Public Assessment Report
ENHERTU

INFORMASI PRODUK

Nama obat	:	ENHERTU
Bentuk sediaan	:	Serbuk Untuk Larutan Konsentrat Untuk Infus
Zat aktif	:	Tiap vial mengandung: - Trastuzumab deruxtecan 107 mg
Kemasan	:	Dus, 1 vial @ 10 mL
Pendaftar	:	PT. AstraZeneca Indonesia, Bekasi
Produsen	:	Diproduksi dan dikemas oleh Baxter Oncology GmbH, Halle/Westfalen, Federal Republic of Germany Dirilis oleh Daiichi Sankyo Europe GmbH, Pfaffenhofen, Federal Republic of Germany
Kategori Registrasi	:	Produk Biologi Baru
Indikasi yang diajukan:	:	***Breast cancer*** ***HER2-positive breast cancer*** *Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.* ***HER2-low breast cancer*** *Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see section 4.2).*
Posologi yang diajukan	:	*Enhertu should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products. In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.* *Enhertu should not be substituted with trastuzumab or trastuzumab emtansine.* ***Patient selection*** ***HER2-positive breast cancer*** *Patients treated with trastuzumab deruxtecan for breast cancer should have documented HER2-positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) or by fluorescence in situ hybridization (FISH) assessed by a CE-marked in vitro diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test.* ***HER2-low breast cancer*** *Patients treated with trastuzumab deruxtecan should have documented HER2-low tumour status, defined as a score of IHC 1+ or IHC 2+/ISH-, as assessed by a CE-marked IVD medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test (see section 5.1).* ***Posology*** ***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.
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 (see section 4.8). Enhertu should be permanently discontinued in case of severe infusion reactions.

Premedication
Enhertu is emetogenic (see section 4.8), which includes delayed nausea and/or vomiting. Prior to each dose of Enhertu, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

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

Dose reduction schedule	***Breast cancer***
Recommended starting dose	*5.4 mg/kg*
First dose reduction	*4.4 mg/kg*
Second dose reduction	*3.2 mg/kg*
Requirement for further dose reduction	*Discontinue treatment*

Table 2: Dose modification 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 × 10^9/L)*		*Interrupt Enhertu until resolved to Grade 2 or less, then maintain dose.*
	Grade 4 (less than 0.5 × 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 1.0 × 10^9/L and temperature greater than 38.3 °C or a sustained temperature of 38 °C or greater for more than one hour.*		· *Interrupt Enhertu until resolved.* · *Reduce dose by one level (see Table 1).*
Left ventricular ejection fraction (LVEF) decreased	*LVEF greater than 45% and absolute decrease from baseline is 10% to 20%*		*Continue treatment with Enhertu.*
	LVEF 40% to 45%	*And absolute decrease from baseline 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 5.0 (NCI-CTCAE v.5.0).

Delayed or missed dose

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

Special populations

Elderly

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

Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CLcr] ≥ 60 and < 90 mL/min) or moderate (CLcr ≥ 30 and < 60 mL/min) renal impairment (see section 5.2). The potential need for dose adjustment in patients with severe renal impairment or end-stage renal disease cannot be determined as severe renal impairment was an exclusion criterion in clinical studies. A higher incidence of Grade 1 and 2 ILD/pneumonitis leading to an increase in discontinuation of therapy has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully for adverse reactions including ILD/pneumonitis (see section 4.4).

Hepatic impairment

No dose adjustment is required in patients with total bilirubin ≤ 1.5 times upper limit of normal (ULN), irrespective of aspartate transaminase (AST) value. The potential need for dose adjustment in patients with total bilirubin > 1.5 times ULN, irrespective of AST value, cannot be determined due to insufficient data; therefore, these patients should be monitored carefully (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Enhertu in children and adolescents below the age of 18 years have not been established. No data are available.

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 the medicinal product before administration, see section 6.6.

