HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TUKYSA safely and effectively. See full prescribing information for TUKYSA.

TUKYSA™ (tucatinib) tablets, for oral use
Initial U.S. Approval: 2020

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**INDICATIONS AND USAGE**

TUKYSA is a kinase inhibitor indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. (1)

**DOSAGE AND ADMINISTRATION**

- **Recommended dosage:** 300 mg taken orally twice daily with or without food. (2.1)

**ADVERSE REACTIONS**

The most common adverse reactions (≥20%) are diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash. (6.1)

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**WARNINGs AND PRECAUTIONS**

- **Diarrhea:** Severe diarrhea, including dehydration, acute kidney injury, and death, has been reported. Administer anti-diarrheal treatment as clinically indicated. Interrupt dose, then dose reduce, or permanently discontinue TUKYSA based on severity. (2.2, 5.1)

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**CONTRAINDICATIONS**

None. (4)

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**DRUG INTERACTIONS**

- **Strong CYP3A Inducers or Moderate CYP2C8 Inducers:** Avoid concomitant use. (7.1)
- **Strong CYP2C8 Inhibitors:** Avoid concomitant use; reduce TUKYSA dose if concomitant use cannot be avoided. (2.4, 7.1)
- **CYP3A Substrates:** Avoid concomitant use with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. (7.2)
- **P-gp Substrates:** Consider reducing the dose of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. (7.2)

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**ADVERSE REACTIONS**

To report SUSPECTED ADVERSE REACTIONS, contact Seattle Genetics at 1-855-4SEAGEN or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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**HOW SUPPLIED/STORAGE AND HANDLING**

- Tablets: 50 mg and 150 mg. (3)

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**NONCLINICAL TOXICOLOGY**

- **Carcinogenesis, Mutagenesis, Impairment of Fertility:** (13.1)

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**PATIENT COUNSELING INFORMATION**

- **Lactation:** Advise not to breastfeed. (8.2)

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*Sections or subsections omitted from the full prescribing information are not listed.
### Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Grade 3 without anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 with anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Other adverse reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 3</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 ALT or AST (&gt; 5 to 20 × ULN) OR Grade 3 bilirubin (&gt; 3 to 10 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 ALT or AST (&gt; 20 × ULN) OR Grade 4 bilirubin (&gt; 10 × ULN)</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td></td>
<td>ALT or AST &gt; 3 × ULN AND Bilirubin &gt; 2 × ULN</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

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
3. Other adverse reactions [see Adverse Reactions (6.1)]
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS

#### 5.1 Diarrhea
TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death [see Adverse Reactions (6.1)]. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA [see Dosage and Administration (2.2)].

#### 5.2 Hepatotoxicity
TUKYSA can cause severe hepatotoxicity [see Adverse Reactions (6.1)]. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA [see Dosage and Administration (2.2)].

#### 5.3 Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tacitinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose [see Use in Specific Populations (8.1, 8.3)]. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy and contraception information.

### 6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- **Diarrhea** [see Warnings and Precautions (5.1)]
- **Hepatotoxicity** [see Warnings and Precautions (5.2)]

#### 6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**HER2-Positive Metastatic Breast Cancer HER2CLIMB**

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB [see Clinical Studies (14)]. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%).

Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3 summarizes the adverse reactions in HER2CLIMB.

#### Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine N = 404</th>
<th>Placebo + Trastuzumab + Capecitabine N = 197</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3 %</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>3.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitisa</td>
<td>32</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Rashb</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicityc</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemiaa</td>
<td>21</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increasedd</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathyg</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

1. Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, and aphthous ulcer
2. Rash includes rash maculo-papular, rash, dermatitis acneform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plant erythema, skin toxicity, and dermatitis
3. Hepatotoxicity includes hepatitis/fulminant, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury
4. Anemia includes anemia, hemoglobin decreased, and normocytic anemia
5. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function
6. Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy
Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased
the concentration of TUKYSA, which may increase the toxicity associated with a CYP2C8
substrate.

Concomitant use of TUKYSA with a CYP3A substrate increased the
concentration of TUKYSA, which may increase the toxicity associated with a CYP3A
substrate.

Increased ALT

Increased bilirubin

Increased AST

Decreased magnesium

Decreased potassium

Decreased creatinine

Decreased sodium

Increased alkaline phosphatase

Increased sodium

Increased phosphate

Increased ALT

Increased AST

Decreased magnesium

Decreased potassium

Increased creatinine

Increased sodium

Increased alkaline phosphatase

Increased bilirubin

Decreased phosphate

Decreased hemoglobin

Concomitant use of TUKYSA with a strong CYP3A inducer or a
CYP3A substrate decreased the concentration of TUKYSA, which may decrease the
toxicity associated with a CYP3A substrate.

