Summary Report of Benefit-Risk Assessment

ENHERTU POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 100 MG/VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Trastuzumab deruxtecan
Product Registrant	AstraZeneca Singapore Pte Ltd
Product Registration Number	SIN16352P
Application Route	Abridged evaluation
Date of Approval	22 October 2021

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A INTRODUCTION

Enhertu is indicated for the following indications:

Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Enhertu is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received two or more prior regimens, including a trastuzumab-based regimen.

The active substance, trastuzumab deruxtecan, is an antibody-drug conjugate composed of trastuzumab (a HER2-targeted humanised IgG1 monoclonal antibody) and a cytotoxic topoisomerase I inhibitor (a derivative of exatecan), covalently conjugated by a cleavable tetrapeptide-based linker. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes cell internalisation and intracellular linker cleavage. The released drug leads to apoptosis of the target tumour cells via the inhibition of topoisomerase I.

Enhertu is available as a powder for concentrate for solution for infusion containing 100 mg/vial of trastuzumab deruxtecan. Other ingredients are sucrose, L-histidine, L-histidine hydrochloride monohydrate and polysorbate 80.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, trastuzumab deruxtecan, is manufactured at Daiichi Sankyo Chemical Pharma Co. Ltd., Fukushima, Japan. The drug product, Enhertu, is manufactured at Baxter Oncology GmbH, Westfalen, Germany.

Drug substance:

Adequate controls have been presented for the cell banks, raw materials, reagents, monoclonal antibody and drug-linker intermediates. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches at each of the two production facilities in the manufacturing site.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented was adequate to support the approved storage condition and shelf-life. The packaging is a single-use ethylene vinyl acetate copolymer bag in shell system,

and the secondary container closure system is an aluminium bag. The drug substance is approved for storage at -20ºC with a shelf life of 36 months.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the long-term shelf-life of 36 months when stored at 2 - 8ºC, as well as the in-use storage of the reconstituted solution in vials for up to 24 hours at 2 - 8ºC and the diluted solution in IV bags for up to 4 hours at or below 30ºC or up to 24 hours at 2 - 8ºC. The container closure system is a Type I amber glass vial sealed with a rubber stopper and a flip-off crimp cap.

C ASSESSMENT OF CLINICAL EFFICACY

Breast cancer

The clinical efficacy of trastuzumab deruxtecan in the treatment of unresectable or metastatic HER2-positive breast cancer was supported primarily by one pivotal study (U201). This was a Phase II, multicentre, open-label, 2-part study of trastuzumab deruxtecan in subjects with HER2-positive, unresectable or metastatic breast cancer who were previously treated with trastuzumab emtansine (T-DM1). Part 1 of the study consisted of a pharmacokinetics (PK) stage (evaluating three doses: 5.4 mg/kg, 6.4 mg/kg and 7.4 mg/kg) and a dose-finding stage (evaluating two doses: 5.4 mg/kg and 6.4 mg/kg). Part 2 of the study was a single-arm, non-randomised study, in which all subjects received 5.4 mg/kg. Trastuzumab deruxtecan was given as an intravenous infusion once every 3 weeks. The first dose was administered over 90 minutes, and if no infusion-related reaction after the first dose, subsequent doses were administered over 30 minutes.

The primary efficacy endpoint was objective response rate (ORR) assessed by Independent Central Review (ICR), defined as the proportion of subjects who achieved a best overall response (BOR) of complete response (CR) or partial response (PR), with confirmation of response, based on RECIST 1.1. All responses had to be confirmed at the subsequent scan. The use of ORR as a primary endpoint in an uncontrolled study, although not ideal for confirmation of clinical benefit, was considered acceptable in the context of the last-line treatment setting with limited treatment alternatives. The efficacy evaluation relied on the demonstration of an improvement over available therapies based on the magnitude of the response rate and an adequate duration of response.

A total of 253 subjects were included in the study and received at least one dose of trastuzumab deruxtecan. Of these, a total of 184 subjects received the 5.4 mg/kg dose in both parts of the study and provided data for the efficacy evaluation. The median age was 55.0 years (range 28 to 96 years), all subjects were female, and the majority were White (54.9%) or Asian (38.0%). The majority of subjects had metastatic disease (93.5%), with 30.4% having liver metastases and 13.0% having brain metastases. The median number of prior anti-cancer systemic therapy (excluding hormone therapy) for locally advanced or metastatic breast cancer was 5 (range 2 to 17), and 41.3% of subjects received more than 5 anti-cancer systemic therapies. All subjects received prior trastuzumab and T-DM1, and 65.8% received prior pertuzumab.

The primary endpoint of ORR by ICR was 60.3% (95% CI 52.9, 67.5) at the initial data cut-off date (21 March 2019) and this result was maintained at the updated data cut-off (08 June 2020) with an ORR of 61.4% (95% CI 54.0, 68.5). The ORR based on investigator assessment was 64.1% (95% CI 56.7, 71.1) at the initial data cut-off date (21 March 2019) and 66.8% (95% CI 59.5, 73.6) at the updated cut-off date (08 June 2020).

Subgroup analyses of ORR by ICR showed consistent ORR across the subgroups analysed, including in patients with brain metastases (58.3%; 95% CI 36.6, 77.9) and without brain metastases (60.6%; 95% CI 52.6, 68.2), patients with ≥3 (58.7%; 95% CI 50.8, 66.2) and <3 prior treatment regimen (76.5%; 95% CI 50.1, 93.2), patients with prior pertuzumab (63.6%; 95% CI 54.4, 72.2) and without prior pertuzumab treatment (54.0%; 95% CI 40.9, 66.6), as well as in Asian (58.6%; 95% CI 46.2, 70.2) and White (59.4%; 95% CI 49.2, 69.1) subjects.

The secondary endpoint of duration of response (DOR) at the updated data cut-off date (08 June 2020) showed an estimated median DOR of 20.8 months (95% CI 15.0, NE) with a median follow-up of 20.5 months. The estimated median progression-free survival (PFS) was 19.4 months (95% CI 14.1, NE) and the estimated median overall survival (OS) was 24.6 months (95% CI 23.1, NE). It should, however, be noted that the PFS and OS data were immature. Furthermore, meaningful conclusions cannot be drawn based on these time-to-event endpoints due to the lack of a comparator arm in a single-arm, non-comparative study.

Summary of efficacy results from study U201

	5.4 mg/kg (N = 184)	
	Data cut-off date 21 Mar 2019	**Data cut-off date 08 Jun 2020**
Confirmed ORR by ICR n (%) (95% CI)	 111 (60.3%) (52.9, 67.5)	 113 (61.4%) (54.0, 68.5)
Confirmed BOR by ICR Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not estimable (NE)	 8 (4.3%) 103 (56.0%) 68 (37.0%) 3 (1.6%) 2 (1.1%)	 12 (6.5%) 101 (54.9%) 66 (35.9%) 3 (1.6%) 2 (1.1%)
Confirmed ORR by Investigator n (%) (95% CI)	 118 (64.1%) (56.7, 71.1)	 123 (66.8%) (59.5, 73.6)
Confirmed BOR by Investigator CR PR SD PD NE	 6 (3.3%) 112 (60.9%) 61 (33.2%) 4 (2.2%) 1 (0.5%)	 9 (4.9%) 114 (62.0%) 56 (30.4%) 4 (2.2%) 1 (0.5%)
DOR by ICR (months) Median	 NE	 20.8

(95% CI)	(NE, NE)	(15.0, NE)
PFS by ICR (months) Median (95% CI)	 NE (10.6, NE)	 19.4 (14.1, NE)
OS (months) Median (95% CI)	 NE (NE, NE)	 24.6 (23.1, NE)

In order to interpret and contextualise the ORR results from the pivotal study in the absence of a comparator arm, the applicant provided historical control data from two additional studies: the Unicancer study and a literature-based study (DS8201-PMx004). In the Unicancer study, individual patient data were collected and analysed from the database of the Unicancer network in France comprising 18 French Comprehensive Cancer Centres (FCCCs). From the Unicancer database, a matched cohort of 115 evaluable patients treated for metastatic HER2-positive breast cancer with comparable baseline characteristics to those of the subjects in Study U201 were identified and used for analysis of response. In the literature-based study (DS8201-PMx004), an analysis was performed from 9 published studies comprising 619 patients with HER2-positive advanced breast cancer who had been treated with a median of at least two prior chemotherapies or at least two prior anti-HER2-based therapies.

The comparisons showed that the ORR of 61.4% observed in the pivotal study U201 was higher than that of historical controls in a similar patient population. While cross-study comparisons have inherent limitations and should be interpreted with caution, the ORR with trastuzumab deruxtecan compared favourably to historical controls and could be considered promising in the context of the heavily pre-treated population. Taking into consideration the limited treatment options in the third- or later-line setting, as well as the high magnitude of responses with trastuzumab deruxtecan that represented a meaningful improvement over available therapies, the efficacy data based on a surrogate endpoint ORR in the single-arm non-comparative study could be considered adequate in the intended patient population who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Although the inclusion criteria in study U201 allowed recruitment of both males and females, all patients recruited in the study were females, which was not unexpected as breast cancer in males is rare. There is no biologic or mechanistic basis to expect that the drug would work differently in males compared to females. Hence, the indication that specifies “treatment of patients” in general, which would include use in both males and females, was considered acceptable.