PENGANTAR

Enhertu adalah *antibody-drug conjugate* (ADC) dalam bentuk serbuk untuk larutan konsentrat untuk infus dalam kemasan vial mengandung 100 mg trastuzumab deruxtecan sebagai zat aktif. Trastuzumab deruxtecan mengandung trastuzumab, antibodi monoklonal anti-HER2 manusia yang dihasilkan dalam sel ovarium

hamster (*Chinese Hamster Ovary*, CHO), terikat kovalen pada deruxtecan, suatu inhibitor topoisomerase I (DXd) melalui suatu penghubung. Sekitar 8 molekul deruxtecan terikat pada setiap molekul antibodi trastuzumab. Fungsi bagian antibodi adalah berikatan dengan HER2 yang diekspresikan pada permukaan sel tumor tertentu. Setelah berikatan, kompleks trastuzumab deruxtecan kemudian mengalami internalisasi dan pembelahan penghubung intraseluler oleh enzim lisosom yang diregulasi dalam sel kanker. Setelah dilepaskan, DXd yang permeabel terhadap membran menyebabkan kerusakan DNA dan kematian sel apoptosis. Enhertu dievaluasi dengan mekanisme *reliance* terhadap EMA. Mengingat Enhertu merupakan produk biologi baru, maka evaluasi Enhertu dilakukan secara menyeluruh terhadap data mutu, studi non klinik dan klinik sesuai dengan indikasi dan posologi yang diajukan, serta kesesuaian dokumen dengan EMA.

ASPEK MUTU

Enhertu terdaftar dengan bentuk sediaan Serbuk Untuk Larutan Konsentrat Untuk Infus. Zat tambahan yang digunakan adalah Sucrose, L-Histidine, L-Histidine Monohydrochloride Monohydrate, Polysorbate 80. Sebelum digunakan, serbuk di-rekonstitusi dengan air untuk injeksi. Larutan yang dihasilkan bersifat steril dan hanya dimaksudkan untuk satu kali penggunaan. Setelah itu, larutan tersebut diencerkan dalam *infusion bag* menggunakan larutan glukosa 5% sebelum diberikan melalui infus intravena. Enhertu dikemas dalam vial dengan 1 besar kemasan, yaitu setiap dus terdapat 1 vial produk jadi trastuzumab deruxtecan 100 mg. Obat ini harus disimpan pada suhu dingin (2-8°C).

Zat Aktif

Bulk zat aktif diproduksi, diuji, disimpan, diberi label dan dikemas sesuai dengan cGMP. Uraian proses produksi diserahkan dengan rincian dan memadai. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan.

Obat Jadi

Enhertu diproduksi, diuji, disimpan, diberi label dan dikemas sesuai dengan cGMP. Proses produksi secara umum mencakup proses *thawing* zat aktif dan *compounding, sterile filtration, aseptic filling, lyophilization, capping*. Uraian proses produksi diserahkan dengan rincian dan memadai. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan. Validasi terhadap proses produksi telah dilakukan, mencakup proses formulasi, fill finish dan validasi media fill. Validasi proses dilakukan untuk menunjukkan bahwa prosedur manufaktur yang telah ditetapkan akan secara konsisten menghasilkan Produk Jadi yang memenuhi spesifikasi mutu dan proes dapat dilakukan secara konsisten dalam parameter proses yang telah ditetapkan. Spesifikasi obat jadi telah ditetapkan, mencakup parameter uji, referensi metode uji serta kriteria penerimaannya. Prosedur uji telah divalidasi. Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang, variabilitas proses produksi maupun metode analisis dan data pengembangan proses yang relevant. Data stabilitas Produk jadi Enhertu mendukung penyimpanan obat jadi selama 48 bulan pada suhu 2°C - 8°C.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

Profil non klinik trastuzumab deruxtecan diteliti melalui studi farmakologi, farmakokinetik, dan toksikologi dengan hasil evaluasi sebagai berikut.

1. Studi-studi *in vitro* menunjukkan bahwa trastuzumab deruxtecan menunjukkan aktivitas pengikatan spesifik pada protein HER2 manusia dan *cynomolgus monkey*.
2. Penelitian *in vivo* menunjukkan bahwa trastuzumab deruxtecan menunjukkan yang lebih besar dibandingkan trastuzumab dan efek antitumor ini bersifat *dose-dependent*. Aktivitas antitumor trastuzumab deruxtecan utamanya berasal dari aktivitas obat terkonjugasi *topoisomerasi 1 inhibitor*. Trastuzumab deruxtecan juga menunjukkan hasil yang efektif pada tumor kanker payudara positif HER2 dengan T-DM1 *refractory* dan pada tumor kanker lambung positif HER2 yang tidak merespons T-DM1.
3. Adsorpsi, distribusi jaringan dan ekskresi konsisten dengan antibodi monoklonal pada umumnya. Trastuzumab deruxtecan (konjungasi obat antibodi) dan inhibitor topoisomerase I (MAAA-1181a) (*drug payload)* ditemukan dalam plasma tikus atau monyet tetapi <1%. Ekskresi MAAA-1181a ditemukan terutama melalui jalur empedu/feses sebagai MAAA-1181a yang tidak berubah.
4. Tidak ada efek samping terkait pengobatan terhadap fungsi kardiovaskular, pernapasan, atau sistem