Concomitant use of TUKYSA with a weak CYP3A inducer decreased the
concentration of TUKYSA, which may decrease the toxicity associated with a weak
CYP3A inducer.

Concomitant use of TUKYSA with a weak CYP3A inducer decreased the
concentration of TUKYSA, which may decrease the toxicity associated with a weak
CYP3A inducer.

Concomitant use of TUKYSA with a strong CYP3A inducer decreased the
concentration of TUKYSA, which may decrease the toxicity associated with a strong
CYP3A inducer.

Clinical Impact

Management

Concomitant use of TUKYSA with a strong CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Concomitant use of TUKYSA with a weak CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Concomitant use of TUKYSA with a strong CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Concomitant use of TUKYSA with a weak CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Increased Creatinine

Clinical Impact

Management

Concomitant use of TUKYSA with a strong CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Concomitant use of TUKYSA with a weak CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Concomitant use of TUKYSA with a strong CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

Concomitant use of TUKYSA with a weak CYP3A inducer decreased the
cellular activity of TUKYSA and increased cell death.

7.2 Effects of TUKYSA on Other Drugs

Table 6 summarizes the effect of other drugs on TUKYSA.

Table 6: TUKYSA Drug Interactions that Affect Other Drugs

<table>
<thead>
<tr>
<th>CYP3A Substrates</th>
<th>Clinical Impact</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate [see Clinical Pharmacology (12.3)], which may increase toxicity associated with a CYP3A substrate.</td>
<td>Avoid concomitant use of TUKYSA with a CYP3A substrate, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.</td>
<td></td>
</tr>
<tr>
<td>Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate [see Clinical Pharmacology (12.3)], which may increase the toxicity associated with a P-gp substrate.</td>
<td>Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.</td>
<td></td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information.

Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures > 1.3 times the human exposure (AUC) at the recommended dose (see Data). Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In pilot embryo-fetal development studies, pregnant rats and rabbits received oral doses of tucatinib up to 150 mg/kg/day during the period of organogenesis.

In rats, oral administration of tucatinib resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption) at doses ≥ 90 mg/kg/day. Fetal effects included reduced number of live fetuses, decreased fetal weight, and fetal abnormalities (increase in skeletal variations, incomplete ossification) at ≥ 50 mg/kg/day (approximately 3.5 times the human exposure at the recommended dose based on AUC). In rabbits, oral administration of tucatinib resulted in increased resorptions, decreased percentages of live fetuses, and skeletal, visceral, and external malformations in fetuses at doses ≥ 90 mg/kg/day (1.3 times the human exposure at the recommended dose based on AUC). Fetal abnormalities included domed head, brain dilation, incomplete ossification of frontal and parietal bones, and a hole in the parietal bone.

8.2 Lactation

Risk Summary

TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information.

There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. In clinical trials, TUKYSA was administered to a limited number of pregnant women. In these trials, the laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2. There is no definition for Grade 2 events (NCI-CTCAE v5.0).

Table 5: Drug Interactions that Affect TUKYSA

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Clinical Impact</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed [see Clinical Pharmacology (12.3)].</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.4 Pediatric Use

The safety and effectiveness of TUKYSA in pediatric patients have not been established.

8.5 Geriatric Use

In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

8.6 Renal Impairment

The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CrCl < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment.

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance (CrCl) 30 to 89 mL/min).

8.7 Hepatic Impairment

Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
Tukacinib is a kinase inhibitor. The chemical name is (N4-(4-(1,2,4-triazolo[1,5-a]pyridin-7-yl)oxy)-3-methylphenyl)-1H-4,4-dimethyl-4-hydroxooxazol-2-yl)guanidine-4,6-diamine. The molecular formula is C30H36N6O4, and the molecular weight is 490.52 g/mol. The chemical structure is as follows:

TUKYSA (tukacinib) is supplied as 50 mg and 150 mg film-coated tablets for oral use and contain the following inactive ingredients:

Tablet core: copovidone, crospovidone, sodium chloride, potassium chloride, sodium bicarbonate, colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.

Coating: yellow film coat: polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, and yellow iron oxide non-irradiated.