Comparison of efficacy results with historical controls

Endpoint	Study U201 5.4 mg/kg (N = 184)[a]	Unicancer Study Matched Cohort (N = 115)	DS8201-PMx004 (N = 619)[b]
ORR n (%) (95% CI)	 61.4% (54.0, 68.5)	 12.2% (6.2, 18.2)	 15% (9, 30)
DOR (months) Median (95% CI)	 20.8 (15.0, NE)	 ---	 ---
PFS (months) Median (95% CI)	 19.4 (14.1, NE)	 4.7 (3.8, 6.0)	 4.8 (3.3, 5.45)
OS (months) Median (95% CI)	 24.6 (23.1, NE)	 24.1 (18.5, 26.4)	 15.8 (11, 28)

[a] Data cut-off date 08 June 2020.
[b] Studies with a median of at least two prior chemotherapies or at least two prior anti-HER2-based regimens.

A Phase III study (U301) is currently ongoing and is expected to provide confirmatory clinical evidence for the use of trastuzumab deruxtecan in the target patient population. The study is a randomised, open-label, active-controlled study of trastuzumab deruxtecan compared to investigator's choice of treatment (trastuzumab and capecitabine or lapatinib and capecitabine) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1 (N = ~600). The applicant will be required to submit the final results of this study to confirm the efficacy and safety of trastuzumab deruxtecan in the treatment of HER2-positive breast cancer.

Gastric cancer

The clinical efficacy of trastuzumab deruxtecan in the treatment of locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma was supported by one pivotal study (J202). This was a Phase II, multicentre, open-label, randomised study evaluating trastuzumab deruxtecan compared to treatment of physician's choice (irinotecan or paclitaxel) in subjects with HER2-overexpressing advanced gastric or GEJ adenocarcinoma who have progressed on two or more prior regimens, including a fluoropyrimidine, platinum and trastuzumab.

Subjects were randomised in a 2:1 ratio to receive:

- trastuzumab deruxtecan 6.4 mg/kg IV infusion every 3 weeks; or
- physician's choice of chemotherapy consisting of either:
  - irinotecan 150 mg/m^2 every 2 weeks; or
  - paclitaxel 80 mg/m^2 weekly.

The choice of irinotecan or paclitaxel as the comparator regimen is acceptable and consistent with the recommended treatment options in the clinical practice guidelines in the second- or subsequent-line therapy setting. The dosing regimens used for irinotecan and paclitaxel in the comparator arm were within the recommended doses in the clinical practice guidelines and were appropriate. Blinding was not performed due to the different treatment schedules and different adverse event profiles between the active and comparator treatment regimens. To reduce potential bias, the independent central reviewers (ICR) were blinded to the treatment assignment when assessing the primary endpoint of ORR.

The primary efficacy endpoint was ORR (CR and PR) assessed by ICR based on RECIST 1.1. The key secondary endpoint was OS, defined as the time from randomisation to death due to any cause. ORR by ICR and OS were analysed hierarchically to control the overall type I error at a significance level of a 2-sided alpha of 0.05. One pre-specified interim analysis of OS was conducted at the time of the primary analysis for ORR. The interim analysis of OS was tested only if the ORR showed statistical significance at 2-sided alpha of 0.05. The overall alpha was to be controlled using the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary. The multiplicity adjustments applied for the multiple endpoints and analyses were appropriate.

The chosen primary endpoint, ORR, is not ideal as it is typically expected that a confirmatory trial for advanced gastric cancer would be able to show treatment benefit in terms of prolongation of survival. Nevertheless, OS was specified as a key secondary endpoint with appropriate statistical powering and hierarchical testing applied. The OS endpoint was the key endpoint of interest in this setting.

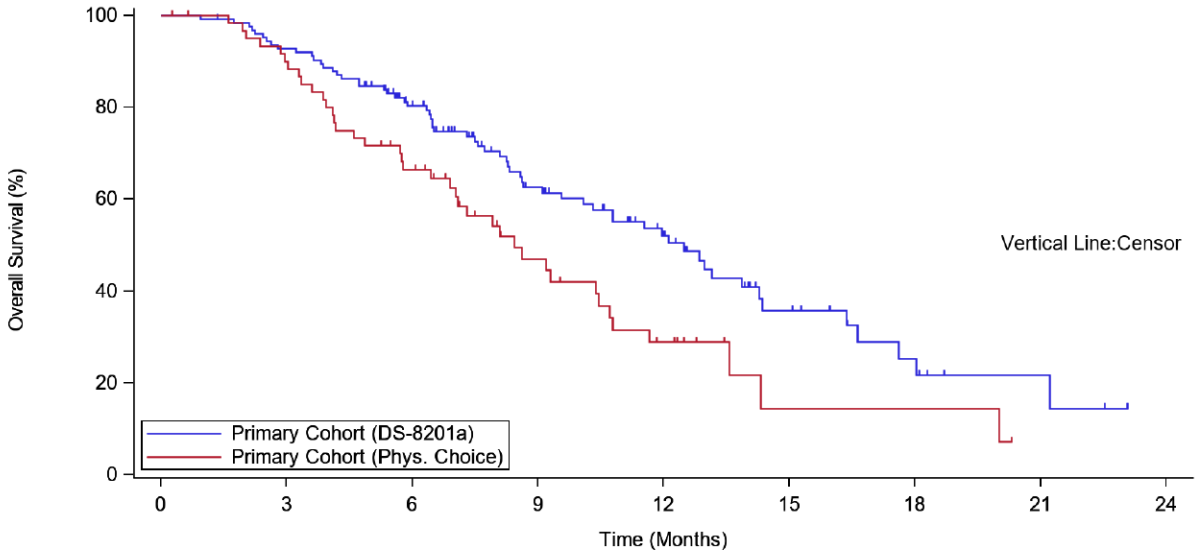
A total of 188 subjects were randomised and included in the intent-to-treat (ITT) analysis set. Of these, 187 subjects received treatment and were included in the full analysis set (FAS): 125 subjects in the trastuzumab deruxtecan group and 62 subjects in the physician's choice group. The Response Evaluable Set included 175 subjects who had measurable tumours at baseline: 119 subjects in the trastuzumab deruxtecan group and 56 in the physician's choice group. In the FAS, the majority of subjects were male (75.9%), all were Asians (79.7% from Japan and 20.3% from Korea), and the median age was 66.0 years (range 28 to 82 years). The majority of subjects had gastric cancer (87.2%) and 12.8% had GEJ cancer. Almost all subjects had Stage IV tumours (97.3%); 67.9% had intestinal and 24.6% had diffuse histological subtype. The median number of prior anti-cancer regimens for locally advanced/metastatic disease was 3 (range 2 to 9), representing a heavily pre-treated population of patients for whom there are currently limited treatment options.

The primary endpoint, ORR based on ICR, in the Response Evaluable Set was 51.3% (95% CI 41.9, 60.5) in the trastuzumab deruxtecan group and 14.3% (95% CI 6.4, 26.2) in the physician's choice group, and the difference between treatment groups was statistically significant (Cochran-Mantel-Haenszel [CMH] test, $p<0.0001$; Fisher's exact test, $p<0.0001$). ORR based on ICR in the ITT analysis set was 48.4% (95% CI 39.4, 57.5) in the trastuzumab deruxtecan group and 12.9% (95% CI 5.7, 23.9) in the physician's choice group (CMH test, $p<0.0001$; Fisher's exact test, $p<0.0001$).

As a supportive analysis, confirmed ORR per ICR was analysed with confirmation of response no earlier than 4 weeks from the first documented response of CR or PR. The confirmed ORR based on ICR in the Response Evaluable Set was 42.9% (95% CI 33.8, 52.3) in the trastuzumab deruxtecan group and 12.5% (95% CI 5.2, 24.1) in the physician's choice group (CMH test, $p<0.0001$; Fisher's exact test, $p<0.0001$). The confirmed ORR based on ICR in the ITT analysis set was 40.5% (95% CI 31.8, 49.6) in the trastuzumab deruxtecan group and 11.3% (95% CI 4.7, 21.9) in the physician's choice group (CMH test, $p<0.0001$; Fisher's exact test, $p<0.0001$).

The pre-specified interim OS analysis was conducted at the time of the data cut-off for the primary analysis for ORR (08 November 2019). A total of 101 OS events were reported: 62 events (49.6%) in the trastuzumab deruxtecan group (n = 125) and 39 events (62.9%) in the physician's choice group (n = 62). The median OS was 12.5 months (95% CI 9.6, 14.3) for the trastuzumab deruxtecan group and 8.4 months (95% CI 6.9, 10.7) for the physician's choice group (stratified log-rank test, $p=0.0097$; statistical significance was met based on the O'Brien Fleming boundary = 0.0202). The adjusted OS hazard ratio (HR) for the trastuzumab deruxtecan group vs the physician's choice group was 0.59 (95% CI 0.39, 0.88). The updated OS analysis results (data cut-off date of 03 June 2020) were subsequently provided and showed consistent results with that of the interim analysis. At the updated analysis, a total of 133 OS events were reported: 84 events (67.2%) in the trastuzumab deruxtecan group and 49 events (79.0%) in the physician's choice group. The median OS was 12.5 months (95% CI 10.3, 15.2) for the trastuzumab deruxtecan group and 8.9 months (95% CI 6.4, 10.4) for the physician's choice group. The adjusted OS HR for the trastuzumab deruxtecan group vs the physician's choice group was 0.60 (95% CI 0.42, 0.86; $p=0.0051$).

