10 December 2020
EMA/2446/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Enhertu

International non-proprietary name: trastuzumab deruxtecan

Procedure No. EMEA/H/C/005124/0000

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List of abbreviations

2L+	Second line or later
ΔQTcF	change from baseline in QTcF
AC	Adjudication Committee
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADME	Absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	Accumulation ratio
AST	aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	area under the serum concentration-time curve
AUC17d	area under the concentration-time curve from time zero to Day 17
AUC0-21d	area under the serum concentration-time curve from time 0 to 21 days
AUClast	area under the serum concentration-time curve from time zero to the time of the last quantifiable serum concentration
AUCss	area under the serum concentration-time curve at steady state
AUCtau	area under the serum concentration-time curve during the dosing interval
ATT	All tumor types safety pool
BC	Breast cancer
BCRP	breast cancer resistance protein
BOR	best overall response
BSEP	Bile salt export pump
BLQ	Below the limit of quantitation
Cav	average concentration
CavORR	average concentration from beginning of treatment to the time of ORR
CBR	clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CLdug	elimination clearance of released drug (MAAA-1181a)
CLuptake	intrinsic uptake clearance
CNS	Central nervous system
Cmax	maximum serum concentration
Cmax,ss	maximum observed serum concentration at steady state
Cmin	minimum observed serum concentration
CMC	Chemistry, Manufacturing and Controls
CR	complete response
CrCL	Creatinine clearance
CSR	clinical study report

CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough serum concentration
CYP	cytochrome P450
ΔQTcF	change from baseline in QTcF over time
CWRES	Conditional weighted residuals
DAR	drug-to-antibody ratio
DCO	data cut-off
DCR	disease control rate
DDI	drug-drug interaction
DLT	Dose-limiting toxicity(ies)
DoR	duration of response
DP	drug product
DS	drug substance
DS-8201a	product code for trastuzumab deruxtecan
Dxd	deruxtecan
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EMA	European Medicines Agency
ER	exposure-response
ESME	Epidemiological Strategy and Medical Economics
ESMO	European Socitety for Medical Oncology
ESS	effective sample size
ETA	Random between-subject effect
FCCC	French Comprehensive Cancer Center
FDA	Food and Drug Administration
FIH	first in human
FL-DP1, FL-DP2	frozen liquid drug product 1, frozen liquid drug product 2
GEJ	Gastroesophageal junction
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IC_{50}	50% inhibitory concentration
ICR	independent central review
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent to treat
IV	intravenous
Km	Michaelis constant

Krel	Release rate constant
LBA	literature-based analysis
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized drug product
MAA	Marketing Authorisation Application
MAAA-1162a	drug-linker in trastuzumab deruxtecan
MAAA-1181a	released drug in trastuzumab deruxtecan, drug payload
MAAL-9001	anti-HER2 component of trastuzumab deruxtecan
mAb	monoclonal antibody
MATE1	multidrug and toxin extrusion protein 1
MATE2-K	multidrug and toxin extrusion protein 2-K
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP	multidrug resistance protein
MTD	Maximum tolerated dose
MUGA	multigated acquisition
NCA	noncompartmental analysis
NCI	National Cancer Institute
OAT	organic anion transporter
OATP	organic anion transporting peptide
OCT	organic cation transporter
ODWG	organ dysfunction working group
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PMDA	Pharmaceutical and Medical Devices Agency
PopPK	population pharmacokinetics
PR	partial response
PS	propensity score
PT	preferred term
Q3W	every 3 weeks
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results

SmPC	summary of product characteristics
SMQ	Standardised MedDRA queries
SMRW	standardized mortality ratio weighting
SoC	standard of care
SoD	sum of diameters
t1/2	apparent terminal elimination half-life
TBL	total bilirubin
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TL	target lesion
Tmax	time to maximum serum concentration
TTR	time to response
ULN	upper limit of normal
US	United States
Vc	central volume of distribution
Vdrug	released drug (MAAA-1181a) volume of distribution
VPC	Visual predictive check
vs.	versus
WBC	white blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Daiichi Sankyo Europe GmbH submitted on 22 May 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Enhertu, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

The applicant applied for the following indication:

Enhertu as monotherapy 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.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the Regulation No 726/2004.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance trastuzumab deruxtecan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
25 January 2018	EMEA/H/SA/3714/1/2017/HTA/II	*Ms Blanca Garcia Ochoa and Prof. Dieter Deforce*
31 May 2018	EMEA/H/SA/3715/2/2018/I	*Dr Serena Marchetti and Dr Jens Reinhardt*
19 September 2019	EMEA/H/SA/3715/4/2019/I	*Dr Elena Wolff-Holz and Dr Juha Kolehmainen*

The Scientific advice pertained to the following *quality, and clinical* aspects:

