Date: 20 September 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Pharmaceutical form: powder for concentrate for solution for infusion

Dosage strength(s): 100 mg

Route(s) of administration: intravenous

Marketing Authorisation Holder: Daiichi Sankyo (Schweiz) AG

Marketing Authorisation No.: 67967

Decision and Decision date: extension of therapeutic indication approved on 30 June 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
BC	Breast cancer
BICR	Blinded independent central review
CI	Confidence interval
CNS	Central nervous system
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DOR	Duration of response
DXd	Deruxtecan
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor-2
HR	Hazard ratio
IA	Interim analysis
ILD	Interstitial lung disease
IRR	Infusion-related reactions
KM	Kaplan Meier
MAH	Marketing Authorisation Holder
Nab	Neutralising antibody
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
Q3W	Every three weeks
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TDM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent adverse event
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme coordinated by the US FDA to assess promising cancer treatments. It provides a framework for concurrent submission and review of oncology products among international partners. It currently involves the regulatory authorities of:
Australia (TGA), Brazil (ANVISA), Canada (HC), Israel (MOH), Singapore (HSA), Switzerland (Swissmedic) and the United Kingdom (MHRA).

Extension(s) of the therapeutic indication(s)
The applicant requested to add to or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Enhertu monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen.

2.2.2 Approved Indication

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens, including trastuzumab and a taxane, and had a progression either in the metastatic setting or within 6 months after finalisation of an adjuvant or neoadjuvant therapy (see section "Properties/Effects").

2.2.3 Requested Dosage

Summary of the applied standard dosage:
5.4 mg/kg body weight as intravenous infusion once every 3 weeks (Q3W).

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	13 December 2021
Formal control completed	14 December 2021
Predecision	14 April 2022
Answers to Predecision	30 May 2022
Final Decision	30 June 2022
Decision	approval

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3 Medical Context

Breast cancer (BC) is the most frequent cancer in women and the leading cause of death from cancer in women, with a median overall survival (OS) of approximately 3 years and a 5-year survival of about 25%.

The human epidermal growth factor receptor-2 (HER2) is a transmembrane protein overexpressed by approximately 15-20% of invasive breast carcinomas.
Established first-line treatment of HER2-positive metastatic breast cancer is the combination of the anti-HER2 antibodies trastuzumab and pertuzumab with a taxane, resulting in a median progression-free survival (PFS) of 18.5 months.
After progression on or after the first-line treatment, trastuzumab emtansine (TDM1), an antibody-drug conjugate (ADC), alongside other EGFR targeting alternatives has shown efficacy.

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) consisting of the humanised monoclonal antibody trastuzumab attached to the topoisomerase I inhibitor MAAA-1181a via a cleavable peptide linker. After cell internalisation, the released drug leads to apoptosis of the target tumour cells via the inhibition of topoisomerase I.

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4 Nonclinical Aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication for Enhertu as a monotherapy indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen. This was considered acceptable since there are no changes with regard to posology and method of administration. The data package from the initial submission is considered sufficient to cover the safety aspects for the new indication and does not suggest any additional safety risks for the requested indication.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed indication extension.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Bioanalytical methods: Existing, previously validated bioanalytical methods were used for the pharmacokinetic (PK) and anti-drug antibody (ADA) sample analysis.

Biopharmaceutics: The commercial formulation was used in the pivotal Phase 3 study U302. Therefore, no bridging between a commercial formulation and the Phase 3 material is required.

PopPK analysis: Overall, 19,584 PK samples for serum trastuzumab deruxtecan (T-DXd) concentrations and 19,683 for serum deruxtecan (DXd) concentrations from nine studies, including study U302, were included in the dataset. Five of these studies were part of the original BC application. Total anti-HER2 antibody was not used in the analysis because of the similarity to the PK profile of T-DXd.

> **T-DXd**: Consistent with the previous population pharmacokinetic (PopPK) analysis; in the final model, the PK of T-DXd is described by a two-compartment model with linear elimination.
>
> **DXd:** Consistent with the previous PopPK analysis; in the final model, the PK of DXd was described by a one-compartment model with a two-component, time-varying release rate constant that varies over time, and primary elimination.

The newly submitted popPK analysis compares well with the popPK analysis in support of the original application. Thus, the change in line of treatment had no clinically meaningful impact on the exposures observed with the dosing regimen of 5.4 mg/kg Q3W. In addition, no new covariates were identified and no dose adjustments are required based on covariates such as gender, race, weight or height. The effects of high body weight on exposures are similar to the effects previously observed in the original analysis for third-line treatment.

Immunogenicity: Overall, 2.1% (27 of 1,311) of subjects developed a treatment-emergent ADA following treatment with T-DXd across all doses evaluated in the nine clinical studies (including study U302). Similar to ADA, the prevalence of neutralising antibodies (Nab) against T-DXd was low. The incidence of NAb against T-DXd was 0.1% (1/1,311). No relationship was identified between PK, efficacy or infusion related reactions (IRRs) (as a measure of safety) and immunogenicity of T-DXd.

5.2 Dose Finding and Dose Recommendation

No new dose-finding study was submitted; the study dose corresponds to the currently temporarily authorised dose of 5.4 mg/kg Q3W.

5.3 Efficacy

Study U302 (DS8201-A-U302) is a Phase 3 multicentre, randomised, active-controlled, open-label, study to compare the efficacy of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and a taxane.