Kaplan-Meier plot of OS (FAS) (data cut-off date 08 November 2019)



No. of Subjects at Risk

DS-8201a	125	115	88	54	33	14	7	3	0
Phys. Choice	62	54	37	19	10	2	2	0	0

PFS events by ICR were reported in 109 subjects: 73 subjects (58.4%) in the trastuzumab deruxtecan group (n = 125) and 36 subjects (58.1%) in the physician's choice group (n = 62). The median PFS by ICR was 5.6 months (95% CI 4.3, 6.9) in the trastuzumab deruxtecan group and 3.5 months (95% CI 2.0, 4.3) in the physician's choice group (stratified log-rank test, p=0.0003). The adjusted PFS HR for the trastuzumab deruxtecan group vs the physician's choice group was 0.47 (95% CI 0.31, 0.71).

The median DOR was 8.4 months (95% CI 5.5, NE) in the trastuzumab deruxtecan group and 3.9 months (95% CI 3.0, 4.9) in the physician's choice group. The median duration of confirmed response was 11.3 months (95% CI 5.6, NE) in the trastuzumab deruxtecan group and 3.9 months (95% CI 3.0, 4.9) in the physician's choice group.

The subgroup analyses showed generally consistent ORR per ICR across the subgroups analysed, except that the ORR was higher in subjects with HER2 status of IHC3+ in central laboratory (n = 91; 58.2% [95% CI 47.4, 68.5]) than in subjects with HER2 status of IHC2+/ISH+ (n = 28; 28.6% [95% CI 13.2, 48.7]) in the trastuzumab deruxtecan group. The ORR in subjects with IHC2+/ISH+ was comparable between the trastuzumab deruxtecan and physician's choice group (n = 12; 25.0% [95% CI 5.5, 57.2]). In addition, an OS benefit was not shown in the subgroup with ICH2+/ISH+ (OR HR 1.14; 95% CI 0.52, 2.50). It should be noted that the sample size in the subgroup with IHC2+/ISH+ was much smaller and the 95% CI was wide, hence definitive conclusions cannot be drawn based on these subgroup analyses.

Overall, the efficacy of trastuzumab deruxtecan in the treatment of patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had received at least two prior regimens, including a fluoropyrimidine, platinum and trastuzumab, was adequately demonstrated in terms of a statistically significant and clinically meaningful prolongation of OS in the trastuzumab deruxtecan arm compared to the physician's choice

group, which was supported by the consistent treatment benefit demonstrated in terms of ORR, PFS and DOR.

Summary of efficacy results from study J202

	Trastuzumab deruxtecan	Physician's Choice
Unconfirmed ORR by ICR in the Response Evaluable Set n/N (%) (95% CI)	61/119 (51.3%) (41.9, 60.5)	8/56 (14.3%) (6.4, 26.2)
CMH test (p-value) Fisher's exact test (p-value)	<0.0001 <0.0001	
Best overall response (unconfirmed) by ICR CR PR SD PD NE	 11 (9.2%) 50 (42.0%) 42 (35.3%) 14 (11.8%) 2 (1.7%)	 0 (0.0%) 8 (14.3%) 27 (48.2%) 17 (30.4%) 4 (7.1%)
Confirmed ORR by ICR in the Response Evaluable Set n/N (%) (95% CI)	51/119 (42.9%) (33.8, 52.3)	7/56 (12.5%) (5.2, 24.1)
CMH test (p-value) Fisher's exact test (p-value)	<0.0001 <0.0001	
Best overall response (confirmed) by ICR CR PR SD PD NE	 10 (8.4%) 41 (34.5%) 51 (42.9%) 14 (11.8%) 3 (2.5%)	 0 (0.0%) 7 (12.5%) 28 (50.0%) 17 (30.4%) 4 (7.1%)
OS in FAS Median (months) (95% CI) Adjusted HR (95% CI) Stratified log-rank p-value	12.5 (9.6, 14.3) 0.59 (0.39, 0.88) 0.0097[a]	8.4 (6.9, 10.7)
PFS in FAS Median (months) (95% CI) Adjusted HR (95% CI) Stratified log-rank p-value	5.6 (4.3, 6.9) 0.47 (0.31, 0.71) 0.0003	3.5 (2.0, 4.3)
Duration of unconfirmed response in FAS Median (months) (95% CI)	8.4 (5.5, NE)	3.9 (3.0, 4.9)
Duration of confirmed response in FAS Median (months) (95% CI)	11.3 (5.6, NE)	3.9 (3.0, 4.9)

Data cut-off date 08 November 2019
NE = not estimated
[a] Statistically significant based on the O'Brien Fleming boundary of significance for the 2-sided p-value of 0.0202.

D ASSESSMENT OF CLINICAL SAFETY

Breast cancer

The safety evaluation of trastuzumab deruxtecan for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens was based on the pooled safety data from the pivotal Phase II study U201 and the supportive Phase I study J101, which was an open-label, non-randomised, first-in-human, dose-finding study in subjects with advanced solid malignant tumours.

As of the data cut-off date of 01 August 2019, the safety database included 542 subjects who had received at least one dose of trastuzumab deruxtecan, of whom 234 subjects with HER2-

positive unresectable or metastatic breast cancer were treated with the recommended dose of 5.4 mg/kg (pooled analysis set comprising 184 subjects in study U201 and 50 subjects in study J101). In this pooled analysis set, the median duration of exposure to trastuzumab deruxtecan was 9.82 months (range 0.7 to 37.1).

Overview of safety profile

	Study J101 (N = 50)	**Study U201 (N = 184)**	**Pooled (N = 234)**
Any AE	50 (100.0%)	183 (99.5%)	233 (99.6%)
Treatment-related AE	50 (100.0%)	183 (99.5%)	233 (99.6%)
≥Grade 3 AE	23 (46.0%)	105 (57.1%)	128 (54.7%)
Treatment-related ≥Grade 3 AE	18 (36.0%)	89 (48.4%)	107 (45.7%)
Serious AE (SAE)	12 (24.0%)	42 (22.8%)	54 (23.1%)
Treatment-related SAE	4 (8.0%)	23 (12.5%)	27 (11.5%)
AE leading to treatment discontinuation	8 (16.0%)	28 (15.2%)	36 (15.4%)
Treatment-related AE leading to treatment discontinuation	6 (12.0%)	27 (14.7%)	33 (14.1%)
AE leading to dose reduction	5 (10.0%)	43 (23.4%)	48 (20.5%)
Treatment-related AE leading to dose reduction	4 (8.0%)	40 (21.7%)	44 (18.8%)
AE leading to dose interruption	22 (44.0%)	65 (35.3%)	87 (37.2%)
Treatment-related AE leading to dose interruption	15 (30.0%)	53 (28.8%)	68 (29.1%)
AE leading to death	3 (6.0%)	9 (4.9%)	12 (5.1%)
Treatment-related AE leading to death	1 (2.0%)	2 (1.1%)	3 (1.3%)

Almost all subjects (99.6%) experienced at least one treatment-emergent adverse event (AE). The most common AEs were primarily gastrointestinal or haematologic in nature, with nausea (79.9%) reported with the highest incidence, followed by fatigue (49.1%), vomiting (48.7%), alopecia (46.2%), constipation (35.9%), decreased appetite (34.6%), anaemia (33.8%), neutrophil count decrease (32.5%), diarrhoea (30.8%), platelet count decrease (23.1%), cough (21.4%), white blood cell count decrease (20.5%), abdominal pain (18.8%) and headache (18.8%). Both gastrointestinal and haematological events are known side effects of topoisomerase inhibitors and are expected for an antibody-drug conjugate such as trastuzumab deruxtecan.

Serious adverse events (SAEs) were reported in 54/234 (23.1%) subjects, and included pneumonitis (2.6%), pneumonia (2.1%), respiratory failure (2.1%), cellulitis (1.7%), vomiting (1.7%), pleural effusion (1.3%), nausea (1.3%), intestinal obstruction (1.3%) and hypokalaemia (1.3%). AEs leading to treatment discontinuation were reported in 36/234 (15.4%) subjects, including interstitial lung disease (9.0%) and platelet count decrease (0.9%) that were reported in more than one subject.

Treatment-emergent AEs associated with an outcome of death were reported in 12/234 (5.1%) subjects in the pooled analysis set. One subject had two AEs reported with an outcome of death: acute hepatic failure and acute kidney injury, both of which were attributed to disease progression. The other AEs with an outcome of death were respiratory failure (3 [1.3%] subjects), disease progression (2 [0.9%] subjects) and one subject (0.4%) each with haemorrhagic shock, general physical health deterioration, acute respiratory failure, lymphangitis, pneumonia, and pneumonitis. The investigator considered the AEs associated with an outcome of death to be treatment-related in 3 subjects (respiratory failure in 2 subjects and pneumonitis in 1 subject).

Interstitial lung disease (ILD) is an important identified risk associated with trastuzumab deruxtecan treatment. An independent ILD adjudication committee was established to adjudicate all events of potential ILD reported in the clinical trials. A total of 35/234 (15.0%)

subjects had events adjudicated as an ILD event. Of these, 32 subjects (13.7%) had treatment-related events of Grade 1 in 6 (2.6%) subjects, Grade 2 in 19 (8.1%) subjects, Grade 3 in 1 (0.4%) subject, Grade 4 in none and fatal outcome (Grade 5) in 6 (2.6%) subjects. There appeared to be a dose-response relationship in the occurrence of ILD events, with subjects treated with the higher dose of ≥6.4 mg/kg experiencing more events than those treated with the recommended 5.4 mg/kg dose (24.8% vs 13.7%). The median time to onset of ILD was 4.4 months (range 1.2 to 11.1 months). The management of ILD requires close monitoring, dose modification and early intervention. The package insert for trastuzumab deruxtecan has included adequate warnings on ILD/pneumonitis including monitoring advice, recommendations for corticosteroid treatment, dose interruption for asymptomatic (Grade 1) events and permanent discontinuation for symptomatic (Grade 2 or higher) events.

