	34	20	10	4	0
Pbo+Tras+ Cape	202	191	160	119	77	48	32	19	7	5	2	1	0

Figure 3. Kaplan-Meier curves of progression-free survival (per BICR) in patients with brain metastases



5.2 Pharmacokinetic properties

Plasma tucatinib exposure (AUC_{inf} and C_{max}) demonstrated dose proportional increases at oral doses from 50 to 300 mg (0.17 to 1 time the recommended dose). Tucatinib exhibited 1.7-fold accumulation for AUC and 1.5-fold accumulation for C_{max} following administration of 300 mg tucatinib twice daily for 14 days. Time to steady-state was approximately 4 days.

Absorption

Following a single oral dose of 300 mg tucatinib, the median time to peak plasma concentration was approximately 2.0 hours (range 1.0 to 4.0 hours).

Effects of food
Following administration of a single dose of tucatinib in 11 subjects after a high-fat meal (approximately 58% fat, 26% carbohydrate, and 16% protein), the mean AUC_{inf} increased by 1.5-fold, the T_{max} shifted from 1.5 hours to 4.0 hours, and C_{max} was unaltered. The effect of food on the pharmacokinetics of tucatinib was not clinically meaningful, thus tucatinib may be administered without regard to food.

Distribution

The apparent volume of distribution of tucatinib was approximately 1670 L in healthy subjects after a single dose of 300 mg. The plasma protein binding was 97.1% at clinically relevant concentrations.

Biotransformation

Tucatinib is metabolized primarily by CYP2C8 and to a lesser extent via CYP3A and aldehyde oxidase.

In Vitro drug interaction studies

Tucatinib is a substrate of CYP2C8 and CYP3A.
Tucatinib is a reversible inhibitor of CYP2C8 and CYP3A and a time-dependent inhibitor of CYP3A, at clinically relevant concentrations.
Tucatinib has low potential to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and UGT1A1 at clinically relevant concentrations.
Tucatinib is a substrate of P-gp and BCRP. Tucatinib is not a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP.
Tucatinib inhibits MATE1/MATE2-K-mediated transport of metformin and OCT2/MATE1-mediated transport of creatinine. The observed serum creatinine increase in clinical studies with tucatinib is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1.

Elimination

Following a single oral dose of 300 mg, tucatinib is cleared from plasma with a geometric mean half-life of approximately 8.5 hours and apparent clearance of 148 L/h in healthy subjects.

Excretion
Tucatinib is predominantly eliminated by the hepatobiliary route and is not appreciably renally eliminated. Following a single oral dose of 300 mg ^{14}C-tucatinib, approximately 85.8% of the total radiolabelled dose was recovered in faeces (15.9% of the administered dose as unchanged tucatinib) and 4.1% in urine with an overall total recovery of 89.9% within 312 hours post-dose. In plasma, approximately 75.6% of the plasma radioactivity was unchanged, 19% was attributed to identified metabolites, and approximately 5% was unassigned.

Special populations

Based on population pharmacokinetic analysis according to demographic characteristics, age (<65 years (N=211); ≥ 65 years (N=27)), albumin (25.0 to 52.0 g/L), creatinine clearance (CLcr 60 to 89 mL/min (N=89); CLcr 30 to 59 mL/min (N=5)), body weight (40.7 to 138.0 kg), and race (White (N=168), Black (N=53), or Asian (N=10)) did not have a clinically meaningful effect on tucatinib exposure. There are no data for subjects with severely impaired renal function.

Renal impairment
The pharmacokinetics of tucatinib have not been evaluated in a dedicated renal impairment study.

Hepatic impairment
Mild (Child–Pugh A) and moderate (Child-Pugh B) hepatic impairment had no clinically relevant effect on tucatinib exposure. Tucatinib AUC_{inf} was increased by 1.6-fold in subjects with severe (Child-Pugh C) hepatic impairment compared to subjects with normal hepatic function. There are no data for breast cancer patients with severely impaired hepatic function.

5.3 Preclinical safety data

Carcinogenicity studies have not been conducted with tucatinib.
Tucatinib was not clastogenic or mutagenic in the standard battery of genotoxicity assays.

In repeat-dose toxicity studies in rats, decreased corpora lutea/corpus luteum cyst, increased interstitial cells of the ovary, atrophy of the uterus, and mucification of the vagina were observed at doses of ≥ 6 mg/kg/day administered twice daily, equivalent to 0.09 times the human exposure based on AUC_{0-12} at the recommended dose. No histological effects were observed on male or female reproductive tracts in cynomolgus monkeys or on male reproductive tracts in rats at doses resulting in exposures up to 8 times (in monkey) or 13 times (in rat) the human exposure at the recommended dose based on AUC_{0-12}.

Embryo-foetal development studies were conducted in rabbits and rats. In pregnant rabbits, increased resorptions, decreased percentages of live foetuses, and skeletal, visceral, and external malformations were observed in foetuses at ≥90 mg/kg/day; at this dose, maternal exposure is approximately equivalent to the human exposure at the recommended dose based on AUC. In pregnant rats, decreased maternal body weight and body weight gain were observed at doses of ≥90 mg/kg/day. Foetal effects of decreased weights and delayed ossification were observed at ≥120 mg/kg/day; at this dose, maternal exposure is approximately 6-fold higher than human exposure at the recommended dose based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone
Microcrystalline cellulose
Crospovidone
Sodium chloride
Potassium chloride
Sodium hydrogen carbonate
Silica, colloidal anhydrous
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide
Macrogol 4000
Talc
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

oPA/ALU/PVC blister sealed with aluminium foil.

TUKYSA 50 mg film-coated tablets

Each carton contains 88 film-coated tablets (11 blisters with 8 tablets each).

TUKYSA 150 mg film-coated tablets

Each carton contains 84 film-coated tablets (21 blisters with 4 tablets each).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Marketing Authorization Number

TUKYSA 50 mg film-coated tablets: 170 32 36950 99
TUKYSA 150 mg film-coated tablets: 170 33 36951 99

7. Manufacturer

Seagen B.V., Schiphol, The Netherlands

8. License Holder

Merck Sharp & Dohme (Israel – 1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon

Revised in September 2022 according to MOHs guidelines