saraf pusat pada dosis tunggal 78.8 mg/kg yang diadministrasikan dengan rute intravena pada monyet jantan.

5. Berdasarkan studi toksisitas pada hewan, perkiraan dosis mematikan untuk administrasi tunggal pada monyet *cynomolgus* ditentukan sebesar estimasi 78,8 mg/kg. *No observed adverse effect level* (NOAEL) yang dipertimbangkan, 197 mg/kg pada tikus dan 78,8 mg/kg pada monyet *cynomolgus*.
6. Tidak ada studi tentang kemungkinan toksisitas reproduksi atau *developmental* yang dilakukan pada hewan dengan trastuzumab deruxtecan. Berdasarkan hasil studi toksisitas pada hewan secara umum dan mekanisme aksi trastuzumab deruxtecan DXd – diketahui mereka bersifat toksik terhadap sel yang membelah dengan cepat (organ limfatik/hematopoietik, usus, atau testis), dan dapat menghentikan pembelahan sel yang menunjukkan kemungkinan trastuzumab deruztecan akan menyebabkan embriotoksisitas dan teratogenisitas. Selain itu, DXd (muatan) bersifat genotoksik dan dapat meningkatkan risiko terkena kanker.

Studi Klinik

Diserahkan 4 laporan studi klinik fase I dan 1 laporan studi klinik fase 2, yaitu:

Type of Study	**Study Identifier**	**Location of Study Report/ Synopsis**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treatment Median (Min, Max)**	**Study Status; Type of Report**
PK, tolerability, and efficacy	DS8201-A-A103	5.3.3.2	To assess the safety and tolerability of DS-8201a in subjects of Chinese descent To assess the PK profiles of DS-8201a, total anti-HER2 antibody, and MAAA-1181a To investigate the anti-tumor activity of DS-8201a To assess the incidence of anti-drug antibodies (ADAs) against DS-8201a	Phase 1, multicenter, non-randomized, open-label study	DS-8201a 6.4 mg/kg IV infusion Q3W	**Planned**: 12 **Treated**: 12	Pathologically documented HER2 positive advanced/ unresectable or metastatic gastric, gastro-esophageal junction adenocarcinoma or breast cancer, with both HER2-positve disease and documented disease progression	Treatment continued until unacceptable toxicity, progressive disease, or withdrawal of consent. Median: 140.0 days (range: 84-168)	Complete DCO (14 Sep 2018) CSR Full
Efficacy, safety, and PK	DS8201-A-J101	5.3.3.2	To determine the maximum tolerated dose or the recommended Phase 2 dose of DS-8201a To assess the safety and tolerability, PK, ADA of DS-8201a. To assess the efficacy of DS-8201a	Phase 1, multicenter, non-randomized, open-label, multiple dose, first-in human study in 2 parts: Dose Escalation (Part 1) and Dose Expansion (Part 2)	DS-8201a IV infusion Q3W **Dose Escalation (Part 1)**: 0.8 mg/kg; 1.6 mg/kg; 3.2 mg/kg; 5.4 mg/kg; 6.4 mg/kg; 8.0 mg/kg **Dose Expansion (Part 2)**: 5.4 mg/kg; 6.4 mg/kg	**Planned**: Dose Escalation (Part 1): At least 18 Dose Expansion (Part 2): approximately 260 **Treated**: Part 1: 27 Overall: 289	**Part 1**: Advanced unresectable or metastatic breast cancer and gastric or gastroesophageal junction adenocarcinoma **Part 2a**: T-DM1-treated HER2-positive breast cancer **Part 2b**: Trastuzumab-treated HER2-positive gastric or gastroesophageal junction adenocarcinoma **Part 2c**: HER2 low expressing breast cancer **Part 2d**: HER2 expressing other solid malignant tumor/HER2 mutated tumor **Part 2e**: HER2 expressing breast cancer.	Treatment continued until withdrawal of consent, disease progression, or unacceptable toxicity occurred **Part 1**: Median: 8.7 months (range: 1.4-40.4) **Overall**: Median: 7.4 months (range: 0.7-40.4)	Complete DCO (01 Feb 2019) CSR Full