Cardiac dysfunction including congestive heart failure (CHF) and left ventricular ejection fraction (LVEF) decrease are known AEs with anti-HER2 therapies. AEs of ejection fraction decreased were reported in 3/234 (1.3%) subjects and cardiac failure in 2/234 (0.85%) subjects treated with trastuzumab deruxtecan. In addition, LVEF was measured based on laboratory parameters (echocardiogram [ECHO] or multigated acquisition [MUGA] scanning) and graded. A total of 37 (16.9%) of the 219 subjects with post-baseline data met the laboratory criteria for a Grade 2 value (i.e. resting LVEF 50%-40%; 10-19% decrease from baseline). No subject met the laboratory criteria for Grade 3 or 4 LVEF decrease; no subject had a post-baseline resting LVEF of <40%. It should be noted that patients with a history of clinically significant cardiac disease or LVEF <50% were excluded from the studies. This information has been reflected in the package insert and adequate warnings on LVEF decrease and CHF, including recommendations for monitoring and dose modifications have been described.

A total of 6/234 (2.6%) subjects had events categorised under the group term of infusion-related reactions (IRR), comprising IRR in 4 subjects, hypersensitivity in 1 subject and flushing in 1 subject. All events were mild to moderate (Grade 1 to 2) in severity, with one report of an SAE of Grade 1 hypersensitivity, and one subject had dosing interrupted. All IRR events resolved without need for treatment discontinuation or dose reduction, and no severe allergic reactions were observed.

Overall, the safety profile of trastuzumab deruxtecan was considered acceptable in the target population of patients with unresectable or metastatic HER2-positive breast cancer who have already received two anti-HER2-based regimens and have limited treatment options. The main safety risks, including ILD/pneumonitis, haematological AEs and left ventricular dysfunction, have been adequately described in the package insert and can be managed with monitoring and dose modifications.

Gastric cancer

The safety evaluation of trastuzumab deruxtecan for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received two or more prior regimens including an anti-HER2 therapy was based primarily on data from the pivotal Phase II study J202 and supplemented by supportive data from the Phase I study J101. In addition, the safety data for gastric cancer subjects who received trastuzumab deruxtecan at the recommended dose of 6.4 mg/kg in studies J101 (N = 25) and J202 (N = 125) were pooled (referred to as the T-DXd Pool).

As of the data cut-off dates of the individual studies (08 November 2019 for study J202 and 01 August 2019 for study J101), the median treatment duration for trastuzumab deruxtecan in the T-DXd Pool was 4.6 months (range 0.7 to 22.3). In study J202, the median treatment duration

was 4.6 months (range 0.7 to 22.3) for the trastuzumab deruxtecan arm and 2.8 months (range 0.5 to 13.1) for the control arm (irinotecan/paclitaxel).

Overview of safety profile

	Study J202		Study J101 (N = 25)	T-DXd Pool (N = 150)
	Trastuzumab deruxtecan (N = 125)	Physician's Choice (N = 62)		
Any AE	125 (100.0%)	61 (98.4%)	25 (100.0%)	150 (100.0%)
Treatment-related AE	122 (97.6%)	56 (90.3%)	25 (100.0%)	147 (98.0%)
≥Grade 3 AE	107 (85.6%)	35 (56.5%)	20 (80.0%)	127 (84.7%)
Treatment-related ≥Grade 3 AE	94 (75.2%)	27 (43.5%)	16 (64.0%)	110 (73.3%)
Serious AE (SAE)	55 (44.0%)	15 (24.2%)	7 (28.0%)	62 (41.3%)
Treatment-related SAE	27 (21.6%)	5 (8.1%)	3 (12.0%)	30 (20.0%)
AE leading to treatment discontinuation	19 (15.2%)	4 (6.5%)	4 (16.0%)	23 (15.3%)
Treatment-related AE leading to treatment discontinuation	12 (9.6%)	3 (4.8%)	3 (12.0%)	15 (10.0%)
AE leading to dose reduction	40 (32.0%)	21 (33.9%)	9 (36.0%)	49 (32.7%)
Treatment-related AE leading to dose reduction	38 (30.4%)	21 (33.9%)	9 (36.0%)	47 (31.3%)
AE leading to dose interruption	78 (62.4%)	23 (37.1%)	13 (52.0%)	91 (60.7%)
Treatment-related AE leading to dose interruption	64 (51.2%)	19 (30.6%)	11 (44.0%)	75 (50.0%)
AE leading to death	8 (6.4%)	2 (3.2%)	1 (4.0%)	9 (6.0%)
Treatment-related AE leading to death	1 (0.8%)	0	0	1 (0.7%)

Similar to the breast cancer studies, the safety profile of trastuzumab deruxtecan in gastric cancer patients was mainly characterised by high incidences of gastrointestinal (nausea, vomiting) and haematological AEs (neutropenia, anaemia, thrombocytopenia, lymphopenia), as well as ILD. The incidences of these AEs were generally higher with trastuzumab deruxtecan compared to the physician's choice treatment comprising irinotecan or paclitaxel.

In study J202, all subjects (100.0%) in the trastuzumab deruxtecan group and 98.4% of subjects in the physician's choice group experienced at least one treatment-emergent AE. The majority were gastrointestinal or haematologic in nature, the most common being nausea which was reported with a higher incidence in the trastuzumab deruxtecan group compared to the physician's choice group (63.2% vs 46.8%). Other AEs reported with higher incidence with trastuzumab deruxtecan included decreased appetite (60.0% vs 45.2%), neutropenia (63.2% vs 35.5%), anaemia (57.6% vs 30.6%), thrombocytopenia (39.2% vs 6.5%), malaise (34.4% vs 16.1%), vomiting (26.4% vs 8.1%), pyrexia (24.0% vs 16.1%), alopecia (22.4% vs 14.5%), lymphopenia (21.6% vs 3.2%), stomatitis (11.2% vs 4.8%), weight decreased (13.6% vs 8.1%), aspartate aminotransferase (AST) increased (9.6% vs 4.8%) and ILD (9.6% vs 0%).

SAEs were reported with a higher incidence in the trastuzumab deruxtecan group compared to the physician's choice group (44.0% vs 24.2%), the most common of which were decreased appetite (10.4% vs 1.6%) and ILD (4.0% vs 0%). AEs leading to treatment discontinuation were also reported with a higher incidence in the trastuzumab deruxtecan group compared to the physician's choice group (15.2% vs 6.5%), mainly contributed by events of ILD (5.6% vs 0%), pneumonia (1.6% vs 0%) and anaemia (1.6% vs 0%).

Treatment-emergent AEs associated with an outcome of death were reported in 8/125 (6.4%) subjects in the trastuzumab group and 2/62 (3.2%) subjects in the physician's choice group. Fatal AEs in the trastuzumab deruxtecan group included disease progression/neoplasm progression (5 subjects), disseminated intravascular coagulation (1 subject), large intestine

perforation (1 subject) and pneumonia (1 subject). Of these, the event of pneumonia was considered by the investigator to be treatment-related.

Similar to the breast cancer studies, events of neutropenia were one of the more commonly reported AEs with trastuzumab deruxtecan, although the incidence appeared to be higher in the gastric cancer trials. In study J202, events of neutropenia were reported in 63.2% of subjects in the trastuzumab deruxtecan group and 35.5% in the physician's choice group. Febrile neutropenia was reported in 6/125 (4.8%) subjects (all Grade 3) in the trastuzumab deruxtecan group and 2/62 (3.2%) subjects (1 Grade 3 and 1 Grade 4) in the physician's choice group. In the T-DXd Pool, neutropenia was reported in 60.7% of subjects. The median time to onset of neutropenia was 16.0 days (range 6 to 187). Febrile neutropenia was reported in 7/150 (4.7%) subjects, all of which were Grade 3. Action taken for febrile neutropenia was dose reduction in 3/150 (2.0%) subjects and dose interruption in 1/150 (0.7%) subject. None had study drug discontinued due to febrile neutropenia. A total of 29/150 (19.3%) subjects in the T-DXd Pool and 10/62 (16.1%) subjects in the physician's choice group received treatment with a granulocyte-colony stimulating factor (G-CSF) within 28 days after onset of an event of neutropenia or febrile neutropenia. The majority of subjects had their events of neutropenia resolved or recovered (85.7% in the T-DXd Pool vs 77.3% in the physician's choice group). The package insert has included adequate warnings on neutropenia and febrile neutropenia, including recommendations for monitoring of complete blood counts and dose modifications.