- The key CMC development activities to support MAA, including the drug-linker intermediate, active substance master file, designation of starting materials, extractables and leachables for drug substance and drug product; preparation, qualification and comparability of a new working cell bank for commercialization, drug product process validation strategy, shelf life setting for drug product, monoclonal antibody, drug substance and drug product specifications, and drug-linker specification;
- the overall development plan of DS-8201a in HER2-positive metastatic breast cancer (such as study design, comparator choice, appropriateness of endpoints, inclusion/exclusion criteria) to support a conditional approval based on the ongoing Phase 1 DS8201-A-J101 and Phase 2 DS8201-A-U201 trial results;
- the Phase 3 program consisting of a Phase 3 randomized confirmatory trial and an additional Phase 3 randomized trial to extend the metastatic breast cancer indication into an earlier line setting;

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	22 May 2020
Accelerated Assessment procedure was agreed-upon by CHMP on	26 March 2020
The procedure started on	18 June 2020

The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	30 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	10 November 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Enhertu on	10 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for trastuzumab deruxtecan is monotherapy 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.

2.1.2. Epidemiology

Breast cancer is the most commonly diagnosed female cancer worldwide (11.6% of all cancer sites) and the leading cause of cancer death in women (6.6% of all cancer deaths in 2018). Breast cancer is mainly a female disease with only 1% of cases occurring in males worldwide and it occurs more frequently in women over 40 years of age. According to GLOBOCAN 2018 data, 67% of patients with breast cancer are diagnosed between the ages of 45 years and 74 years, with 43% of patients diagnosed between the ages of 55 years and 74 years. In 2018, there were an estimated 1,410,831 women living with breast cancer in the EU-27 who were diagnosed in the last 5 years, corresponding to a 5-year prevalence rate of 623.6 per 100,000.

2.1.3. Biologic features

Approximately 20% of patients with breast cancer have HER2-positive tumours and HER2 positivity is associated with a more aggressive disease and a younger patient population. Although treatment with anti-HER2 targeted therapies has improved the disease outcomes, these are not curative in the locally advanced/metastatic setting and the disease invariably progresses.

2.1.4. Clinical presentation, diagnosis and prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmed by pathological assessment. Disease stage should be assessed according to the AJCC TNM staging system. HER2 testing should be carried out according to the American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP) guidelines (Cardoso et al., 2019[1]). HER2 is defined as positive by IHC (3+) when more than 10% of the cells harbor a complete membrane staining, and by ISH if the number of HER2 gene copies is ≥6, or the HER2/chromosome 17 (CEP17) ratio is ≥2 and HER2 copies ≥4, or HER2/CEP17 <2 and HER2 copies ≥6 (Wolff et al., 2018[2]).

The signs of more advanced locoregional disease include axillary adenopathy (suggesting locoregional disease) or skin findings such as erythema, thickening, or dimpling of the overlying skin (peau d'orange), suggesting inflammatory breast cancer. Symptoms of metastatic breast cancer depend on the organs involved, with the most common sites of involvement being the bone (e.g., back or leg pain), liver (abdominal pain, nausea, jaundice), and lungs (e.g., shortness of breath or cough).

HER2-positive metastatic breast cancer remains an incurable disease. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic breast cancer, the disease invariably progresses. Especially, the incidence of brain metastases, for which effective treatment options are limited, has increased such that brain metastases may develop in up to half of patients. The estimated median OS of metastatic breast cancer is about 3 years and the 5-year survival rate is only ~25% (Cardoso et al., 2018[3]).

2.1.5. Management

Current Treatment Options for Patients with Unresectable or Metastatic HER2-Positive Breast Cancer

[1] Cardoso F., et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; 30: 1194-1220.
[2] Wolff AC, Hammond MEH, Allison KH et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. J Clin Oncol 2018; 36(20): 2105–2122.
[3] Cardoso F, Spence D, Mertz S et al. Global analysis of advanced/metastatic breast cancer: decade report (2005–2015). Breast 2018; 39: 131–138.

Several anti-HER2 therapies have been approved in the EU for the treatment of HER2-positive breast cancer. The first approved anti-HER2 therapy was trastuzumab, and other HER2-targeting agents now approved include the HER2-targeting ADC trastuzumab emtansine (T-DM1) as monotherapy for patients previously received trastuzumab and a taxane separately or in combination; the tyrosine kinase inhibitor (TKI) neratinib as monotherapy in early-stage breast cancer; and the mAb pertuzumab and the TKI lapatinib in combination with other chemotherapeutic agents.