Each TUKYSA 50 mg tablet contains 0.258 mg (0.258 mg) potassium and 9.21 mg (0.401 mg) sodium.

Each TUKYSA 150 mg tablet contains 0.775 mg (0.775 mg) potassium and 27.64 mg (1.202 mg) sodium.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Tukacinib is a tyrosine kinase inhibitor of HER2. In vitro, tukacinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream MAPK and AKT signaling and cell proliferation, and showed anti-tumor activity in HER2 expressing tumor cells. In vivo, tukacinib inhibited the growth of HER2 expressing tumors. The combination of tukacinib and trastuzumab showed increased anti-tumor activity in vivo and in vivo compared to either drug alone.

**12.2 Pharmacodynamics**

**Exposure Response Relationship**

Tukacinib exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.

**Cardiac Electrophysiology**

No large mean increase in QTC (i.e., > 20 ms) was detected following treatment with TUKYSA at the recommended dose of 300 mg taken orally twice daily.

**12.3 Pharmacokinetics**

Tukacinib AUC(0-Inf) and Cmax increases proportionally over a dosage range from 50 mg to 300 mg (0.17 to 1 times the approved recommended dosage). Tukacinib exhibited 1.7-fold accumulation for AUC and 1.5-fold accumulation for Cmax following administration of TUKYSA 300 mg twice daily for 14 days. Time to steady state was approximately 4 days.

**Absorption**

The median time to peak plasma concentration of tukacinib was approximately 2 hours (range 1 to 4 hours).

**Effects of Food**

Following administration of a single oral dose of TUKYSA in 11 subjects after a high-fat meal (approximately 58% fat, 26% carbohydrate, and 16% protein), the mean AUC(0-Inf) increased by 1.5-fold, the T1/2 shifted from 1.5 hours to 4 hours, and Cmax was unaltered. The effect of food on the pharmacokinetics of tukacinib was not clinically meaningful.

**Distribution**

The geometric mean (CV%) apparent volume of distribution of tukacinib was approximately 1670 L (69%). The plasma protein binding was 97.1% at clinically relevant concentrations.

**Elimination**

The geometric mean (CV%) half-life of tukacinib was approximately 8.5 (21%) hours and apparent clearance was 148 L/h (55%).

**Metabolism**

Tukacinib is metabolized primarily by CYP2C8 and to a lesser extent via CYP3A.

**Excretion**

Following a single oral dose of 300 mg radiolabeled tukacinib, approximately 86% of the total radiolabeled dose was recovered in feces (16% of the administered dose as unchanged tukacinib) and 4.1% in urine with an overall total recovery of 90% within 13 days post-dose. In plasma, approximately 76% of the plasma radioactivity was unchanged, 19% was attributed to identified metabolites, and approximately 5% was unassigned.

**Specific Populations**

Age (< 65 (n =211); > 65 (n = 27)), albumin (25 to 52 g/L), creatinine clearance (creatinine clearance [ClCr] 60 to 89 mL/min (n = 89); ClCr 30 to 59 mL/min (n = 5)), body weight (41 to 136 kg), and race (White (n=168), Black (n=53), or Asian (n=10)) did not have a clinically meaningful effect on tukacinib exposure.

**Renal Impairment**

No clinically significant differences in the pharmacokinetics of tukacinib were observed in patients with mild to moderate renal impairment (creatinine clearance: 30 to 89 mL/min by Cockcroft-Gault). The effect of severe renal impairment (creatinine clearance: < 30 mL/min) on the pharmacokinetics of tukacinib is unknown.

**Hepatic Impairment**

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment had no clinically relevant effect on tukacinib exposure. Tukacinib AUC(0-Inf) was increased by 1.6 fold in subjects with severe (Child-Pugh C) hepatic impairment compared to subjects with normal hepatic function.

**Drug Interaction Studies**

**Clinical Studies**

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been conducted with tukacinib.

Tukacinib was not mutagenic in an in vitro bacterial reverse mutation assay (Ames) assay. Tukacinib was not clastogenic in either in vitro chromosome aberration assay or in vivo mouse bone marrow micronucleus assay.

Fertility studies in animals have not been conducted. In repeat-dose toxicity studies up to 13 weeks duration, decreased corpora lutea/corpus luteum cyst, increased intestinal cells of the ovary, atrophy of the uterus, and mucusification of the vagina were observed in female rats at doses ≥ 8 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose based on AUC). Atrophy and edema of the testes and oligospermia/germ cell debris in the epididymides were observed in male rats at ≥ 120 mg/kg/day (approximately 13 times the human exposure at the recommended dose based on AUC).