The primary objective of the study was progression-free survival (PFS) assessed by a blinded independent central review (BICR); an interim analysis (IA) for PFS was planned at 70% of PFS events. The key secondary endpoint was overall survival (OS), which in addition to the final analysis included two preplanned IAs, the first to be performed at the time of the PFS IA, and the second planned at the time of the final PFS analysis. Other secondary endpoints were overall response rate (ORR), duration of response (DOR) and PFS based on investigator assessment.

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Trastuzumab deruxtecan was administered at 5.4 mg/kg as an intravenous infusion once every 3 weeks, on day 1 of each 21-day cycle. Treatment was to be continued until disease progression, unacceptable toxicity or withdrawal of consent. Treatment response was assessed every 6 weeks.

Eligible patients had unresectable or metastatic BC that was resistant to first-line treatment containing taxol and trastuzumab, and had documented clinical or radiographic progression of disease. In addition, patients needed an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and adequate organ and bone marrow function. Patients with a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis or unstable brain metastases were excluded from the trial.

In total, 524 subjects were randomised. At the data cut-off (DCO) of 21 May 2021, 51.4% of the subjects were still on treatment in the T-DXd arm and 18% in the T-DM1 arm. In total, 60% of subjects had previously been treated with pertuzumab. Around 10% of patients had HER2 2+ tumours, while the majority were HER2 3+. Around half of subjects were hormone receptor positive. Around 15% of subjects had baseline CNS metastases. In total, 41.4% of subjects in the T-DXd arm and 38.8% in the T-DM1 arm had received one prior line of treatment (including hormonal therapy) before the study treatment. Demographic characteristics were generally well balanced in the two arms, except for the percentage of non-smokers (87.1% in the TDM-1 arm vs 73.2% in the T-DXd arm) and ECOG performance status 0 (66.5% in the TDM-1 arm vs 59.0% in the T-DXd arm).

At the DCO of the first PFS IA, the median duration of PFS follow-up was 15.5 months for the T-DXd arm and 13.9 months for the T-DM1 arm. In total, 33.3% of subjects had a PFS event in the T-DXd arm versus 60.1% in the T-DM1 arm. PFS based on BICR was significantly longer in the T-DXd arm than in the T-DM1 arm with a stratified hazard ratio (HR) of 0.28 (95% CI: 0.22, 0.37; p-value <0.000001). The p-value was below the Haybittle-Peto efficacy stopping boundary of 0.000204. Median PFS was not estimable (NE) by the Kaplan Meier (KM) method in the T-DXd arm vs 6.8 months in the T-DM1 arm. KM curves showed an early separation and remained separated. The estimated PFS rate at 12 months was 75.8% in the T-DXd arm and 34.1% in the T-DM1 arm. This result is clinically meaningful. The benefit in PFS was observed consistently across all prespecified subgroups, including subjects with CNS metastases and those who received one prior line of therapy.

Given the statistical significance of the primary endpoint PFS, the first of the two preplanned IAs of the key secondary endpoint (OS) was performed. In total, 12.6% of subjects had an OS event in the T-DXd arm and 20.2% in the T-DM1 arm. The stratified HR for OS was 0.55 (95% CI: 0.36, 0.86) in favour of the T-DXd arm, with a p-value of 0.007172 that did not yet cross the pre-specified boundary for the interim analysis (p<0.000265). Median OS was not reached in either arm; the estimated 12-months survival rate was 94.1% in the T-DXd arm and 85.9% in the T-DM1 arm. The KM curves showed an early separation and remained separated. Since the result of the first IA for OS was not statistically significant, the second IA will be performed when approximately 153 OS events have occurred as per protocol.

5.4 Safety

Safety data are presented in three groups: for study U302 (Group 1, n = 257), for all HER2-positive breast cancer at a dose of 5.4 mg/kg (Group 2, n = 491 subjects) and for any type of cancer at any dose (Group 3, n = 1,219 subjects).
The safety analysis set of study U302 represents 98.5% of subjects in the T-DXd arm and 99.2% of the T-DM1 arm. Median relative dose intensity was 100% in both arms. Median treatment duration was 14.3 months in the T-DXd arm and 6.9 months in the T-DM1 arm.
Treatment-emergent adverse events (TEAEs) were reported in 99.6% of patients in the T-DXd arm and 95.4% in the T-DM1 arm; TEAEs with CTCAE ≥ Grade 3 were reported in about half of subjects in both arms (52.1% and 48.3 %, respectively), while serious TEAEs were observed in about one-fifth of patients (19.1% and 18.0%, respectively).

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TEAEs associated with study drug discontinuation in the T-DXd arm were around double those in the TDM-1 arm (13.6 vs 6.5%), as were TEAEs associated with study drug interruption (44.0 vs 23.4%). Dose reductions due to TEAEs were more frequent in the T-DXd arm than in the TDM-1 arm (23.7 vs 13.4%).
The most common TEAEs in the T-DXd arm were nausea (75.9%), fatigue (49.0%), vomiting (49.0%), neutropenia (42.8%), alopecia (37.0%), constipation (34.2%), anaemia (32.7%), leukopenia (30.4%). thrombocytopenia (25.7%) and increased aspartate aminotransferase (25.7%).
The only TEAE ≥Grade 3 reported in ≥10% of subjects in the T-DXd arm was neutropenia (19.1%). The most frequent serious adverse events (SAEs) in the T-DXd arm were ILD (2.3%), vomiting (1.9%), pneumonia (1.6%) and pyrexia (1.6%). Febrile neutropenia occurred in 0.8% of subjects in the T-DXd arm. TEAEs associated with death were reported in 5 (1.9%) subjects in each treatment arm; none of the deaths was considered related to the treatment.
Overall, 10.9% of subjects in the T-DXd arm developed ILD, which was the most frequent SAE (2.3%) and the primary cause for study drug discontinuation for AEs (8.2%) in the T-DXd arm. One subject had ILD Grade 4 and 1 subject had ILD associated with an outcome of death; however, both were judged not to be drug-related. Just over half (55.6%) of subjects recovered from ILD. Decreased ejection fraction was reported in 2.3% of subjects in the T-DXd arm. The toxicity profile was in line with that observed in previous trials of Enhertu.