The current SoC for newly-diagnosed metastatic HER2-positive breast cancer in Europe, according to guidelines from the European Society for Medical Oncology (ESMO), is a combination of pertuzumab, trastuzumab, and taxane based on results from the CLEOPATRA study, followed by treatment with single-agent TDM1 as established by the EMILIA study. In the CLEOPATRA study, newly-diagnosed patients with HER2-positive metastatic breast cancer were randomized to receive trastuzumab plus docetaxel with or without the addition of pertuzumab as first-line therapy. The addition of pertuzumab improved the median PFS from 12.4 months to 18.5 months and the median overall survival (OS) from 40.8 months to 56.5 months. In the EMILIA study, TDM1 was compared to combined therapy with lapatinib plus capecitabine in patients, who had progressed after treatment with the trastuzumab plus taxane combination, which resulted in improved outcomes compared to treatment with lapatinib plus capecitabine, with an ORR of 43.6% (95%CI: 38.6, 48.6) in the TDM1 arm vs. 30.8% (95%CI: 26.3, 35.7) in the lapatinib plus capecitabine arm; a median PFS of 9.6 months vs. 6.4 months (HR 0.65 [95%CI: 0.55, 0.77]), respectively; and a median OS of 30.9 months vs. 25.1 months (HR 0.68 [95%CI: 0.55, 0.85]), respectively.

Treatment options for HER2-positive MBC after 2 or more anti-HER2 based regimens

It is agreed that there is no clearly defined SoC for patients with metastatic HER2-positive breast cancer after 2 or more anti-HER2-based regimens, which is the proposed setting for trastuzumab deruxtecan. Moreover, some of the approved regimens have moved to the setting of early breast cancer, such as TDM1 and pertuzumab.

Treatment options licensed in the European Union in this setting include lapatinib + capecitabine, trastuzumab + capecitabine, trastuzumab + lapatinib, or trastuzumab + other agents. The most recently published clinical studies in subjects with HER2-positive metastatic breast cancer who had received ≥2 prior lines of anti-HER2 therapy are the NALA, SOPHIA, and HER2CLIMB studies, which have sought to establish SoC regimens. The reference arms of these studies represent the most recent data for subjects receiving the current European SoC in the target population. In the NALA study, the reference therapy was lapatinib + capecitabine; in the SOPHIA study, the reference therapy trastuzumab + chemotherapy; and in the HER2CLIMB study, the reference therapy was placebo + trastuzumab + capecitabine. The results of these studies are provided in Table 1.

Table 1: Summary of Results of the NALA, SOPHIA, and HER2CLIMB Studies

Study		Median (95% CI)			
Treatment Arm		**ORR (%)**	**DoR (months)**	**PFS (months)**	**OS (months)**
NALA Study[1]					
Investigational therapy	neratinib + capecitabine (N = 307)	32.8 (27.1, 38.9)	8.5 (5.6, 11.2)	5.6 (4.9, 6.9)	21.0 (17.7, 23.8)
Licensed therapy	lapatinib + capecitabine (N = 314)	26.7 (21.5, 32.4)	5.6 (4.2, 6.4)	5.5 (4.3, 5.6)	18.7 (15.5, 21.2)
SOPHIA Study[2,3]					
Investigational therapy	Margetuximab + chemotherapy (N = 266)	22.1 (17.3, 27.7)	6.1 (4.1, 9.1)	5.8 (5.5, 7.0)	18.9 (16.2, 25.1)
Licensed therapy	Trastuzumab + chemotherapy (N = 270)	16.0 (11.8, 21.0)	6.0 (4.0, 6.9)	4.9 (4.2, 5.6)	17.2 (15.8, 33.3)
HER2CLIMB[4]					
Investigational therapy	tucatinib + trastuzumab + capecitabine (N = 410)	40.6 (35.3, 46.0)	Not reported	7.8 (7.5, 9.6)	21.9 (18.3, 31.0)
Licensed therapy	placebo + trastuzumab + capecitabine (N = 202)	22.8 (16.7, 29.8)	Not reported	5.6 (4.2, 7.1)	17.4 (13.6, 19.9)
U201					
Investigational therapy	trastuzumab deruxtecan	60.9 (53.7, 68.3)	20.8 (15.0, NE)	19.4 (14.1, NE)	24.6 (23.1, NE)

CI = confidence interval; DoR = duration of response; NE = not evaluated or not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival
Source: EMA Tables 14.2.2.1, 1.1, 1.2, 1.3, 1.4