**14 CLINICAL STUDIES**

**14.1 HER2-Positive Metastatic Breast Cancer**

The efficacy of TUKYSA in combination with trastuzumab and capecitabine was evaluated in 612 patients in HER2CLIMB (NCT02614794), a randomized (2:1), double-blind, placebo-controlled trial. Patients were required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases, and prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. HER2 positivity was based on archival or fresh tissue tested with an FDA-approved test at a central laboratory prior to enrollment with HER2 positivity defined as HER2 IHC 3+ or ISH positive.

Patients with brain metastases, including those with progressing or untreated lesions, were eligible provided they were neurologically stable and did not require immediate radiation or surgery. The trial excluded patients with leptomeningeal disease. Randomization 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).

Patients received TUKYSA 300 mg or placebo orally twice daily with a trastuzumab loading dose of 8 mg/kg on Day 1 of Cycle 1 if needed and then a maintenance dose of 6 mg/kg on Day 1 of every 21-day cycle thereafter and capecitabine 1000 mg/m² orally twice daily on Days 1 through 14 of every 21-day cycle. An alternate trastuzumab dosing regimen was 600 mg administered subcutaneously on Day 1 of every 21-day cycle. Patients were treated until disease progression or unacceptable toxicity. Tumor assessments, including brain-MRI in patients with presence or history of brain metastases at baseline, occurred every 6 weeks for the first 24 weeks and every 9 weeks thereafter.
The major efficacy outcome measure was progression-free survival (PFS) in the first 480 randomized patients assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were evaluated in all randomized patients and included overall survival (OS), PFS among patients with a history or presence of brain metastases (PFSbrain), and confirmed objective response rate (ORR).

The median age was 54 years (range: 22 - 82); 116 (19%) patients were age 65 or older. The majority were White (73%) and female (99%) and 51% had an ECOG performance status of 0. Sixty percent had estrogen and/or progesterone receptor-positive disease. Forty-eight percent had a presence or history of brain metastases; of these patients, 23% had untreated brain metastases, 40% had treated but stable brain metastases, and 37% had treated but radiographically progressing brain metastases. Seventy-four percent of patients had visceral metastases. Patients had received 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 and T-DM1 and all but two patients had prior pertuzumab. Efficacy results are summarized in Table 9 and Figure 1 and 2. Efficacy results were consistent across patient subgroups defined by stratification factors (presence or history of brain metastases, ECOG status, region of world) and hormone receptor status.

### Table 9: Efficacy Results in HER2CLIMB

<table>
<thead>
<tr>
<th></th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N=320</td>
<td>N=160</td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>178 (56)</td>
<td>97 (61)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>7.8 (7.5, 9.6)</td>
<td>5.6 (4.2, 7.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.54 (0.42, 0.71)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>OS</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N=410</td>
<td>N=202</td>
</tr>
<tr>
<td>Number of deaths (%)</td>
<td>130 (32)</td>
<td>85 (42)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>21.9 (18.3, 31.0)</td>
<td>17.4 (13.6, 19.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.66 (0.50, 0.87)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>PFSbrain</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>N=198</td>
<td>N=93</td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>106 (53.5)</td>
<td>51 (54.8)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>7.6 (6.2, 9.5)</td>
<td>5.4 (4.1, 5.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.48 (0.34, 0.69)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>Confirmed ORR with Measurable Disease</strong></td>
<td>N=340</td>
<td>N=171</td>
</tr>
<tr>
<td>ORR (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>40.6 (35.3, 46.0)</td>
<td>22.8 (16.7, 29.8)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>3 (0.9)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>PR (%)</td>
<td>135 (39.7)</td>
<td>37 (21.6)</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td>N=320</td>
<td>N=160</td>
</tr>
<tr>
<td>Median, months (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8.3 (6.2, 9.7)</td>
<td>6.3 (5.8, 8.9)</td>
</tr>
</tbody>
</table>

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.
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, ECOG status, and region of world).
3. Hazard ratio calculated using the complementary log-log transformation method (Collett, 1994).
4. Hazard ratio and 95% confidence intervals calculated using the complementary log-log transformation method (Collett, 1994).
5. Hazard ratio and 95% confidence intervals calculated using the stratified Cox proportional hazards regression model controlling for stratification factors (presence or history of brain metastases, ECOG status, and region of world).
6. Hazard ratio and 95% confidence intervals calculated using the stratified Cox proportional hazards regression model controlling for stratification factors (presence or history of brain metastases, ECOG status, and region of world).