In study J202, adjudicated ILD events were reported in 12 (9.6%) subjects in the trastuzumab deruxtecan group and none in the physician's choice group. In the T-DXd Pool, adjudicated ILD events were reported in 16 (10.7%) subjects. Of these, 15 (10.0%) subjects had events assessed as treatment-related, with the majority reported as either Grade 1 (3/150 [2.0%]) or Grade 2 (9/150 [6.0%]); Grade 3 ILD events were reported in 2/150 (1.3%) subjects and Grade 4 ILD events in 1/150 (0.7%) subject. None of the events were associated with an outcome of death. The median time to onset of the first ILD event was 2.8 months (range 1.2 to 21.0). Treatment-related ILD events were associated with discontinuation of study treatment in 9/150 (6.0%) subjects and dose interruption in 6/150 (4.0%) subjects. None were associated with dose reduction.

In study J202, there were no AEs of left ventricular dysfunction reported. One subject in study J101 experienced a Grade 3 AE of LVEF decreased. None of the 62 subjects in the physician's choice arm had reports of events of potential left ventricular dysfunction. A total of 10/142 (7.0%) subjects with post-baseline LVEF data in the T-DXd Pool met the laboratory criteria for Grade 2 LVEF decrease and 1/142 (0.7%) met the criteria for Grade 3 LVEF decrease. No subject had a post-baseline resting LVEF of <45%.

Overall, the safety profile of trastuzumab deruxtecan in gastric cancer patients was generally consistent with that in the breast cancer population, with ILD/pneumonitis, neutropenia and left ventricular dysfunction being the main safety risks associated with trastuzumab deruxtecan, and was considered acceptable for the intended patient population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Breast cancer

Advanced or metastatic breast cancer is a serious, life-threatening and incurable disease, and the goals of treatment are mainly palliative in nature to delay disease progression, prolong

survival and reduce cancer-related symptoms. For patients who have received two or more prior HER2-based regimens, response rates with historical controls are low (ranging from 12% to 15%) with limited durability, and survival is poor with 4 to 5 months of median PFS.

The efficacy of trastuzumab deruxtecan in the treatment of patients with unresectable or metastatic HER2-positive breast cancer had been demonstrated in respect of a high ORR by ICR of 60.3% (95% CI 52.9, 67.5) at the initial data cut-off date (21 March 2019) in study U201. The ORR results remained consistent at the updated data cut-off date (08 June 2020), with an ORR of 61.4% (95% CI 54.0, 68.5).

The ORR results from the pivotal study U201 (61.4%) could be considered promising and compared favourably with that of historical controls in a similar patient population (ORR 12-15%). The magnitude of the response could be considered clinically meaningful in the context of the heavily pre-treated population who have received two or more prior HER2-based regimens and have limited treatment options.

At the updated data cut-off date (08 June 2020), the estimated median DOR was 20.8 months (95% CI 15.0, NE), median PFS was 19.4 months (95% CI 14.1, NE) and median OS was 24.6 months (95% CI 23.1, NE). However, meaningful conclusions could not be drawn from these time-to-event endpoints in the absence of a comparator arm in a single-arm study.

Gastrointestinal events were the most frequent AEs reported with trastuzumab deruxtecan, with nausea (79.9%) reported with the highest incidence, followed by vomiting (48.7%), constipation (35.9%), diarrhoea (30.8%) and abdominal pain (18.8%). Haematological AEs were also commonly reported, including anaemia (33.8%), neutrophil count decrease (32.5%), platelet count decrease (23.1%) and white blood cell count decrease (20.5%). Both gastrointestinal and haematological events are expected side effects of cytotoxic drugs such as topoisomerase inhibitors and can be adequately managed with monitoring and dose modifications.

ILD is an important identified risk for trastuzumab deruxtecan. A total of 15.0% of subjects had AEs adjudicated as an ILD event with fatal outcome in 2.6% of subjects. The management of ILD requires close monitoring, dose modification and early intervention. The package insert for trastuzumab deruxtecan has included adequate warnings on ILD/pneumonitis including monitoring advice, recommendations for corticosteroid treatment, dose interruption for asymptomatic (Grade 1) events and permanent discontinuation for symptomatic (Grade 2 or higher) events.

The safety profile was considered acceptable in the intended patient population who have limited treatment options. The main safety risks, including ILD/pneumonitis, haematological AEs and left ventricular dysfunction, have been adequately described in the package insert.

Overall, the ORR observed with trastuzumab deruxtecan together with the durability of the responses were considered promising and the safety profile was considered acceptable for the treatment population. Taken together, the benefit-risk profile of trastuzumab deruxtecan in the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting was considered favourable.

Gastric cancer

Locally advanced or metastatic gastric or GEJ cancer is a serious, life-threatening condition. There is currently no approved HER2-targeted therapy for patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have progressed on chemotherapy with fluoropyrimidine, platinum agents and trastuzumab. Survival outcomes in the third-line setting and beyond are poor, with an estimated median survival of approximately 6-8 months.

The efficacy of trastuzumab deruxtecan in the treatment of patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma had been adequately demonstrated in study J202 based on a statistically significant and clinically meaningful improvement in OS for trastuzumab deruxtecan compared to physician's choice of chemotherapy (median 12.5 months vs 8.4 months; HR 0.59; 95% CI 0.39, 0.88; p=0.0097) at the initial data cut-off date (08 November 2019), which was maintained at the updated cut-off date (03 June 2020) (median 12.5 months vs 8.9 months; HR 0.60; 95% CI 0.42, 0.86; p=0.0051).

The primary endpoint, ORR based on ICR, in the Response Evaluable Set was higher in the trastuzumab deruxtecan group (51.3%; 95% CI 41.9, 60.5) compared to the physician's choice group (14.3%; 95% CI 6.4, 26.2), and the difference was statistically significant (p<0.0001). Similar ORR results were seen in the ITT analysis set: 48.4% (95% CI 39.4, 57.5) in the trastuzumab deruxtecan group compared to 12.9% (95% CI 5.7, 23.9) in the physician's choice group (p<0.0001).

The PFS was prolonged with trastuzumab deruxtecan compared to physician's choice (5.6 vs 3.5 months; HR 0.47; 95% CI 0.31, 0.71; p=0.0003). The median DOR was 8.4 months (95% CI 5.5, NE) in the trastuzumab deruxtecan group compared to 3.9 months (95% CI 3.0, 4.9) in the physician's choice group.

Similar to the breast cancer studies, the safety profile of trastuzumab deruxtecan in gastric cancer patients was mainly characterised by high incidences of gastrointestinal (nausea, vomiting) and haematological AEs (neutropenia, anaemia, thrombocytopenia, lymphopenia), as well as ILD. The most commonly reported AEs and their incidences (trastuzumab deruxtecan vs physician's choice) in the gastric cancer study were nausea (63.2% vs 46.8%), decreased appetite (60.0% vs 45.2%), neutropenia (63.2% vs 35.5%), anaemia (57.6% vs 30.6%), thrombocytopenia (39.2% vs 6.5%), malaise (34.4% vs 16.1%), vomiting (26.4% vs 8.1%), pyrexia (24.0% vs 16.1%), alopecia (22.4% vs 14.5%), lymphopenia (21.6% vs 3.2%), stomatitis (11.2% vs 4.8%), weight decreased (13.6% vs 8.1%), AST increased (9.6% vs 4.8%) and ILD (9.6% vs 0%).

Adjudicated ILD events were reported in 12 (9.6%) subjects in the trastuzumab deruxtecan group and none in the physician's choice group. Treatment-related ILD events were associated with discontinuation of study treatment in 6.0% of subjects and dose interruption in 4.0% of subjects. None of the events were associated with an outcome of death or required dose reduction.

Overall, the safety profile of trastuzumab deruxtecan in gastric cancer patients was generally consistent with that in the breast cancer population, and the main safety risks (ILD/pneumonitis, haematological AEs and left ventricular dysfunction) have been adequately described in the package insert including recommendations for monitoring and dose modifications.

Trastuzumab deruxtecan had been demonstrated to provide a statistically significant and clinically meaningful improvement in OS and ORR compared to currently available

chemotherapy options. While the treatment was associated with significant toxicities, the clinical benefits were considered to outweigh the risks in patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received two or more prior regimens, including a trastuzumab-based regimen.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits-risks of Enhertu was considered favourable for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens in the metastatic setting, and for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received two or more prior regimens, including a trastuzumab-based regimen. Approval of the product registration was granted on 22 October 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

ENHERTU®
(trastuzumab deruxtecan)

1. NAME OF THE MEDICINAL PRODUCT

ENHERTU powder for concentrate for solution for infusion 100 mg
trastuzumab deruxtecan.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

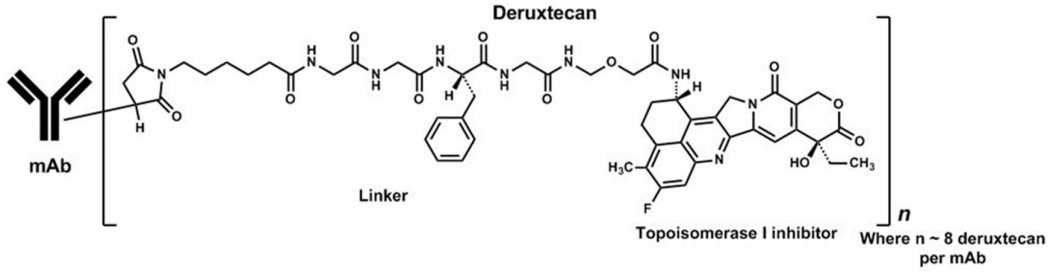
ENHERTU Powder for Concentrate for Solution for Infusion 100 mg

One vial of lyophilized powder for concentrate for solution for infusion delivers 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of trastuzumab deruxtecan (see section 6.6).