In Study U201, at the most recent data cut-off (DCO) of 08 Jun 2020 (the EMA DCO), the confirmed ORR by ICR was 61.4% (95%CI: 54.0, 68.5), with a duration of response (DoR) of 20.8 months (95%CI: 15.0, NE). The median progression-free survival (PFS) was 19.4 months (95%CI: 14.1, NE), and the median overall survival (OS) was 24.6 months (95%CI: 23.1, NE). Thus, trastuzumab deruxtecan offers clinically meaningful benefit compared with the current SOCs. The median PFS for trastuzumab deruxtecan of 19.4 months is higher than the reported median PFS for the reference therapies used in the NALA, SOPHIA or HER2CLIMB studies (≤5.6 months); indeed, the lower bound of the trastuzumab deruxtecan 95%CI for the PFS of 14.1 months is higher than the reported upper bound for PFS from the reference arms of the NALA, SOPHIA, and HER2CLIMB studies (which were all below ≤7.1 months). Hence, trastuzumab deruxtecan is considered to offer clinically meaningful benefit compared with the investigational therapies used in the NALA, SOPHIA, and HER2CLIMB studies, where the median PFS was≤7.8 months, and the upper bound of the 95%CI was 9.6 months.

Unmet Medical Need in the Proposed Indication

Metastatic HER2-positive breast cancer remains an uncurable disease. Although treatment with anti-HER2-based regimens has improved the disease outcomes for patients with unresectable locally-advanced or metastatic HER2-positive breast cancer, the disease invariably progresses. Efficacy outcomes from current treatments approved in the EU for previously treated patients with HER2-positive metastatic breast cancer summarized by the Applicant show that the ORRs for available treatments range from 16-26.7% and a duration of response of approximately 6 months and PFS in the range between 4.9-5.6 months for licensed therapies. The lack of clearly preferential and effective treatment options after 2 or more prior anti-HER2-based regimens for HER2-positive metastatic breast cancer, as reflected by the absence of guideline-specific recommendations and low reported ORRs, highlights the remaining unmet medical need for these patients and the continued need for new HER2-targeted agents in this particular setting.

About the product

Trastuzumab deruxtecan exhibits HER2 specific antitumor activity via a mechanism of action that combines Trastuzumab deruxtecan is a HER2 targeted antibody and topoisomerase I inhibitor conjugate, a so-called antibody-drug conjugate (ADC). The anti-HER2 component, MAAL 9001, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that has the same amino acid sequence as trastuzumab and thus, trastuzumab deruxtecan is similarly targeted to HER2 expressing tumours. The released drug, MAAA-1181a, is a topoisomerase I inhibitor derivative of exatecan. The mAb is covalently conjugated to a drug-linker, MAAA 1162a, that is composed of a cleavable maleimide tetrapeptide linker and the released drug. The tetrapeptide linker is designed to be stable in plasma to reduce systemic exposure to the released drug. After cell internalization, the released drug leads to apoptosis of the target tumour cells via the inhibition of topoisomerase I. The released drug is cell-membrane permeable, giving the ability to penetrate and act in surrounding cells.

The claimed and approved indication for trastuzumab deruxtecan is as monotherapy 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.

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.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on

- The Applicant's summary of the efficacy of existing therapies.
- It is agreed that there still exists a high unmet medical need for the patient population, who have received two prior lines of anti-HER2 treatment-based regimens.
- It is agreed that there is no clear SOC in the targeted setting after two prior lines of anti-HER2 treatment-based regimens. The efficacy results with the treatments currently used in the proposed setting show response rates (ORR) from 9-41% and duration of response (DOR) and PFS in the range of 3.3 to 7.8 months, so there exists an unmet medical need for better treatments in the targeted setting.
- Trastuzumab deruxtecan demonstrated antitumor activity with confirmed objective response rate (ORR) of 60.9% (95% CI: 53.4, 68.0) in Study U201, with median duration of response (DoR) at 14.8 months (95% CI: 13.8, 16.9).
- The strength of evidence presented is deemed sufficient for an accelerated assessment of an application of a CMA, since the efficacy and safety data have been updated since the primary analysis and there are efficacy data for 235 patients from a single-arm trial, who have received the proposed dose with relevant and acceptable exposure.
- The safety database comprises 234 patients, which is also considered acceptable for a CMA.
- The Applicant has several randomised comparative studies ongoing, of which the 301 study is considered to be able to provide relevant confirmatory efficacy and safety data within a reasonable timeframe.