5.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

Breast cancer (BC) is the most frequent cancer in women and the leading cause of death from cancer in women. HER2-positive breast cancer represents 15-20% of invasive breast carcinomas.
While considerable progress has recently been made in the treatment of metastatic HER2-positive breast cancer, there remains an important medical need.
Trastuzumab deruxtecan (T-DXd) is an ADC composed of the humanised monoclonal antibody trastuzumab attached to the topoisomerase I inhibitor MAAA-1181a. The drug has been temporarily approved in Switzerland in November 2021 for patients who have already received at least two treatment regimens directed against HER2, including trastuzumab, and have had disease progression during or after therapy with trastuzumab emtansine (T-DM1).

The applicant requested an indication extension for T-DXd for the second-line treatment of unresectable and metastatic HER2-positive BC after at least one prior anti-HER2 regimen, which included taxol and trastuzumab. The applicant provided efficacy data from the pivotal phase 3 DESTINY-Breast03 study (U302), a randomised study comparing T-DXd with T-DM1, the standard currently approved second-line treatment. 524 patients were randomised; the dose of T-DXd used in the trial was 5.4 mg/kg, the same dose currently approved in third-line treatment.

Beneficial effects
Efficacy in the T-DXd arm as compared to the TDM-1 arm was clinically meaningful. PFS based on BICR, analysed at the DCO of 21 May 2021 of the first preplanned interim analysis (IA) (70% of events), was significantly longer in the T-DXd arm than in the T-DM1 arm, with an HR of 0.28 (95% CI:0.22, 0.37; p-value <0.000001). The number of OS events recorded at the DCO for the first pre-planned IA for OS was 33 in the T-DXd arm (12.6%) and 53 (20.2%) in the T-DM1 arm. The HR for OS was 0.55 (95% CI: 0.36, 0.86) in favour of the experimental T-DXd arm, with a p-value of 0.007172, which did not cross the prespecified boundary for the interim analysis (p<0.000265). KM curves both of PFS and OS showed an early separation and remained separated. The second IA for OS is planned when approximately 153 OS events have occurred.

Uncertainty in the knowledge about the beneficial effects
Both the PFS and OS data from study U302 are immature (33.3% and 12.6% events for PFS and OS have occurred in the T-DXd arm at the DCO, respectively). Despite the statistically and clinically significant benefit shown by the PFS data, it is relevant that a benefit is also demonstrated in OS, as PFS is not established as a validated surrogate for OS in metastatic breast cancer. As study U302 was

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an open label study there is a potential risk of bias, even though PFS was determined by blinded independent review.

Unfavourable effects (risks)
The safety assessment is based primarily on n=257 patients with HER2-positive BC treated at the proposed dose level of 5.4 mg/kg in study U302 and additionally on the comparison with the results from the all breast cancers study (n= 491) and from all patients treated with T-DXd in any indication. The toxicity observed was a combination of the known toxicity profile of trastuzumab and the topoisomerase inhibitor I component MAAA-1181a, with high rates of haematological and gastrointestinal toxicity. An important identified risk of T-DXd is pneumonitis/ILD, which affected 10.9% of subjects in the T-DXd arm in study U302.

Uncertainty in the knowledge about the unfavourable effects
Patients with history of ILD or pneumonitis that required steroids, patients with uncontrolled or significant cardiovascular disease, patients with ECOG performance status 2 and patients with clinically active brain metastasis were excluded from study U302, and therefore safety data on these clinically relevant subgroups are missing. Moreover, evidence for patients older than 75 years and for male patients was limited. ILD/pulmonitis continues to be a side effect of special interest and of particular clinical relevance in this study.

Summary
The results of the first interim analysis of PFS data showed a statistically significant and clinically meaningful benefit of T-DXd compared to T-DM1. The toxicity reported in the study was manageable by an expert physician and was in line with the known toxicity profile of the drug.
The OS data are still immature, and the first interim analysis of OS showed a trend in favour of T-DXd with an HR of 0.55 (95% CI: 0.36, 0.86, p-value 0.007172) and an early and constant separation of KM curves.
In conclusion, the risk-benefit analysis is positive for T-Dxd in the second-line setting of metastatic HER2-positive breast cancer patients.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Enhertu was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Enhertu is temporarily authorised – see "Properties/Effects" section.

Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with Enhertu. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue Enhertu in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.

Enhertu 100 mg powder for concentrate for solution for infusion

Composition

Active substances

Trastuzumabum deruxtecanum is composed of an antibody (produced in Chinese hamster ovary cells by recombinant DNA technology) conjugated via a linker to the topoisomerase I inhibitor, DXd.

Excipients

L-histidinum, L-histidini hydrochloridum monohydricum, saccharum, polysorbatum 80.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.
White to yellowish white lyophilised powder.
One vial of lyophilised powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan.