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology and the topoisomerase I inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

For excipients, see section 6.1.



3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to yellowish-white lyophilized powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received two or more prior regimens, including a trastuzumab-based regimen.

4.2 Posology and method of administration

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.

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.

Posology

Metastatic Breast Cancer

The recommended dose of ENHERTU is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Locally Advanced or Metastatic Gastric Cancer

The recommended dose of ENHERTU is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

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	Breast Cancer	Gastric Cancer
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment.	Discontinue treatment.

Table 2 Dose Modifications for Adverse Reactions

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 4.4).
	Symptomatic ILD/Pneumonitis (Grade 2 or greater)	• Permanently discontinue ENHERTU. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section 4.4).
Neutropenia	Grade 3 (less than 1.0-0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than 0.5 x 10^9/L)	• Interrupt ENHERTU until resolved to Grade 2 or less. • Reduce dose by one level (see Table 1).
Febrile Neutropenia	Absolute neutrophil count of less than 1 x 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.

Adverse Reaction	Severity		Treatment Modification
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	• Continue treatment with ENHERTU. • Repeat LVEF assessment within 3 weeks.
		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 4.03 (NCI CTCAE v.4.03).

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

Geriatrics

No dose adjustment of ENHERTU is required in patients aged 65 years or older.

Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall difference in efficacy was

observed based on age. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (49%) as compared to younger patients (39%).

Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall difference in efficacy was observed based on age. There was a higher incidence of ≥Grade 3 adverse reactions observed in younger patients (87%) as compared to patients aged 65 years or older (76%).

Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of trastuzumab deruxtecan.

Pediatrics

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 pediatric population.

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. No data are available in patients with severe renal impairment.

Hepatic Impairment

No dose adjustment is required in patients with mild (total bilirubin ≤ULN and any 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. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment.

Method 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 ENHERTU before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Interstitial Lung Disease/Pneumonitis

Cases of interstitial lung disease (ILD) and/or pneumonitis have been reported with ENHERTU (see section 4.7). Fatal outcomes have been observed.

Patients should be advised to immediately report cough, dyspnea, 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 radiographic imaging. 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 4.2). 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 4.2). Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

Metastatic Breast Cancer

In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 13.7% of patients as determined by independent review. Most ILD cases were Grade 1 (2.6%), Grade 2 (8.1%), or Grade 3 (0.4%). Grade 5 events occurred in 2.6% of patients. Median time to first onset was 4.4 months (range: 1.2 to 11.1).

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 9.6% of patients as determined by independent review. All ILD cases were Grade 1 (2.4%), Grade 2 (4.8%), Grade 3 (1.6%), or Grade 4 (0.8%). No cases with fatal outcomes were observed. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

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 4.2).

Metastatic Breast Cancer

In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 32.5% of patients and 18.8% had Grade 3 or 4 events. Median time to first onset of decreased neutrophil count was 53 days (range: 8 to 547). Febrile neutropenia was reported in 1.7% of patients.

Locally advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 63.2% of patients and 51.2% had Grade 3 or 4 events. Median time to first onset of decreased neutrophil count was 16 days (range: 6 to 187). Febrile neutropenia was reported in 4.8% of patients.

Left Ventricular Ejection Fraction Decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, three cases (1.3%) of asymptomatic LVEF decrease were reported. Observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 16.9%; all were Grade 2. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive

gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported. Observed frequency of LVEF decreased based on laboratory parameters was 7.7%; all were Grade 2.

No decreases of LVEF to less than 40% were observed. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

LVEF should be assessed prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. 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 4.2).

Embryo-Fetal Toxicity

ENHERTU can cause fetal 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 can also cause embryo-fetal harm when administered to a pregnant woman (see section 4.6).

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 fetus. 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 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Other Medicinal Products on the Pharmacokinetics of ENHERTU

Coadministration 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. No dose adjustment is required during coadministration of ENHERTU with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs 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 that the topoisomerase I inhibitor component of ENHERTU does not inhibit or induce major CYP450 enzymes.

4.6 Pregnancy and lactation

Contraception in Males and Females

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

ENHERTU can cause fetal harm when administered to a pregnant woman. 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 can also cause embryo-fetal harm when administered to a pregnant woman (see section 5.3).

Administration of ENHERTU to pregnant women is not recommended, and patients should be informed of the potential risks to the fetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a woman becomes pregnant during treatment with ENHERTU or within 7 months following the last dose of ENHERTU, close monitoring is recommended.

Breastfeeding

It is not known if ENHERTU is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding prior to initiating treatment with ENHERTU. Women may begin breastfeeding 7 months after concluding treatment.

Women of Childbearing Potential

Pregnancy status of women of childbearing potential should be verified prior to initiation of ENHERTU.

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.

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 counseling 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.

4.7 Undesirable effects

Summary of the Safety Profile

Metastatic Breast Cancer

The safety of ENHERTU has been evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 9.8 months (range: 0.7 to 37.1).

In ENHERTU-treated patients (N=234), the median age was 56 years (range 28 to 96); 99.6% were female; 50.9% were White, 41.5% were Asian, 3.0% were Black or African American; and 57.7% had an Eastern Cooperative Oncology Group (ECOG) performance status 0 and

41.9% had an ECOG performance status of 1. The studies excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease.

The most common adverse reactions (frequency ≥20%) were nausea (79.9%), fatigue (60.3%), vomiting (48.7%), alopecia (46.2%), constipation (35.9%), decreased appetite (34.6%), anemia (33.8%), neutropenia (32.5%), diarrhea (30.8%), thrombocytopenia (23.1%), cough (21.4%), leukopenia (20.5%), and headache (20.1%). The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03) Grade ≥3 adverse reactions (frequency >1%) were neutropenia (18.8%), anemia (9.0%), nausea (6.8%), fatigue (6.4%), leukopenia (5.6%), lymphopenia (5.1%), vomiting (4.3%), thrombocytopenia (4.3%), hypokalemia (3.4%), ILD (3.0%), diarrhea (2.6%), febrile neutropenia (1.7%), dyspnea (1.7%), abdominal pain (1.3%), decreased appetite (1.3%), and alanine aminotransferase increased (1.3%). In six patients (2.6%) ILD led to death.

Dose interruptions due to adverse reactions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (14.5%), anemia (3.4%), upper respiratory tract infection (3.0%), leukopenia (3.0%), ILD (2.6%), thrombocytopenia (2.6%), and fatigue (2.1%). Dose reductions occurred in 15% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue (3.8%), nausea (3.4%), and neutropenia (3.4%). Discontinuation of therapy due to an adverse reaction occurred in 11% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (9.4%).

Tabulated List of Adverse Reactions

The adverse reactions in 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg 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 Tabulated List of Adverse Reactions in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with Trastuzumab Deruxtecan 5.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Blood and Lymphatic System Disorders	
Neutropenia[a]	Very common
Anemia[b]	Very common
Leukopenia[c]	Very common
Lymphopenia[d]	Very common
Thrombocytopenia[e]	Very common
Febrile neutropenia	Common

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Eye Disorders	
Dry eye	Very common
Gastrointestinal Disorders	
Nausea	Very common
Vomiting	Very common
Diarrhea	Very common
Abdominal pain[f]	Very common
Constipation	Very common
Stomatitis[g]	Very common
Dyspepsia	Very common
General Disorders and Administration Site Conditions	
Fatigue[h]	Very common
Infections and Infestations	
Upper respiratory tract infection[i]	Very common
Injury, Poisoning and Procedural Complications	
Infusion-related reactions[j]	Common
Investigations	
Alanine aminotransferase increased	Very common
Aspartate aminotransferase increased	Very common
Metabolism and Nutrition Disorders	
Hypokalemia	Very common
Decreased appetite	Very common
Nervous System Disorders	
Headache[k]	Very common
Dizziness	Very common
Respiratory, Thoracic and Mediastinal Disorders	
Interstitial lung disease[l]	Very common
Dyspnea	Very common
Cough	Very common
Epistaxis	Very common
Skin and Subcutaneous Tissue Disorders	

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Alopecia	Very common
Rash[m]	Very common

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term
[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.
[b] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased.
[c] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
[d] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[e] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[f] Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.
[g] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.
[h] Grouped term of fatigue includes PTs of fatigue and asthenia.
[i] Grouped term of upper respiratory tract infection includes PTs of influenza, influenza-like illness, and upper respiratory tract infection.
[j] Cases of infusion-related reactions include infusion-related reaction (N=4), hypersensitivity (N=1), and flushing (N=1).
[k] Grouped term of headache includes PTs of headache, sinus headache, and migraine.
[l] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.
[m] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients received intravenously at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or physician's choice of chemotherapy: either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in ENHERTU-treated patients and 2.8 months (range: 0.5 to 13.1) in physician's choice-treated patients: 2.8 months (range: 0.5 to 7.4) in the irinotecan group and 4.6 months (range: 0.9 to 13.1) in the paclitaxel group.

The study population characteristics in the ENHERTU group and the physician's choice group were similar. The median age was 66 years (range 28 to 82), 76% were male, 100% were Asian, and 49% had an ECOG performance status 0 and 51% had an ECOG performance status of 1. The study excluded patients with a history of treated ILD and/or ILD at screening, and patients with a history of clinically significant cardiac disease.