- In conclusion, an accelerated assessment of the application for trastuzumab deruxtecan would be of major interest from the point of view of public health, because the ORR and DOR results show therapeutic advantage compared to available treatments.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) 726/2004, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The Applicant has an ongoing Phase 3 randomized controlled study, which data can serve as confirmatory: DESTINY Breast02 (Study U301) assesses the efficacy and safety of trastuzumab deruxtecan vs. investigator's choice of treatment (trastuzumab plus capecitabine or lapatinib plus capecitabine) in patients, whose disease progressed on T-DM1 (i.e. 3L). A total of 600 patients are planned to be enrolled, 329 randomized as of 13 March 2020. This study is relevant for the claimed target population and provides data on PFS (primary endpoint) and OS (key secondary endpoint). Enrolment is expected to be complete in February 2021 and progression-free survival data are currently projected to be available during the first quarter of 2022 and could be considered as comprehensive data as a specific obligation (SOB) in the context of a CMA. It is considered likely that granting of a CMA will not impact the enrolment of the phase 3 study. A total of 329 out of 600 subjects planned were enrolled as of 13 Mar 2020, therefore 82 new patients were enrolled within a period of about 3 months. Therefore, the planning for the last subject to be enrolled (Feb 2021) is considered reasonable. It is expected that granting of a CMA will not impact the enrolment of the phase 3 study U301.
- Unmet medical needs will be addressed, as there is no clearly defined SoC and reported ORRs of therapeutic regimens administered after 2 or more prior anti-HER2-based regimens range approximately from 9% to 41%, while trastuzumab deruxtecan showed a confirmed ORR of 60.9% (95% CI: 53.4, 68.0) in Study U201 with DoR of 14.8 months (95% CI: 13.8, 16.9). Additionally, the median PFS with currently available treatment options is in the range of 3.3 to 7.8 months and a need for better treatments exist that prolong PFS and ultimately OS. ORR and DoR are substantially higher/longer for trastuzumab deruxtecan than reported for other medicinal products in the target population with at least two prior lines of anti-HER2 treatment.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  Trastuzumab deruxtecan shows substantial antitumor activity with a clinically meaningful ORR and durability of response, representing a clinically significant improvement over available therapies. Trastuzumab deruxtecan was generally tolerable and its safety profile was generally manageable through dose modifications and standard clinical practice. As such, trastuzumab deruxtecan addresses the unmet medical need and the immediate accessibility of patients to trastuzumab deruxtecan will provide a benefit to public health that outweighs the inherent risks associated with the limited availability of long-term safety and efficacy data.

2.2. Quality aspects

2.2.1. Introduction

Enhertu is an antibody-drug conjugate (ADC) presented as a powder for concentrate for solution for infusion in a vial containing 100 mg of trastuzumab deruxtecan as active substance. Enhertu is provided

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

Trastuzumab deruxtecan is formulated with L-histidine, L-histidine hydrochloride monohydrate, sucrose and polysorbate 80.

Prior to use, the powder is reconstituted with water for injections. The reconstituted solution is sterile and intended for single use only. It is then diluted in an infusion bag using 5% glucose solution before dosing via intravenous infusion.

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) that contains trastuzumab, a humanised anti HER2 IgG1 monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells, covalently linked to a topoisomerase I inhibitor via a linker. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

2.2.2. Active Substance

Trastuzumab deruxtecan active substance, also referred to as DS-8201a, results from the conjugation of the following intermediates:

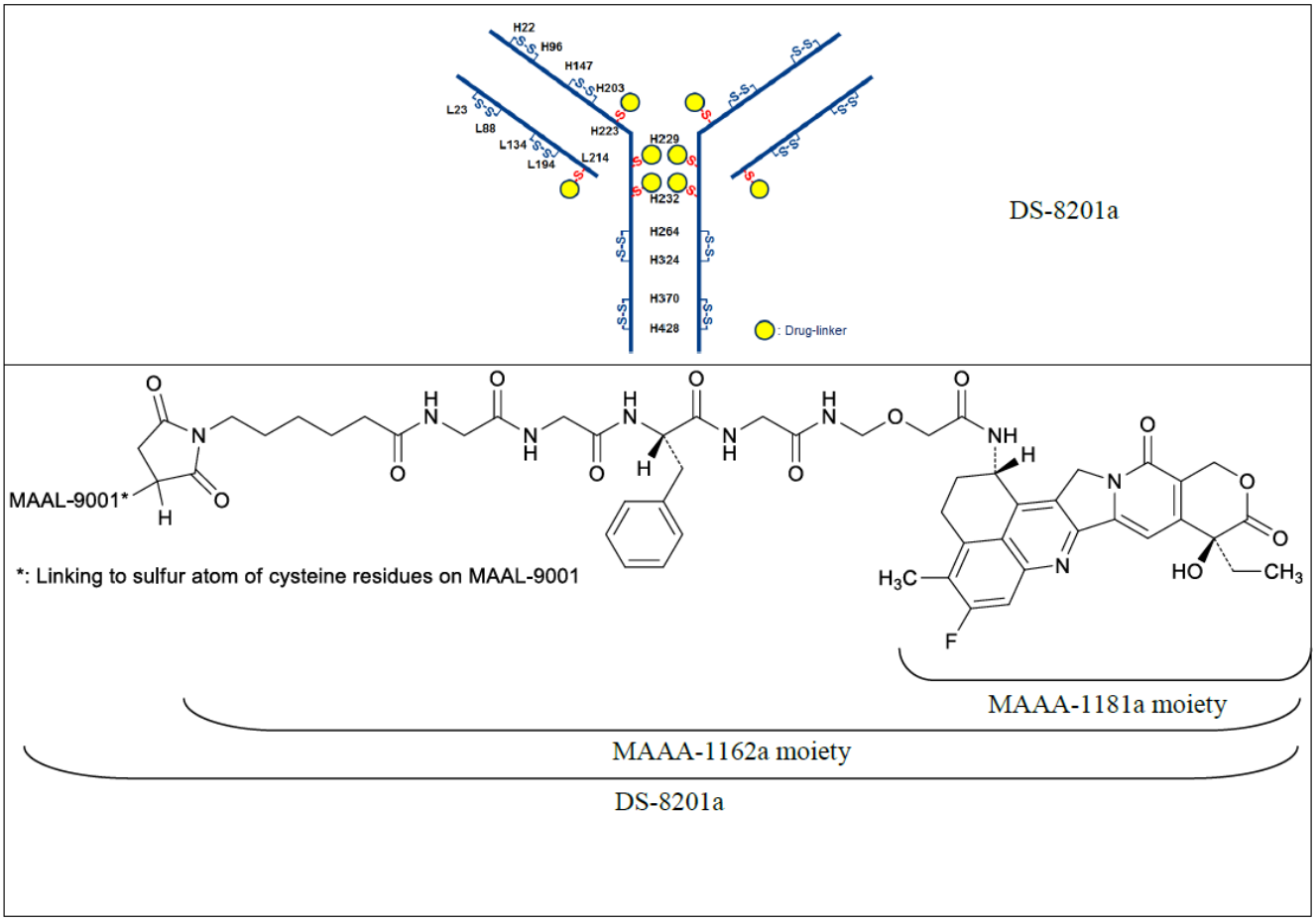
- Trastuzumab monoclonal antibody (MAAL-9001);