Indications/Uses

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens, including trastuzumab and a taxane, and had a progression either in the metastatic setting or within 6 months after finalization of an adjuvant or neoadjuvant therapy (see section “Properties/Effects”).

Dosage/Administration

Enhertu should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products. In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.
Do not substitute Enhertu for or with trastuzumab or trastuzumab emtansine.

Posology

The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every three weeks (21-day cycle) until disease progression or unacceptable toxicity.
The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of Enhertu may be administered as 30-minute infusions.
The infusion rate of Enhertu should be slowed or interrupted if the patient develops infusion-related symptoms. Enhertu should be permanently discontinued in case of severe infusion reactions.
Antiemetics may be administered in accordance with local medical practice as per patient tolerance for prophylaxis or management (moderate emetogenicity).
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Enhertu per guidelines provided in Tables 1 and 2.
Enhertu dose should not be re-escalated after a dose reduction is made.

Table 1: Dose reduction schedule

Dose reduction schedule (Starting dose is 5.4 mg/kg.)	**Dose to be administered**
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment.

Table 2: Dose modifications for adverse reactions

Adverse reaction	**Severity**	**Treatment modification**

Adverse reaction	Severity		Treatment modification
Interstitial lung disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)		Interrupt Enhertu until resolved to Grade 0, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).
	Symptomatic ILD/pneumonitis (Grade 2 or greater)		• Permanently discontinue Enhertu. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section “Warnings and precautions”).
Neutropenia	Grade 3 (less than 1.0-0.5 × 10^9/L)		• Interrupt Enhertu until subsided to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 × 10^9/L)		• Interrupt Enhertu until subsided to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile neutropenia	Absolute neutrophil count of less than 1.0 × 10^9/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour.		• Interrupt Enhertu until resolved. • Reduce dose by one level (see Table 1).
Left ventricular ejection fraction (LVEF) decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with Enhertu.
	LVEF 40% to 45%	And absolute decrease from baseline	• Continue treatment with Enhertu. • Repeat LVEF assessment within 3 weeks.

Adverse reaction	Severity		Treatment modification
		is less than 10%	
		And absolute decrease from baseline is 10% to 20%	• Interrupt Enhertu. • Repeat LVEF assessment within 3 weeks. • If LVEF has not recovered to within 10% from baseline, permanently discontinue Enhertu. • If LVEF recovers to within 10% from baseline, resume treatment with Enhertu at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		• Interrupt Enhertu. • Repeat LVEF assessment within 3 weeks. • If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue Enhertu.
	Symptomatic congestive heart failure (CHF)		• Permanently discontinue Enhertu.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v.5.0).

Delayed or missed dose

If a planned dose is delayed or missed, it should be administered as soon as possible without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion should be administered at the dose and rate the patient tolerated in the most recent infusion.

Special populations

Elderly patients

No dose adjustment of Enhertu is required in patients aged 65 years or older. Limited data are available in patients ≥75 years of age.

Patients with renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (see section “Pharmacokinetics”). No data are available in patients with severe renal impairment.

Patients with hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ upper limit of normal [ULN] and any aspartate transaminase [AST] >ULN or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. There are insufficient data to make a recommendation on dose adjustment in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment (see section “Pharmacokinetics”). No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment.

Children and adolescents

The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of breast cancer.

Mode of administration

Enhertu is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. Enhertu must not be administered as an intravenous push or bolus.
For instructions on reconstitution and dilution of the medicinal product before administration (see section “Other information”, “Instructions and special precautions for handling and disposal”).

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section “Composition”.

Warnings and precautions

Interstitial lung disease/pneumonitis

Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu (see section “Undesirable effects”). Fatal outcomes have been observed. Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by further examination of the lung using imaging techniques. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider

corticosteroid treatment (e.g. ≥0.5 mg/kg/day prednisolone or equivalent). Enhertu should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section “Dosage/Administration”). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g. ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Enhertu should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see section “Dosage/Administration”). Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

Neutropenia

Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of Enhertu. Complete blood counts should be monitored prior to initiation of Enhertu and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, Enhertu may require dose interruption or reduction (see section “Dosage/Administration”).

Left ventricular ejection fraction decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed prior to initiation of Enhertu and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see section “Dosage/Administration”).

Embryo-foetal toxicity

Enhertu can cause foetal harm when administered to a pregnant woman. In postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section “Pregnancy, lactation”).
The pregnancy status of females of reproductive potential should be verified prior to the initiation of Enhertu. The patient should be informed of the potential risks to the foetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of Enhertu. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Enhertu and for at least 4 months after the last dose of Enhertu (see section “Pregnancy, lactation”).

Interactions

Effects of other medicinal products on the pharmacokinetics of Enhertu

In vitro, DXd was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.
Co-administration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, resulted in no clinically meaningful increase in exposures of Enhertu or the released topoisomerase I inhibitor, DXd. No dose adjustment is required during co-administration of Enhertu with medicinal products that are inhibitors of OATP1B or CYP3A.
No clinically meaningful interaction is expected with medicinal products that are inhibitors of P-glycoprotein (P-gp), MATE2-K, MRP1, or BCRP transporters.

Effects of Enhertu on the pharmacokinetics of other medicinal products

In vitro studies indicate DXd does not inhibit or induce major CYP450 enzymes including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. *In vitro* studies indicate that DXd does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters. No clinically meaningful drug-drug interaction is expected with medicinal products that are substrates of OAT1 or OATP1B1 transporters.