The most common adverse reactions in patients treated with ENHERTU 6.4 mg/kg (frequency ≥20%) were neutropenia (63.2%), nausea (63.2%), decreased appetite (60.0%), anemia (57.6%), fatigue (55.2%), thrombocytopenia (39.2%), leukopenia (37.6%), diarrhea (32.0%), vomiting (26.4%), constipation (24.0%), pyrexia (24.0%), alopecia (22.4%), and lymphopenia (21.6%). The most common NCI CTCAE v.4.03 Grade ≥3 adverse reactions (frequency >2%) were neutropenia (51.2%), anemia (37.6%), leukopenia (20.8%), decreased appetite (16.8%), thrombocytopenia (11.2%), lymphopenia (11.2%), fatigue (8.8%), febrile neutropenia (4.8%), nausea (4.8%), hypokalemia (4.0%), hepatic function abnormal (3.2%), blood alkaline

phosphatase increased (3.2%), diarrhea (2.4%), dehydration (2.4%), aspartate aminotransferase increased (2.4%), and ILD (2.4%).

Dose interruptions due to adverse reactions occurred in 55.2% of patients treated with 6.4 mg/kg of ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (28.0%), anemia (11.2%), decreased appetite (8.8%), leukopenia (8.0%), fatigue (7.2%), thrombocytopenia (4.0%), ILD (3.2%), lymphopenia (3.2%), pneumonia (3.2%), upper respiratory tract infection (3.2%), diarrhea (2.4%), and hypokalemia (2.4%). Dose reductions occurred in 30.4% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia (12.8%), decreased appetite (9.6%), fatigue (8.0%), nausea (4.8%), and febrile neutropenia (2.4%). Discontinuation of therapy due to an adverse reaction occurred in 11.2% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (5.6%).

Tabulated List of Adverse Reactions

The adverse reactions in 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who received at least one dose of ENHERTU 6.4 mg/kg are presented in Table 4. 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 4 Tabulated List of Adverse Reactions in Patients with Locally Advanced or Metastatic HER2-positive Gastric or GEJ Adenocarcinoma Treated with Trastuzumab Deruxtecan 6.4 mg/kg

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Blood and Lymphatic System Disorders	
Neutropenia[a]	Very common
Anemia[b]	Very common
Leukopenia[c]	Very common
Thrombocytopenia[d]	Very common
Lymphopenia[e]	Very common
Febrile neutropenia	Common
Gastrointestinal Disorders	
Nausea	Very common
Diarrhea	Very common
Stomatitis[f]	Very common
Abdominal pain[g]	Very common
Vomiting	Very common

MedDRA System Organ Class/Preferred Term or Grouped Term	Frequency
Constipation	Very common
General Disorders and Administration Site Conditions	
Fatigue[h]	Very common
Pyrexia	Very common
Edema peripheral	Very common
Hepatobiliary Disorders	
Hepatic function abnormal	Common
Infections and Infestations	
Pneumonia	Common
Upper respiratory tract infection[i]	Common
Injury, Poisoning and Procedural Complications	
Infusion-related reactions[j]	Common
Investigations	
Blood alkaline phosphatase increased	Common
Aspartate aminotransferase increased	Common
Alanine aminotransferase increased	Common
Blood bilirubin increased	Common
Metabolism and Nutrition Disorders	
Decreased appetite	Very common
Hypokalemia	Common
Dehydration	Common
Respiratory, Thoracic and Mediastinal Disorders	
Interstitial lung disease[k]	Common
Cough	Common
Epistaxis	Common
Dyspnea	Uncommon
Skin and Subcutaneous Tissue Disorders	
Alopecia	Very common
Pruritis	Common
Rash[l]	Common

MedDRA = Medical Dictionary for Regulatory Activities
PT = preferred term
[a] Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

[b] Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.
[c] Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.
[d] Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[e] Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.
[f] Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.
[g] Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain lower, and abdominal pain upper.
[h] Grouped term of fatigue includes PTs of fatigue, malaise, and asthenia.
[i] Grouped term of upper respiratory tract infection includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.
[j] Cases include PT of infusion-related reaction.
[k] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.
[l] Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 1.7% (14/807) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with ENHERTU. There was no association between development of antibodies and allergic-type reactions.

4.8 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies
ATC code: L01XC41

Mechanism of Action

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

Pharmacodynamic Effects

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 in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.

Clinical Efficacy

Metastatic Breast Cancer

The efficacy and safety of ENHERTU were demonstrated in a Phase 2, single-agent, open-label, multicenter study: DESTINY-Breast01.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2 regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumor 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 and patients with a history of clinically significant cardiac disease. ENHERTU was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression, death, withdrawal of consent, 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 (ICR). Duration of response (DOR) and progression-free survival (PFS) were additional outcome measures.

DESTINY-Breast01 (N=184) 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 summarized in Table 5.

Table 5 Efficacy Results by Independent Central Review in DESTINY-Breast01 (Intent-to-Treat Analysis Set)

Efficacy Parameter	**DESTINY-Breast01 N=184**
Confirmed Objective Response Rate (95% CI)	61.4% (54.0, 68.5)
Complete Response	6.5%
Partial Response	54.9%
Stable Disease	35.9%
Progressive Disease	1.6%
Not Evaluable	1.1%
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)
Progression-free Survival Median, months (95% CI)[†]	19.4 (14.1, NR)

ORR 95% CI calculated using Clopper-Pearson method

CI = confidence interval
95% CIs calculated using Brookmeyer-Crowley method
†Based on Kaplan-Meier estimates
NR = not reached

Consistent antitumor activity was observed with ENHERTU regardless of prior pertuzumab therapy and hormone receptor status. In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 66% (95% CI: 57, 76), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 55% (95% CI: 42, 68). The subgroup of patients who were hormone receptor positive at baseline had a confirmed ORR of 59% (95% CI: 48, 69), and those who were hormone receptor negative at baseline had a confirmed ORR of 68% (95% CI: 56, 77).

Locally Advanced or Metastatic Gastric Cancer

The efficacy and safety of ENHERTU were demonstrated in a Phase 2, multicenter, open-label, randomized study: DESTINY-Gastric01. The study included adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine agent, and a platinum agent. Patients were randomized 2:1 to receive either ENHERTU (N=126) or physician's choice of chemotherapy: either irinotecan (N=55) or paclitaxel (N=7). Randomization was stratified by HER2 status (IHC 3+ or IHC 2+/ISH+), ECOG performance status (0 or 1), and region (Japan or South Korea). ENHERTU was administered by intravenous infusion at 6.4 mg/kg every three weeks. Irinotecan monotherapy was administered by intravenous infusion biweekly at 150 mg/m^2. Paclitaxel monotherapy was administered by intravenous infusion weekly at 80 mg/m^2. Tumor samples were required to have centrally confirmed HER2 positivity defined as IHC 3+ or IHC 2+/ISH+. The study excluded patients with a history of treated ILD and/or ILD at screening, patients with a history of clinically significant cardiac disease, and patients with active brain metastases. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was ORR assessed by ICR based on RECIST v1.1. Overall survival (OS) was a key secondary endpoint. PFS, DOR, and confirmed ORR were additional secondary outcome measures.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 188 patients, the median age was 66 years (range 28 to 82); 76% were male; 100% were Asian. Patients had an ECOG performance status of either 0 (49%) or 1 (51%); 87% had gastric adenocarcinoma and 13% had GEJ adenocarcinoma; 76% were IHC 3+ and 23% were IHC 2+/ISH+; 65% had inoperable advanced cancer; 35% had postoperative recurrent cancer; 54% had liver metastases; 29% had lung metastases; the sum of diameters of target lesions was <5 cm in 47%, ≥5 to <10 cm in 30%, and ≥10 cm in 17%; 55 % had two and 45% had three or more prior regimens in the locally advanced or metastatic setting.

The study demonstrated a statistically significant and clinically meaningful improvement in ORR and OS in the ENHERTU-treated group compared to the chemotherapy-treated group. Efficacy results are summarized in Table 6 and the Kaplan-Meier curve for OS is shown in Figure 1.

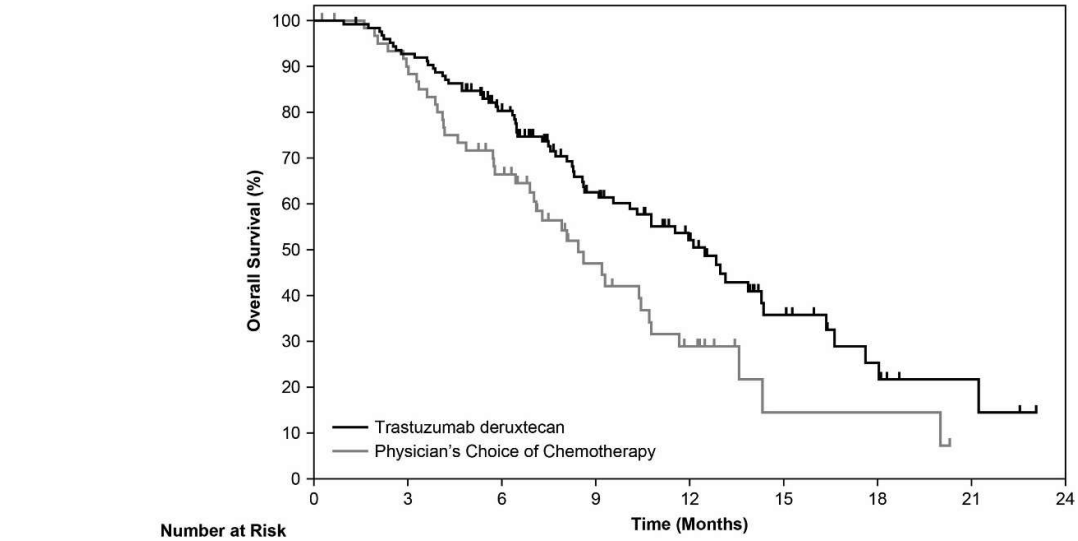
Table 6 Efficacy Results in DESTINY-Gastric01 (Intent-to-Treat Analysis Set)