- A drug-linker (MAAA-1162a) comprised of a Topoisomerase I inhibitor derivative of exatecan (MAAA-1181a) and a tetrapeptide based cleavable linker (MFAH).

MAAL-9001 is covalently conjugated to approximately 8 molecules of MAAA-1162a. The linker is designed to be stable in plasma to reduce systemic exposure to the released MAAA-1181a drug. After cell internalisation, the released MAAA-1181a drug leads to apoptosis of the target tumour cells via the inhibition of topoisomerase I. The released MAAA-1181a drug is cell-membrane permeable, giving the ability to penetrate and act in surrounding cells. The effect of the ADC derives primarily from the released MAAA-1181a drug and to a lesser extent to the antibody-dependent cellular cytotoxic (ADCC) effector function of the conjugated antibody.

The quality of MAAL-9001 antibody, MAAA-1162a drug-linker and the conjugated antibody is described in separate sections. The structures of DS-8201a, MAAA-1162a, MAAA-1181a, and MAAL-9001 are provided in Figure 1.

Figure 1 – Schematic Structures of DS-8201a, MAAA-1162a, MAAA-1181a, and MAAL-9001



2.1. Drug-linker intermediate MAAA-1162a (MFAH linker and MAAA-1181a topoisomerase I inhibitor)

General information

Full information for the active substance intermediate MAAA-1162a ($C_{52}H_{56}FN_9O_{13}$, MW 1034.05) was provided in the dossier. MAAA-1162a is composed of DX-8951·MsOH (drug intermediate) and MFAH (linker intermediate with maleimide functionality). The maleimide moiety reacts with the antibody (MAAL-9001) in the conjugation reaction to yield trastuzumab deruxtecan (DS-8201a). MAAA-1162a contains 3 stereogenic centres. General information was provided for solid state form, melting point, moisture sorption, UV-Vis absorption, optical rotation and solubility.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

The manufacturing process of MAAA-1162a is a convergent synthesis. The synthesis includes defined starting materials and isolated intermediates. A QP Declaration and GMP certificates were provided. This is acceptable.

The process description is appropriately described, including all relevant in-process, operational controls and critical process parameters (CPPs).

Typical batch sizes for MAAA-1162a are defined within the dossier.

Control of materials

The control of materials including starting materials, reagents, solvents, catalysts and other auxiliary materials are appropriate. These are generally adequately controlled with and the adequate justification of starting materials has also been provided along with a discussion on the fate of related observed impurities.

Control of critical steps and intermediates

The control of critical step and intermediate specifications are generally adequate and in-process controls (IPCs) and operational controls are suitably justified.

Process validation

The manufacture of MAAA-1162a does not involve aseptic processing or sterilisation. Therefore, in-line with ICH M4Q (R1), requirements for process validation data do not apply. Confirmation of process validation has been given, which is accepted.