Pregnancy, lactation

Women of childbearing potential/contraception in males and females

Pregnancy status of women of childbearing potential should be verified prior to initiation of Enhertu.
Women of childbearing potential should use effective contraception during treatment with Enhertu and for at least 7 months following the last dose.
Men with female partners of childbearing potential should use effective contraception during treatment with Enhertu and for at least 4 months following the last dose.

Pregnancy

There are no available data on the use of Enhertu in pregnant women. However, in postmarketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section “Preclinical data”).
Enhertu must not be used during pregnancy unless clearly necessary. If Enhertu is administered during pregnancy, or if a woman becomes pregnant during treatment or within 7 months following the last dose of Enhertu, it is necessary to point out the possibility of harm to the foetus.

Lactation

It is not known if trastuzumab deruxtecan is excreted in human milk. Due to the potential for serious adverse reactions in breast-feeding infants, women should discontinue breast-feeding prior to initiating treatment with Enhertu and breast-feeding must not take place during treatment. Women may begin breast-feeding 7 months after concluding treatment.

Fertility

No dedicated fertility studies have been conducted with Enhertu. Based on results from animal toxicity studies, Enhertu may impair male reproductive function and fertility (see section “Preclinical data”). It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek counselling on sperm storage. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of Enhertu.

Effects on ability to drive and use machines

Enhertu is not expected to affect patients’ ability to drive or use machines. Because of potential adverse reactions such as fatigue, headache and dizziness (see section “Undesirable effects”), patients should be advised to use caution when driving or operating machinery.

Undesirable effects

Summary of the safety profile

The pooled safety population has been evaluated for patients who received at least one dose of Enhertu 5.4 mg/kg and above (n =1219) across multiple tumour types in clinical studies. The median duration of treatment in this pool was 7.7 months (range: 0.7 to 41.0 months).

- The most common adverse reactions were nausea (73.7%), fatigue (58.3%), decreased appetite (43.8%), vomiting (42.5%), neutropenia (39.0%), anaemia (38.2%), alopecia (36.8%), constipation (33.1%), diarrhoea (33.1%), thrombocytopenia (27.2%), leukopenia (26.7%), transaminases increased (24.3%), and musculoskeletal pain (23.5%).
- The most common serious adverse reactions were interstitial lung disease (ILD, 4.9%), pneumonia (2.7%), decreased appetite (2.3%), vomiting (1.7%), nausea (1.3%), anemia (1.3%) and thrombocytopenia (1.1%).
- The most common National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0) Grade 3 or 4 adverse reactions were neutropenia (23.0%), anaemia (16.1%), leukopenia (9.7%), thrombocytopenia (7.7%), fatigue (7.6%), nausea (6.1%), lymphopenia (6.1%), decreased appetite (4.7%), hypokalaemia (4.1%), transaminases increased (3.9%), vomiting (2.5%), pneumonia (2.2%), febrile neutropenia (2.2%), diarrhoea

(2.1%), weight decreased (1.3%), blood alkaline phosphatase increased (1.3%), ILD (1.2%), and dyspnoea (1.2%).
Grade 5 adverse reactions occurred in 2.2% of patients, including ILD (1.8%).

- Dose interruptions due to adverse reactions occurred in 36.9% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were neutropenia (15.1%), anaemia (5.8%), fatigue (4.8%), leukopenia (3.9%), upper respiratory tract infection (3.4%), ILD (3.1%), pneumonia (3.0%), thrombocytopenia (3.0%), decreased appetite (2.5%), and nausea (2.0%). Dose reductions occurred in 25.7% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were fatigue (7.5%), nausea (5.7%), neutropenia (4.6%), decreased appetite (3.2%) and thrombocytopenia (2.1%). Discontinuation of therapy due to an adverse reaction occurred in 15.1% of patients treated with Enhertu. The most frequent adverse reaction associated with permanent discontinuation was ILD (11.0%).

Tabulated list of adverse reactions

The adverse reactions in patients who received at least one dose of Enhertu in clinical studies are presented in Table 3. The adverse reactions are listed by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as 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); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with trastuzumab deruxtecan in multiple tumour types

System organ class/preferred term or grouped term	**Any Grade (%)**		**Grade 3-4 (%)**
Infections and infestations			
Upper respiratory tract infection[a]	Very common	19.9	0.3
Pneumonia	Common	8.5	2.2
Blood and lymphatic system disorders			
Neutropenia[b]	Very common	39.0	23.0
Anaemia[c]	Very common	38.2	16.1
Leukopenia[d]	Very common	26.8	9.7
Lymphopenia[e]	Very common	11.9	6.1

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Thrombocytopenia[f]	Very common	27.3	7.7
Febrile neutropenia	Common	2.3	2.2
Metabolism and nutrition disorders			
Hypokalaemia[g]	Very common	12.9	4.1
Decreased appetite	Very common	43.8	4.7
Dehydration	Common	3.9	0.6
Nervous system disorders			
Headache[h]	Very common	14.4	0.2
Peripheral neuropathy[i]	Very common	10.7	0.2
Dizziness	Common	9.8	0.3
Dysgeusia	Common	8.4	0
Eye disorders			
Vision blurred	Common	2.5	0
Dry eye	Common	5.9	0.1
Cardiac disorders			
Ejection fraction decreased[j]	Very common	15.3	0.8
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease[k]	Very common	14.8	1.2
Dyspnoea	Very common	10.8	1.2
Cough	Very common	14.5	0.2
Epistaxis	Common	9.5	0.1
Gastrointestinal disorders			
Nausea	Very common	73.7	6.1
Vomiting	Very common	42.5	2.5
Diarrhoea	Very common	33.1	2.1
Abdominal pain[l]	Very common	16.5	0.9