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied
TUKYSA 50 mg tablets are supplied as yellow, film-coated, round tablets containing 50 mg of tucatinib. Each tablet is debossed with “TUC” on one side and “30” on the other side, and is packaged as follows: 50 mg tablets: 60 count in 75 cc bottle: NDC 51144-001-60

TUKYSA 150 mg tablets are supplied as yellow, film-coated, oval-shaped tablets containing 150 mg of tucatinib. Each tablet is debossed with “TUC” on one side and “150” on the other side, and is packaged as follows:

- 150 mg tablets: 60 count in 75 cc bottle: NDC 51144-002-60
- 150 mg tablets: 120 count in 150 cc bottle: NDC 51144-002-12

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Dispense to patient in original container only. Store in original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant.

Once opened, use within 3 months. Discard any unused tablets 3 months after opening the bottle.

### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

#### Diarrhea
- Inform patients that TUKYSA has been associated with severe diarrhea. Instruct patients on how to manage diarrhea and to inform their healthcare provider immediately if there is any change in bowel patterns [see Warnings and Precautions (5.1)].

#### Hepatotoxicity
- Inform patients that TUKYSA has been associated with severe hepatotoxicity and that they should report signs and symptoms of liver dysfunction to their healthcare provider immediately [see Warnings and Precautions (5.2)].

#### Embryo-Fetal Toxicity
- Inform pregnant women and females of reproductive potential of the risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)].

#### Lactation
- Advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose [see Use in Specific Populations (8.2)]. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information.
What are the possible side effects of TUKYSA?

TUKYSA may cause serious side effects, including:

- **Diarrhea.** Diarrhea is common with TUKYSA and can sometimes be severe. Tell your healthcare provider if you have a change in your bowel movements or severe diarrhea. Severe diarrhea can lead to loss of too much body fluids (dehydration), low blood pressure, kidney problems and death. Your healthcare provider may prescribe medicines to treat your diarrhea during treatment with TUKYSA.

- **Liver Problems.** TUKYSA can cause severe liver problems. Your healthcare provider will do blood tests to check your liver function before and every 3 weeks during treatment with TUKYSA, or as needed. Tell your healthcare provider right away if you have any signs and symptoms of liver problems including:
  - itching
  - yellowing of your skin or eyes
  - dark or brown urine (tea-colored)
  - pain in the upper right side of your stomach-area (abdomen)

  **Important:** TUKYSA may cause fertility problems in males and females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

  These are not all of the possible side effects of TUKYSA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

The most common side effects of TUKYSA:

- diarrhea
- rash, redness, pain, swelling or blisters on the palms of your hands or soles of your feet
- nausea
- tiredness
- increased liver function blood tests
- vomiting

Your healthcare provider may change your dose of TUKYSA, temporarily stop, or permanently stop treatment with TUKYSA if you have certain side effects.

TUKYSA may cause fertility problems in males and females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of TUKYSA.

How should I store TUKYSA?

- Store TUKYSA at room temperature 68°F to 77°F (20°C to 25°C).
- Keep TUKYSA in its original container. The TUKYSA bottle contains a desiccant packet to help keep your tablets dry (protect from moisture). Keep the desiccant in the bottle.
- Tightly close the bottle of TUKYSA after you take your dose.
- TUKYSA must be used within 3 months after opening the bottle. Throw away (discard) any unused tablets 3 months after opening the bottle.

Keep TUKYSA and all medicines out of reach of children.

General information about the safe and effective use of TUKYSA.

Medicines are sometimes prescribed for conditions not listed in the Patient Information. Do not use TUKYSA for a condition for which it was not prescribed. Do not give TUKYSA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TUKYSA that is written for healthcare professionals.

What are the ingredients of TUKYSA?

**Active ingredient:** tucatinib

**Inactive ingredients:**
- Tablet core: copovidone, crospovidone, sodium chloride, potassium chloride, sodium bicarbonate, colloidal silicon dioxide, magnesium stearate, and micro-crystalline cellulose.
- Tablet coating: yellow film coat: polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, and yellow iron oxide non-irradiated.

Manufactured by Seattle Genetics, Inc., Bothell, WA 98021

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For more information, call 1-855-473-2436 (1-855-4SEAGEN) or go to www.TUKYSA.com.