Manufacturing process development

The manufacturing process was optimised during development to improve the manufacturing efficiency while maintaining the desired quality of the drug-linker.

The discussion on manufacturing process development outlines the optimisation of the manufacturing process.

Characterisation

Elucidation of structure

The structure of MAAA-1162a was confirmed using elemental analysis, infrared (IR), ultra-violet (UV), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), mass spectrometry (MS) and single crystal X-ray structure analysis where relevant. The methods employed are appropriate for structure elucidation of MAAA-1662a.

Impurities

An exhaustive list and discussion of observed and potential impurities was provided.

The control strategy for the impurities including organic impurities, stereoisomers, residual solvents, elemental impurities and mutagenic impurities for MAAA-1162a was provided.

With reference to ICH Q3A (R2) "Impurities in New Drug Substances", each step of the MAAA-1162a drug-linker synthetic process was examined for observed and potential impurities.

Potential impurities, which might be present in each isolated intermediate and MAAA-1162a drug-linker were identified based upon knowledge of the chemical reaction conditions and the following information:

- Starting materials, intermediates, reagents, solvents, and auxiliary materials used in each manufacturing step;

- Impurities observed and specified in the proposed regulatory starting materials based upon knowledge of the upstream synthesis;

- Impurities observed and specified in the isolated intermediates and MAAA-1162a drug-linker;

- Potential reaction by-products originating from starting materials, intermediates and reagents, and

- Potential reaction by-products originating from observed impurities in the starting materials, intermediates and reagents.

Observed impurities in each isolated intermediate were identified based upon testing according to their specifications.

Specification

The specification of MAAA-1162a includes tests for description, identification by IR, specific optical rotation, assay and related substances by reversed phase high performance liquid chromatography (RP-HPLC) and residual solvents by gas chromatography (GC). The proposed limits are acceptable and are based on ICH Q3A, ICH Q6A and batch data.

Justifications are provided for the absence of certain tests. MAAA-1162a will not be released by real-time release testing.

The Applicant provided a risk assessment confirming that there is no risk in relation to nitrosamine impurities (see also Finished medicinal product section).

Analytical methods

Suitably described and validated analytical methods are used and are adequate to control MAAA-1162a on a routine basis. The assay and related substances methods are appropriately validated and were shown to be stability indicating.

Batch analysis

All batches complied with the specification at the time of analysis.

Reference standard

The primary reference standard batch is used as the working standard.

Container closure system

The suitability and compatibility of MAAA-1162a with the primary packaging components were evaluated and confirmed by the registration stability studies conducted under ICH long-term and accelerated storage conditions

Stability

Stability data from long-term and accelerated stability studies are provided for MAAA-1162a manufactured at the commercial manufacturing sites. Stability studies were conducted according to ICH guidance (Q1A, Q1B and Q1E) at 25°C/60% RH (long term) and at 40°C/75% RH (accelerated). No significant changes or trends were observed in tested parameters. Stress testing studies as well as photostability studies have been conducted. The proposed retest period is supported by the stability data.

2.2. Trastuzumab intermediate (MAAL-9001)

General information

MAAL-9001 is a full-length IgG1κ isotype antibody with relative molecular mass of approximately 145 kDa without accounting for glycans (glycosylation site at Asn300). MAAL-9001 consists of two identical heavy chains and light chains composed of 450 and 214 amino acids, respectively. The amino acid sequence of MAAL-9001, deduced from its cDNA sequence, is the same as the one of trastuzumab contained in centrally authorised products (e.g. Herceptin (EMEA/H/C/000278)). The inter-chain disulfide bonds are identified between heavy chains at Cys229 and Cys232, and between Cys214 on the light chain and Cys223 on heavy chain.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

The manufacturing site for MAAL-9001 is provided. A valid GMP certificate has been provided. Valid GMP certificates are also provided for the sites performing WCB and MCB storage as well as for the site performing mycoplasma and adventitious virus testing.

The MAAL-9001 manufacturing process is a standard monoclonal antibody manufacturing process. It consists of a cell culture process (upstream) and a protein purification process (downstream).

The cell culture process involves the propagation of recombinant CHO cells expressing the MAAL-9001 protein from one WCB vial through inoculation of flasks and bioreactors of gradually increasing size up to the final batch production bioreactor. The MAAL-9001 antibodies are harvested and is purified using a series of chromatography steps (, viral inactivation (ultrafiltration/diafiltration and viral filtration steps. The manufacturing process is well described.

The General Process Parameters (GPP), Key Process Parameters (KPP) and CPPs are defined by the Applicant for each manufacturing stage and listed with their PARs:

- GPP: A process parameter whose variability impacts neither a Key Process Attribute (KPA) (a measure that represents consistency of process performance) nor a Critical Quality Attribute (CQA).