System organ class/preferred term or grouped term	Any Grade (%)		Grade 3-4 (%)
Constipation	Very common	33.1	0.2
Stomatitis[m]	Very common	15.8	0.7
Dyspepsia	Common	8.5	0
Hepatobiliary disorders			
Transaminases increased[n]	Very common	24.4	3.9
Blood bilirubin increased[o]	Common	6.9	0.7
Blood alkaline phosphatase increased	Common	9.4	1.3
Skin and subcutaneous tissue disorders			
Alopecia	Very common	36.8	0.2
Rash[p]	Common	8.8	0.1
Pruritus	Common	6.1	0
Skin hyperpigmentation[q]	Common	4.6	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[r]	Very Common	22.5	0.7
Renal and urinary disorders			
Blood creatinine increased	Common	3.9	0.1
General disorders and administration site conditions			
Fatigue[s]	Very common	58.2	7.6
Weight decreased	Very common	16.8	1.4
Pyrexia	Very common	15.6	0.5
Oedema peripheral	Very common	10.1	0.2
Injury, poisoning and procedural complications			
Infusion-related reactions[t]	Common	2.2	0

[a] Includes influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, rhinitis and upper respiratory tract infection.

[b] Includes neutropenia and neutrophil count decreased.

[c] Includes anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit

System organ class/preferred term or grouped term	Any Grade (%)	Grade 3-4 (%)

decreased.

[d] Includes leukopenia and white blood cell count decreased.

[e] Includes lymphopenia and lymphocyte count decreased.

[f] Includes thrombocytopenia and platelet count decreased.

[g] Includes hypokalaemia and blood potassium decreased.

[h] Includes headache, sinus headache, and migraine.

[i] Includes peripheral neuropathy, peripheral sensory neuropathy, and paraesthesia.

[j] Includes laboratory parameters of LVEF decrease (n=181) and/or preferred terms of ejection fraction decreased (n=22), cardiac failure (n=1) cardiac failure congestive (n=1), and left ventricular dysfunction (n=2).

[k] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis (n=103), interstitial lung disease (n=61), organising pneumonia (n=8), pneumonia (n=2), pulmonary mass (n=1), acute respiratory failure (n=1), lung infiltration (n=1), lymphangitis (n=1), pulmonary fibrosis (n=1), radiation pneumonitis (n=1), respiratory failure (n=9), lung opacity (n=1), and alveolitis (n=2).

[l] Includes abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

[m] Includes stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, and oral mucosal eruption.

[n] Includes transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal and hepatic function abnormal.

[o] Includes blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased and blood bilirubin unconjugated increased.

[p] Includes rash, rash pustular, and rash maculopapular.

[q] Includes skin hyperpigmentation, skin discolouration and pigmentation disorder.

[r] Includes back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain and limb discomfort.

[s] Includes asthenia, fatigue, malaise, and lethargy.

[t] Cases of infusion-related reactions include infusion-related reaction (n=17), hypersensitivity (n=3), infusion site extravasation (n=1), rash (n=1), wheezing (n=1), hypotension (n=1) and flushing (n=3).

Description of selected undesirable effects

Interstitial lung disease/pneumonitis

In clinical studies across multiple tumour types (n = 1219), ILD occurred in 14.8% of patients treated with Enhertu 5.4 mg/kg and above. Most ILD cases were Grade 1 (3.8%) and Grade 2 (8.0%). Grade

3 cases occurred in 1.1% and Grade 4 cases in 0.1% of patients. Grade 5 events occurred in 1.8% of patients. One patient had pre-existing ILD that worsened post treatment leading to Grade 5 ILD. Median time to first onset was 5.4 months (range: -0.5 to 21.0).

Breast cancer

In clinical studies (n = 491), ILD occurred in 12.6% of patients treated with Enhertu 5.4 mg/kg. Most ILD cases were Grade 1 (2.9%), Grade 2 (7.7%) or Grade 3 (0.6%). Grade 5 events occurred in 1.4% of patients. Median time to first onset was 5.5 months (range: 1.1 to 20.8) (see section “Warnings and precautions”).

Neutropenia

In clinical studies (n = 1219) across multiple tumour types in patients treated with Enhertu 5.4 mg/kg and above, neutropenia was reported in 39.0% of patients and 23.0% had Grade 3 or 4 events. Median time of to first onset was 22 days (range: 1 day to 24.8 months), and median duration of the first event was 14 days (range: 2 days to 17.2 months). Febrile neutropenia was reported in 2.3% of patients (see section “Warnings and precautions”).

Left ventricular ejection fraction decrease

In the 1219 patients, across multiple tumour types in clinical studies who received Enhertu 5.4 mg/kg and above, LVEF decrease was reported in 26 patients (2.1%), of which 18 (1.5%) were Grade 2, and 5 (0.4%) were Grade 3. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 173/1123 (15.4%) for Grade 2, and 8 (0.7%) for Grade 3. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The measurement of antibodies is dependent on assay sensitivity and specificity. The rate of antibody positivity found is dependent on numerous factors; therefore, comparison of the rates with other therapies may be misleading. Across all doses evaluated in clinical studies, 2.1% (27/1311) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with Enhertu. The incidence of neutralising antibodies against trastuzumab deruxtecan was 0.1% (1/1311). There was no association between development of antibodies and allergic-type reactions.