DDI	DS8201-A-A104	5.3.3.4	To evaluate the effect of ritonavir and itraconazole on DS-8201a and MAAA-1181a PK To assess safety of DS-8201a with or without ritonavir or itraconazole To evaluate the efficacy of DS-8201a	Phase 1, multicenter, non-randomized, open-label, single sequence crossover study	**Cohort 1**: DS-8201a 5.4 mg/kg IV infusion Q3W in combination with ritonavir 200 mg BID on Day 17 of Cycle 2 until Day 21 of Cycle 3. **Cohort 2**: DS-8201a 5.4 mg/kg IV Q3W in combination with Itraconazole 200 mg BID on Day 17 of Cycle 2 followed by 200 mg QD until Day 21 of Cycle 3.	**Planned**: Cohort 1: 16 Cohort 2: 16 **Treated**: Cohort 1: 17 Cohort 2: 23	Pathologically documented unresectable or metastatic solid malignant tumors with HER2 expression	Treatment continued until there was no longer clinical benefit from therapy or until withdrawal of consent, progressive disease, or unacceptable toxicity occurred **Cohort 1**: Median: 211.0 days (range: 42-254) **Cohort 2**: Median:148.0 d ays (range: 21-213)	Complete DCO (26 Sep 2018) CSR Full
QTc	DS8201-A-J102	5.3.4.2	To assess the effect of DS-8201a on the QTc interval To assess PK after multiple dosing of DS-8201a To assess the safety of DS-8201a To assess the serum concentration of DS-8201a at the time of electrocardiogram (ECG) measurement To evaluate the efficacy of DS-8201a	Phase 1, multicenter, non-randomized, open-label, multiple dose study	DS-8201a 6.4 mg/kg IV infusion Q3W	**Planned**: 50 **Treated**: 51	Pathologically documented unresectable or metastatic breast cancer with HER2 expression	Treatment continued as long as the subject derived clinical benefit or until withdrawal of consent, progressive disease, or unacceptable toxicity. Median: 4.6 months (range: 0.7-9.0)	Complete DCO (05 Dec 2018) CSR Full
Efficacy, Safety, and PK	DS8201-A-U201	5.3.5.2	To assess the efficacy, safety and PK of DS-8201a	Phase 2, multicenter, open-label, multiple-dose, 2-part study	DS-8201a IV infusion Q3W Part 1: 5.4 mg/kg, 6.4 mg/kg or 7.4 mg/kg Part 2: 5.4 mg/kg	**Planned**: Part 1: approximately 120 Part 2: at least 100 **Treated**: Part 1: 119 Part 2:134	HER2-positive, unresectable or metastatic breast cancer Subjects previously treated with T-DM1	Treatment continued until unacceptable toxicity, progressive disease, or withdrawal of consent. **Overall**: Median: 7.0 months (range: 0.7-16.2)	Complete DCO (21 Mar 2019) CSR Full

Diserahkan juga 3 studi klinik pivotal fase III, yaitu:

Type of Study	**Study Identifier**	**Location of Study Report/ Synopsis**	**Objectives of the Study**	**Study Design and Type of Control**	**Test Products; Dosage Regimen; Route of Administration**	**Number of Subjects**	**Geographies Diagnosis of Patients**	**Duration of Treatment Median, Months (Min, Max)**	**Study Status; Type of Report**
Efficacy, safety, and PK	DS8201-A-U302 (DESTINY-Breast03)	5.3.5.1	**Primary objective:** • Compare the PFS benefit of T-DXd to T-DM1 in subjects with HER2-positive, unresectable, and/or mBC previously treated with trastuzumab and a taxane **Secondary objectives:** • Compare the OS benefit of T-DXd to T-DM1 • Evaluate the efficacy of T-DXd compared to T-DM1 on confirmed ORR, DoR, and PFS based on investigator assessment • Further determine the PK of T-DXd • Further evaluate the safety of T-DXd compared to T-DM1 • Evaluate PRO endpoints for T-DXd compared to T-DM1	Phase 3, multicenter, randomized, 2-arm, open-label, active-controlled study of T-DXd versus T-DM1	**T-DXd**: 5.4 mg/kg IV infusion Q3W OR **T-DM1**: 3.6 mg/kg IV infusion Q3W administered according to the approved local label	**Planned:** T-DXd: ~250 T-DM1: ~250 **Treated:** T-DXd: 257 T-DM1: 261	Japan, Republic of Korea, China, Taiwan, Hong Kong, US, Canada, France, Greece, Spain, Belgium, United Kingdom, Italy, Germany, Australia and Brazil HER2-positive, unresectable, and/or mBC subjects previously treated with trastuzumab and a taxane	T-DXd: 18.23 (0.7, 44.0) T-DM1: 6.90 (0.7, 39.3)	Complete[a] Primary analysis DCO: 21 May 2021 (Full CSR) Second OS Interim Analysis: 25 Jul 2022