Efficacy Parameter	ENHERTU N=126	Physician's Choice of Chemotherapy N=62
Overall Survival (OS)*		
Median, months (95% CI)†	12.5 (9.6, 14.3)	8.4 (6.9,10.7)
Hazard ratio (95% CI)‡	0.59 (0.39, 0.88)	
Stratified Log-rank p-value‡	p=0.0097	
Progression-Free Survival (PFS)§		
Median, months (95% CI)†	5.6 (4.3, 6.9)	3.5 (2.0, 4.3)
Hazard ratio (95% CI)‡	0.47 (0.31, 0.71)	
Objective Response Rate (ORR)§		
n (%)	61 (48.4)	8 (12.9)
95% CI¶	(39.4, 57.5)	(5.7, 23.9)
p-value‡,#	p<0.0001	
Complete Response n (%)	11 (8.7)	0 (0.0)
Partial Response n (%)	50 (39.7)	8 (12.9)
Stable Disease n (%)	46 (36.5)	30 (48.4)
Progressive Disease n (%)	15 (11.9)	18 (29.0)
Not Evaluable n (%)	4 (3.2)	6 (9.7)
Confirmed Objective Response Rate (ORR)§		
n (%)	51 (40.5)	7 (11.3)
95% CI¶	(31.8, 49.6)	(4.7, 21.9)
p-value‡,#	p<0.0001	
Complete Response n (%)	10 (7.9)	0 (0.0)
Partial Response n (%)	41 (32.5)	7 (11.3)
Stable Disease n (%)	55 (43.7)	31 (50.0)
Progressive Disease n (%)	15 (11.9)	18 (29.0)
Not Evaluable n (%)	5 (4.0)	6 (9.7)
Duration of Confirmed Response (DOR)§		
Median, months (95% CI)†	11.3 (5.6, NR)	3.9 (3.0, 4.9)

CI = confidence interval; NR = not reached
*OS was evaluated following a statistically significant outcome of ORR.
†Median based on Kaplan-Meier estimate; 95% CI for median calculated using Brookmeyer-Crowley method
‡Stratified by region

§Assessed by independent central review
¶95% exact binomial confidence interval
#Based on the Cochran-Mantel-Haenszel test

Figure 1 Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Analysis Set)



Number at Risk									
Trastuzumab deruxtecan	126	115	88	54	33	14	7	3	0
Physician's Choice of Chemotherapy	62	54	37	19	10	2	2	0	0

In the exploratory subgroup analysis of patients who were HER2 IHC 3+, confirmed ORR was 46.9% for Enhertu (N=96; 95% CI: 36.6, 57.3), and 8.5% for chemotherapy (N=47; 95% CI: 2.4, 20.4). In the subgroup of patients who were IHC 2+/ISH+, confirmed ORR was 20.7% for Enhertu (N=29; 95% CI: 8.0, 39.7), and 20.0% for chemotherapy (N=15; 95% CI: 4.3, 48.1). In the subgroup of patients who were IHC 3+, median OS was 12.8 months for Enhertu (N=96; 95% CI: 10.3, 18.0) and 8.6 months for chemotherapy (N=47; 95% CI: 6.4, 10.7). In the subgroup of patients who were IHC 2+/ISH+, median OS was 10.1 months for Enhertu (N=29; 95% CI: 5.4, 13.1) and 8.4 months for chemotherapy (N=15; 95% CI 3.9, 20.0). The number of IHC 2+/ISH+ patients was small which limits drawing any meaningful conclusions.

5.2 Pharmacokinetic properties

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan was estimated to be 2.78 L.

In vitro, the mean human plasma protein binding of the topoisomerase I inhibitor was approximately 97%.

In vitro, the blood-to-plasma concentration ratio of the topoisomerase I inhibitor was approximately 0.6.

Biotransformation

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the active topoisomerase I inhibitor.

The humanized 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 the topoisomerase I inhibitor is metabolized 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 and locally advanced or metastatic gastric or GEJ adenocarcinoma, the clearance of trastuzumab deruxtecan was estimated to be 0.42 L/day and the clearance of the topoisomerase I inhibitor was 19.6 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan was 5.7-5.8 days and of released topoisomerase I inhibitor was approximately 5.5-5.8 days. In vitro, topoisomerase I inhibitor was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP. Moderate accumulation of trastuzumab deruxtecan was observed at the 5.4 mg/kg and 6.4 mg/kg doses (approximately 35%-39% in cycle 3 compared to cycle 1).

Following intravenous administration of the topoisomerase I inhibitor to rats, the major excretion pathway was feces via the biliary route. The topoisomerase I inhibitor was the most abundant component in urine, feces, and bile. Following single intravenous administration of trastuzumab deruxtecan (6.4 mg/kg) to monkeys, unchanged released topoisomerase I inhibitor was the most abundant component in urine and feces.

Linearity/Nonlinearity

The exposure of trastuzumab deruxtecan and released topoisomerase I inhibitor 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.

Pharmacokinetics in Special Populations

Based on population pharmacokinetic analysis, age (23-96 years), race, ethnicity, sex and body weight did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released topoisomerase I inhibitor.

Renal

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 topoisomerase I inhibitor was not affected by mild to moderate renal impairment as compared to normal renal function (CLcr ≥90 mL/min).

Hepatic

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, higher levels of AST and total bilirubin resulted in a lower clearance of topoisomerase I inhibitor. The impact of these changes in patients with mild hepatic impairment is not expected to be clinically meaningful. The pharmacokinetics of trastuzumab deruxtecan or the topoisomerase I inhibitor in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) is unknown.

Drug Interaction Studies

Effects of Other Medicinal Products on the Pharmacokinetics of Trastuzumab Deruxtecan

In vitro studies indicate that the topoisomerase I inhibitor is metabolized mainly by CYP3A4 and is a substrate of the following transporters: P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.

Coadministration of ritonavir (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a dual inhibitor of OATP1B/CYP3A, increased exposure (AUC) of trastuzumab deruxtecan by 19% and the released topoisomerase I inhibitor by 22%.

Coadministration of itraconazole (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a strong CYP3A inhibitor, increased exposure (AUC) of trastuzumab deruxtecan by 11% and the released topoisomerase I inhibitor by 18%. The impact of these changes is not expected to be clinically meaningful.

No clinically relevant drug-drug interaction is expected with drugs that are inhibitors of P-gp, MATE2-K, MRP1, or BCRP transporters.

Effects of Trastuzumab Deruxtecan on the Pharmacokinetics of Other Medicinal Products

In vitro studies indicate that the topoisomerase I inhibitor does not inhibit or induce major CYP450 enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A. In vitro studies indicate that the topoisomerase I inhibitor does not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters, but has an inhibitory effect on OAT1 and OATP1B1 with IC_{50} values of 12.7 and 14.4 μmol/L, respectively, which are significantly higher than steady-state C_{max} (0.02 μmol/L) of topoisomerase I inhibitor at 5.4 mg/kg dose administered every 3 weeks. No clinically meaningful drug-drug interaction is expected with drugs that are substrates of OAT1 or OATP1B1 transporters.

5.3 Nonclinical safety data

Animal Toxicology and/or Pharmacology

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

In a three-month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at doses up to 30 mg/kg (approximately 9 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and histopathologically characterized by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation which showed reversibility after a three-month recovery period. 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.

Mutagenesis/Carcinogenesis

The topoisomerase I inhibitor component of trastuzumab deruxtecan 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 studies have not been conducted with trastuzumab deruxtecan.

Impairment of Fertility and Teratogenicity

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 the topoisomerase I inhibitor component were toxic to rapidly dividing cells (lymphatic/hematopoietic organs, intestine, or testes), and the topoisomerase I inhibitor was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80

6.2 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.

6.3 Shelf life

Unopened Vial

Please refer to expiry date on the outer carton.

Reconstituted Solution

It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2ºC to 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 (below 30°C) for up to 4 hours or in a refrigerator at 2ºC to 8ºC for up to 24 hours, protected from light. These storage times start from the time of reconstitution.

6.4 Special precautions for storage

Store vials in a refrigerator (2ºC to 8ºC) until time of reconstitution.

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 amber glass vial with an rubber stopper and a flip-off crimp cap contains 100 mg trastuzumab deruxtecan. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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 4.2).
- 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 discoloration. The solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discolored.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 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.

Calculation to determine the volume of reconstituted ENHERTU (mL) to be further diluted:

$$\textbf{Reconstituted ENHERTU (mL)} = \frac{\text{ENHERTU dose (mg/kg) x Patient's Body Weight (kg)}}{\text{20 mg/mL}}$$

Dilution

- Dilute the calculated volume of reconstituted ENHERTU in an infusion bag containing 100 mL of 5% dextrose solution. Do not use sodium chloride solution (see section 6.2). 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 2ºC to 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 (2ºC to 8ºC), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration.
- 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.
- 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.

Product Owner

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