Children and adolescents

Safety has not been established in this population.

Elderly patients

Of the 1219 patients across multiple tumour types in clinical studies treated with Enhertu 5.4 mg/kg and above, 32.7% were 65 years or older and 5.7% were 75 years or older. The incidence of Grade 3-4 adverse reactions observed in patients 65 years or older (56.6%) and in younger patients (51.3%) was similar.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no information on overdose with trastuzumab deruxtecan. In the event of overdose, patients should be monitored and appropriate supportive care should be given.

Properties/Effects

ATC code

L01XC41

Mechanism of action

Enhertu, trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd), bound by a tetrapeptide-based cleavable linker. The ADC is stable in plasma. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. DXd, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.

Pharmacodynamics

The administration of multiple doses of trastuzumab deruxtecan (6.4 mg/kg every 3 weeks) did not show any clinically meaningful effect on the QTc interval (i.e., >20 ms) in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.

Clinical efficacy

Temporary authorisation

The medicinal product Enhertu has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

DESTINY-Breast03

The efficacy and safety of Enhertu were studied in DESTINY-Breast03, a multicentre, open-label, active controlled, randomised, two-arm phase 3 study that enrolled patients with HER2-positive, unresectable or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of (non-infectious) ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with untreated or symptomatic brain metastases, patients with a history of clinically significant cardiac disease, patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomized 1:1 to receive either Enhertu 5.4 mg/kg (n=261) or trastuzumab emtansine 3.6 mg/kg (n=263) administered by intravenous infusion once every three weeks. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression-free survival (PFS) as evaluated by blinded independent central review (BICR) according to RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure.

Patient demographics were balanced between treatment arms. Of the 524 patients randomised, the baseline demographic and disease characteristics were: median age 54 years (range: 20 to 83); 65 years or older (20.2%); 75 years or older (3.1%), female (99.6%); Asian (59.9%), White (27.3%), Black or African-American (3.6%); ECOG performance status 0 (62.8%) or 1 (36.8%); hormone receptor status (positive: 51.9%); presence of visceral disease (73.3%); history of brain metastases (21.8%); and (48.3%) patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who were previously treated with pertuzumab was 61.1%. The percentage of patients who had not received prior treatment for metastatic disease was 9.5% and 6.7% of patients had received exactly one prior anti-HER2 therapy that was intended for the neoadjuvant or adjuvant therapy and experienced disease progression during or within 6 months of completing treatment (12 months for pertuzumab).

At the prespecified interim analysis for PFS based on 245 events (73% of total events planned for final analysis), the study demonstrated a statistically significant improvement in PFS per BICR in patients randomized to Enhertu compared to trastuzumab emtansine.

Table 4: Efficacy results in DESTINY Breast03 (intent-to-treat analysis set)

Efficacy Parameter	Enhertu N=261	trastuzumab emtansine N=263
Progression-Free Survival (PFS) Primary end-point (BICR)		
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value	p< 0.0001	

CI = confidence interval; NE=not estimable; NR = not reached

Similar PFS results were observed across pre-specified subgroups including prior pertuzumab therapy, hormone receptor status, presence of stable brain metastases, and presence of visceral disease.
Data regarding OS are not mature yet. At data cut-off (21.05.2021), there were 33 (12.6%) deaths in the Enhertu arm and 53 (20.2%) deaths in the trastuzumab emtansine arm. The median OS was not estimable for either arm.

DESTINY-Breast01

The efficacy and safety of Enhertu were demonstrated in DESTINY-Breast01, a multicentre, open-label, single-arm Phase 2 study that enrolled patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2-based regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumour samples were required to show HER2-positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of treated ILD or ILD at screening, patients with a history of clinically significant cardiac disease as well as patients with clinically unstable brain metastases. Enhertu was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Secondary efficacy outcome measures were duration of response (DOR) and progression-free survival (PFS).
Of the 184 patients enrolled in DESTINY-Breast01, baseline demographic and disease characteristics were: median age 55 years (range 28 to 96); female (100%); White (54.9%), Asian (38.0%), Black or African-American (2.2%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (55.4%) or 1 (44.0%); hormone receptor status (positive: 52.7%); presence of visceral disease (91.8%); median number of prior therapies in the metastatic setting: 5 (range: 2 to 17); prior pertuzumab therapy (65.8%); sum of diameters of target lesions (<5 cm: 42.4%, ≥5 cm: 50.0%).

Efficacy results are summarised in Table 5.

Table 5: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 **N = 184**
Confirmed objective response rate (95% CI)	61.4% (54.0, 68.5)
Complete response (CR)	6.5%
Partial response (PR)	54.9%
Duration of response‡	
Median, months (95% CI)	20.8 (15.0, NR)
% with duration of response ≥6 months (95% CI)§	81.5% (72.2, 88.0)

ORR 95% CI calculated using Clopper-Pearson method

CI = confidence interval

95% CIs calculated using Brookmeyer-Crowley method

‡Includes 73 patients with censored data

§Based on Kaplan-Meier estimation

NR = not reached

Consistent anti-tumour activity was observed across pre-specified subgroups based on prior pertuzumab therapy and hormone receptor status.