Efficacy, safety, and PK	DS8201-A-U303 (DESTINY-Breast04)	5.3.5.1	**Primary Objective** • The primary objective was to compare the PFS benefit of T-DXd to TPC in the cohort of subjects with HER2-low, hormone receptor-positive BC (ie, the hormone receptor-positive cohort of the FAS), based on BICR. **Secondary Objectives** Key secondary objectives were as follows: • To compare the PFS benefit of T-DXd to TPC in all randomized subjects regardless of hormone-receptor status (ie, the FAS), based on BICR • To compare the OS benefit of T-DXd to TPC in subjects with HER2-low, hormone receptor-positive BC • To compare the OS benefit of T-DXd to TPC in the FAS Other secondary objectives were as follows: • To investigate the efficacy of T-DXd compared to TPC on the following parameters: - PFS in subjects with HER2-low hormone receptor-positive BC, based on investigator assessment	Randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of T-DXd vs TPC	**T-DXd**: 5.4 mg/kg IV infusion Q3W OR **TPC**: Capecitabine 1000-1250 mg/m^2 administered orally BID on Days 1 to 14; 21-day cycle OR Eribulin[a]/ 1.4 mgm^2 IV on Days 1 and 8; 21-day cycle OR Gemcitabine 800-1200 mg/m^2 IV on Days 1, 8, and 15; 28-day cycle OR Paclitaxel Option 1: 175 mg/m^2 IV on Day 1; 21-day cycle Option 2: 80 mg/m^2 IV on Day 1 weekly OR	**Planned:** ~540 subjects T-DXd: ~360 subjects TPC: ~180 subjects **Randomized:** 557 subjects T-DXd: 373 subjects TPC: 184 subjects **Treated:** T-DXd: 371 subjects TPC: 172 subjects capecitabine-36; eribulin-89; gemcitabine-16; paclitaxel-14; nab-paclitaxel-17	**Geographies** US Canada Japan China South Korea Taiwan France Italy Spain Greece Portugal Austria Belgium Hungary Sweden Russia UK Switzerland Israel **Diagnosis** HER2-low, unresectable and/or metastatic BC	Treatment continued until withdrawal of consent, PD, clinical progression, AE, death, pregnancy, lost to follow-up, protocol deviation, physician decision, study termination by sponsor, or another reason occurred. **Treatment Duration (months):** T-DXd: 8.2 months (0.2, 33.3) TPC: 3.5 months (0.3, 17.6) capecitabine 4.1 months (0.3, 17.6); eribulin 3.6 months (0.3, 17.5); gemcitabine 1.6 months (1.1, 6.9); paclitaxel, 4.3 months (0.4, 9.0); nab-paclitaxel	Complete[b] Primary analysis DCO: 11 Jan 2022 Full CSR
			• Confirmed ORR, based on BICR and investigator assessment in subjects with HER2-low hormone receptor-positive BC - DoR, based on BICR in subjects with HER2-low hormone receptor-positive BC - PFS, Confirmed ORR and DoR in the FAS • To determine the PK of T-DXd • To evaluate the safety of T-DXd compared to TPC • To evaluate HEOR endpoints for T-DXd compared to TPC		Nab-paclitaxel Option 1: 260 mg/m^2 IV; 21-day cycle Option 2: 100 mg/m^2 or 125 mg/m^2 IV on Days 1, 8, and 15; 28-day cycle			2.8 months (0.7, 16.8)	
Efficacy, safety, and PK	DS8201-A-U301 (DESTINY-Breast02)	5.3.5.4	**Primary objective:** • Compare the PFS benefit of T-DXd to TPC for HER2-positive, unresectable, and/or mBC subjects previously treated with T-DM1 **Secondary objectives:** • Compare the OS benefit of T-DXd to TPC for HER2-positive, unresectable, and/or mBC subjects previously treated with T-DM1 • Evaluate the efficacy of T-DXd compared to TPC on confirmed ORR and DoR • Further determine the PK of T-DXd • Further evaluate the safety of T-DXd compared to TPC • Evaluate PRO endpoints for T-DXd compared to TPC	Phase 3, randomized, 2-arm, open-label, multicenter study designed to compare the safety and efficacy of T-DXd versus TPC in HER2-positive, unresectable and/or mBC subjects who were previously treated with T-DM1	**T-DXd**: 5.4 mg/kg IV infusion Q3W OR **TPC:** Trastuzumab (8 mg/kg IV loading dose on the first day of treatment followed by 6 mg/kg every 21d [± 2d]) + Capecitabine 1250 mg/m^2 administered PO BID ~ 12 h apart (equivalent to 2500 mg/m^2 total daily dose) on Days 1 to 14 of a 21d [± 2d] schedule) OR Lapatinib 1250 mg PO daily on Days 1 to 21 of a 21d (± 2d) schedule + Capecitabine 1000 mg/m^2 PO BID ~12h apart (equivalent to 2000 mg/m^2 total daily dose) on Days 1 to 14 of a 21d (± 2d) schedule	**Planned:** ~600 **Treated:** T-DXd: 404 Trastuzumab: 87 Capecitabine: 195 Lapatinib: 108	Japan Republic of Korea, United States; Belgium, Czech Republic, France, Germany, Greece, Italy, Spain, and United Kingdom; Australia, Brazil, Israel, and Turkey HER2-positive, unresectable, and/or mBC subjects previously treated with T-DM1	T-DXd: 11.3 (0.7, 45.1) Trastuzumab: 4.4 (0.1, 43.0) Capecitabine: 4.6 (0.1, 42.3) Lapatinib: 4.5 (0.2, 28.7)	Complete[a] Primary analysis DCO: 30 Jun 2022 Full CSR

BID = twice daily; CSR = clinical study report; d = day; DCO = data cut-off; DoR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; h = hour(s); HER2 = human epidermal growth factor receptor 2; IV = intravenous; Max = maximum; mBC = metastatic breast cancer; Min = minimum; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO = patient reported outcomes; Q3W = every 3 weeks; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TPC = the physician's choice/investigator's choice

[a] Study was defined as "complete" if the analyses for the primary endpoint had been performed.

Hasil evaluasi terhadap studi di atas:

1. Untuk mendukung registrasi produk Enhertu sesuai indikasi dan posologi yang diajukan melalui jalur 120 HK (*reliance*, dengan negara referensi Uni Eropa), diserahkan *Assessment Report* EMA dan 3 studi pivotal yaitu studi U301, U302 dan U303.
2. Efikasi Enhertu untuk pengobatan pasien HER2-*positive breast cancer* didukung oleh studi klinik U301 dan U302:
    a. Studi U301 yang dilakukan pada 608 pasien *Breast Cancer* dengan HER2+ (IHC 3+ *or* ISH-*positive*), *unresectable* dan atau pasien metastase yang resisten atau refrakter terhadap trastuzumab emtansine [n=406 trastuzumab deruxtecan (T-DXd) vs 202 *Treatment Physician's Choice* (TPC)]. Studi ini menunjukkan *Progression-Free Survival* (PFS) dan *Overall Survival* (OS) lebih baik signifikan pada pasien yang menerima T-DXd dibandingkan pasien yang TPC berdasarkan *data cut off* (DCO) 30 Juni 2022:
        i. PFS 17.8 bulan (95% CI: 14.3, 20.8) vs 6.9 bulan (95% CI: 5.5, 8.4). HR 0.36 (95% CI: 0.28, 0.45), *2-sided P-value of* <0.001.
        ii. OS *events* 143 (35.2%) vs 86 (42.6%) subjek pada kelompok TPC. Median OS 39.2 bulan (95%CI: 32.7, NE) vs 26.5 bulan (95%CI: 21.0, NE) dengan HR 0.66 (95%CI: 0.50, 0.86), p=0.002.
    b. Studi U302 yang dilakukan pada 524 pada pasien *Breast Cancer* dengan HER2+ (IHC 3+ *or* ISH-*positive*) *unresectable* dan atau pasien metastase yang sebelumnya diterapi dengan trastuzumab plus taxane pada *setting* metastase lanjut atau pasien yang mengalami progresi dalam 6 bulan setelah pengobatan neoadjuvant atau adjuvant yang melibatkan regimen trastuzumab plus taxane. Studi menunjukkan data Progression-Free Survival (PFS) dan Overall Survival (OS) yang signifikan lebih baik pada pasien yang menerima T-DXd dibandingkan dengan pasien yang menerima T-DM1:
        i. PFS: 28,8 bulan vs 6,8 bulan, HR 0.3343 (95%CI: 0.2169, 0.4269), p<0.001.