Pharmacokinetics

At the recommended dosage of trastuzumab deruxtecan, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 131 µg/mL (20%) and 4.4 ng/mL (41%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 770 µg·day/mL (28%) and 27 ng·day/mL (40%), respectively, based on population pharmacokinetic analysis.

Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Absorption

Trastuzumab deruxtecan is administered intravenously. There have been no studies performed with other routes of administration.

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan and topoisomerase I inhibitor, DXd, was estimated to be 2.71 L and 27.0 L, respectively.

In vitro, the mean human plasma protein binding of the topoisomerase I inhibitor, DXd, was approximately 97%.
In vitro, the blood to plasma concentration ratio of DXd was approximately 0.6.

Metabolism

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the DXd. The humanised HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
In vitro metabolism studies in human liver microsomes indicate that DXd is metabolised mainly by CYP3A4 via oxidative pathways.

Elimination

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer, the clearance of trastuzumab deruxtecan was estimated to be 0.42 L/day and the clearance of DXd was 19.4 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan and released DXd was approximately 5.7 days. Excretion pathways were studied in rats and monkeys.

Linearity/non-linearity

The exposure of trastuzumab deruxtecan and released DXd when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate interindividual variability.

Special populations

Based on population pharmacokinetic analysis, race, ethnicity, sex and body weight (27.3-125.4 kg) did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released DXd.

Elderly patients

The population pharmacokinetic analysis showed that age (range 20-96 years) did not affect the pharmacokinetics of trastuzumab deruxtecan.

Patients with renal impairment

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment (estimated by Cockcroft-Gault), the pharmacokinetics of the released DXd was not affected by mild or moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min).

Patients with hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, the impact of changes on pharmacokinetics of trastuzumab deruxtecan in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment is not clinically meaningful.

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of trastuzumab deruxtecan in children or adolescents.

Preclinical data

Safety Pharmacology

In telemetered male cynomolgus monkeys treated with a single intravenous dose of trastuzumab deruxtecan, no effects on the cardiovascular, respiratory, or central nervous systems were observed at dose levels up to 78.8 mg/kg.

Repeated Dose Toxicity

In a six-week repeat-dose toxicity study, up to 197 mg/kg of trastuzumab deruxtecan was administered to rats once every three weeks. Toxicities were observed in intestines, lymphatic/haematopoietic organs (thymus, lymph nodes, bone marrow), kidneys, skin, testes, and incisor teeth. All changes observed, except for kidney, testicular and incisor teeth changes, were reversible following a nine-week recovery period. The severely toxic dose in 10% of the rats (STD_{10}) was determined to be >197 mg/kg (approximately 31 times the clinical dose of 5.4 mg/kg based on AUC).

In a three-month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at 3, 10, and 30 mg/kg. Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and was histopathologically characterised by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation, which showed reversibility after a three-month recovery period. The highest non-severely toxic dose was determined to be 30 mg/kg (approximately 7 times the clinical dose of 5.4 mg/kg based on AUC).

Changes observed in other organs, except for those in the skin and kidney, also showed reversibility or a trend toward reversibility by the end of a three-month recovery period.

Genotoxicity

The topoisomerase I inhibitor component of trastuzumab deruxtecan, DXd, was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an *in vitro* Chinese hamster lung chromosome aberration assay and was not mutagenic in an *in vitro* bacterial reverse mutation assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

Reproductive toxicity

Dedicated fertility studies have not been conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan may impair male reproductive function and fertility.
There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and DXd were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Sodium chloride solution for infusion must not be used for reconstitution or dilution since it may cause particulate formation.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Reconstituted solution
The reconstituted preparation is not preserved. It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2-8ºC for up to 24 hours from the time of reconstitution, protected from light.
Diluted solution
It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature for up to 4 hours or in a refrigerator at 2-8ºC for up to 24 hours, protected from light. These storage times start from the time of reconstitution.

Special precautions for storage

Store in the refrigerator (2-8°C) until time of reconstitution.
Do not freeze.
Keep out of the reach of children.
For storage conditions after reconstitution and dilution of the medicinal product, see section “Other information”, “Shelf life after opening”.

Instructions and special precautions for handling and disposal

In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.
Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used.
Appropriate aseptic technique should be used for the following reconstitution and dilution procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted Enhertu solution required, and the number of vial(s) of Enhertu needed (see section “Dosage/Administration”).
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The solution should be clear and colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.
- If not used immediately, store the reconstituted Enhertu vials in a refrigerator at 2-8ºC for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The product does not contain a preservative. Discard unused Enhertu after 24 hours refrigerated.

Dilution

- Dilute the calculated volume of reconstituted Enhertu in an infusion bag containing 100 mL of 5% glucose solution. Do not use sodium chloride solution (see section “Other information”, “Incompatibilities”). An infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene) is recommended.
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.

- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2-8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2-8ºC), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration, protected from light.
- Administer Enhertu as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. Do not administer as an intravenous push or bolus.
- Cover the infusion bag to protect from light.
- Do not mix Enhertu with other medicinal products or administer other medicinal products through the same intravenous line.

Disposal

The reconstituted product contains no preservative and is intended for single use only. Discard any unused portion left in the vial.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

67967 (Swissmedic)

Packs

Enhertu is provided in 10 mL Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper, and a polypropylene/aluminium yellow flip-off crimp cap.

Pack containing 1 vial with 100 mg of trastuzumab deruxtecan (A)

Marketing authorisation holder

DAIICHI SANKYO (Schweiz) AG, Zürich

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