        ii. OS: Dengan durasi median *study follow up* adalah 28.4 bulan (IQR 22.1-32.9) dengan T-DXd dan 26.5 bulan (14·5-31·3) dengan T-DM1. Median Overall Survival menunjukkan *not reached* (95% CI 40·5 months-not estimable) dengan 72 (28%) *overall survival events* pada kelompok T-DXd (34.0 months-not estimable). Selain itu, *not reached* dengan 97 (37%) perist *overall survival events* ditujukkan pada kelompok T-DM1 (HR 0·64 [95% CI 0·47-0·87]; p=0·0037).
3. Efikasi Enhertu untuk pengobatan pasien HER2-*low* (IHC1+ or IHC2+/ISH *negative*) *unresectable and/or metastatic breast cancer*, didukung oleh studi U303 yang dilakukan pada 557 subjek (373 T-DXd vs 184 TPC). Hasil studi menunjukkan PFS dan OS yang lebih baik pada T-DXD dibanding TPC:
    a. Dalam kohort *hormone receptor-positive*, PFS median adalah 10,1 bulan pada kelompok T-DXd dan 5,4 bulan pada kelompok TPC (*hazard ratio* untuk progresi penyakit atau kematian, 0,51; P<0,001), dan *overall survival* masing-masing sebesar 23,9 bulan dan 17,5 bulan (*hazard ratio untuk* kematian, 0,64; P=0,003). Di antara semua pasien, median *progression-free survival* adalah 9,9 bulan di kelompok T-DXd dan 5,1 bulan di kelompok TPC (*hazard ratio* progresi penyakit atau kematian, 0.50; P<0,001)
    b. OS sebesar 23,9 bulan di kelompok T-DXd dan 17,5 bulan di kelompok TPC (*hazard ratio* untuk kematian, 0,64; P=0,003) pada populasi *hormone receptor-positive;* dan masing-masing 23,4 vs 16,8 bulan (p=0,0010) di populasi keseluruhan.
4. Keamanan.
    a. Berdasarkan data keamanan dari 1287 pasien dengan kanker payudara yang mendapatkan dosis 5,4 mg/kg Q3W, menunjukkan profil keamanan secara umum dapat ditoleransi.
    b. *Treatment-related AEs* yang paling sering dilaporkan, yaitu *nausea* (72,6%), *fatigue* (51,3%), *alopecia* (38,3%), *neutropenia* (35%), *vomiting* (37,4%), *decreased appetite* (28,5%), anemia (30,4%), *constipation* (21,9%), *diarrhea* (22,8%), *thrombocytopenia* (23,5%), *leukopenia* (23,3%), *transaminases increased* (21,6%), *abdominal pain* (12,3%), *lymphopenia* (9,9%), *interstitial lung disease* (*adjudicated drug-related ILD*) (12,8%), *stomatitis* (13,2%), *rash* (5,7%), *palmar-plantar erythrodysaesthesia syndrome* (1,4%).

KEPUTUSAN

Mempertimbangkan data mutu, khasiat, dan keamanan tersebut di atas, diputuskan registrasi baru Enhertu Serbuk Untuk Larutan Konsentrat Untuk Infus **diterima sesuai dengan indikasi dan posologi yang diajukan:**

Indikasi

Breast cancer

HER2-positive breast cancer

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

HER2-low breast cancer

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see section 4.2