- KPP: A process parameter whose variability has an impact on a KPA but not on a CQA.

- CPP: A process parameter whose variability has an impact on a CQA when falling outside the operational range.

Acceptable hold times are applied for the cell culture process and for the purification process, respectively.

Control of materials

The raw materials are listed with appropriate specifications. The TSE risk is considered sufficiently low.

The source, history and generation of the cell substrate has been described in sufficient detail.

The host cell line for expressing MAAL-9001 was generated using the CHO-S system. MAAL-9001 is manufactured from CHO-derived cell substrates employing a two-tiered system consisting of Master Cell Bank (MCB) and Working Cell Bank (WCB). The MCB is extensively tested in accordance with ICH Q5A and ICH Q5D guidelines making the proposed reduced virus testing programme for WCBs acceptable.

A protocol is presented for generation of future cell banks and is acceptable. The stability and lack of contamination of the production cell line has been documented beyond the culturing period.

Control of Critical steps and intermediates

A summary of the CPPs, KPPS and IPCs is given in the dossier and these are found acceptable. IPCs have been defined for each step of the active substance manufacturing process

The IPC methods have been suitably described. Method validation has been provided for non-compendial IPC methods and method suitability has been adequately verified for compendial methods.

Process validation

Process evaluation

The approach to process evaluation was based on extensive process development studies, prior manufacturing experience and process risk assessments.

The Applicant sufficiently summarised the results of the design of experiments (DOE) studies and also provided a rationale as to the potential impact of process parameters (and interactions) on quality attributes. The results from these studies are supportive of a well-characterised process and the approach to setting of PARs is found acceptable.

Process verification

The process validation strategy included process verification (also referred to as PPQ) runs. The results from the PPQ batches are consistent and support a conclusion that the process is robust and well controlled.

Shipping of the MAAL-9001 has been qualified.

Manufacturing process development

The manufacturing process development is adequately described.

Characterisation

Elucidation of structure

MAAL-9001 has been thoroughly characterised. The predicted primary amino acid sequences of MAAL-9001 heavy chains and light chains have been verified.

Post-translational modifications, glycosylation, charge and size heterogeneity, secondary structure, binding activity have been were suitably investigated.

The Applicant included further biological characterisation of MAAL-9001 in the trastuzumab deruxtecan section (see below).

Impurities

Product-related impurities

Product related impurities such as HMWS, including dimer and higher order aggregates, and LMWS were investigated and are controlled to acceptable levels.

Product-related substances

Product-related substances, such as major acidic and basic variants found in MAAL-9001. are suitably controlled to acceptable levels.

Process-related impurities

It is considered demonstrated that process-related impurities are well-controlled and pose no safety risk.

Furthermore, a risk assessment of extractables and leachables from materials used during the manufacture of MAAL-9001 has been conducted.

Specification

The specification for MAAL-9001 performed at release and for stability assessment includes control of identity, purity and impurities, potency and other general tests.

Overall, the parameters included in the MAAL-9001 specifications are found adequate to control the quality of the MAAL-9001. The acceptance criteria for the MAAL-9001 specification parameters are found appropriate.

Analytical methods

The analytical procedures are described in sufficient details. System suitability criteria are specified where relevant and the acceptance criteria have been confirmed during validation of the methods. The Applicant provided validation reports for the non-compendial methods. In general, the non-compendial methods have been validated in line with ICH Q2, and it has been clarified that suitability of the methods has been adequately demonstrated. The suitability of the test for bioburden and test for endotoxin performed according to Ph. Eur. have been demonstrated.

Batch analysis

Data for all batches show that data is comparable across production scales. All batches met the acceptance criteria.

Reference standard

A standard approach with two tier reference standards is in place. Primary reference standard and secondary reference standard are established and have been qualified.

The Applicant has provided the history of the previous MAAL-9001 reference standards and documented the link between the current reference standard and the initial material used for toxicology and clinical studies, including detailed information on the qualification and assessment against the primary reference standard of the secondary reference standard. Information on the generation and storage of future primary and secondary reference standards is given by referring to the description of the procedures used for the preparation of the current primary and secondary reference standards.

Container closure

The MAAL-9001 bulk is filled into bags. The inner fluid contact layer is stated to be compliant with *Ph. Eur. 3.1.7 Ethyl vinyl acetate copolymer for containers and tubing for parenteral nutrition preparations*.

The choice of packaging material for the active substance is considered appropriate.

Stability

The shelf life proposed for MAAL-9001 stored in the container closure system is considered supported by the stability data. These primary/registration lots are considered as representative of the MAAL-9001 commercial process.

2.3. Trastuzumab deruxtecan (DS-8201a)

General information

The active substance trastuzumab deruxtecan, also referred to as DS-8201a, is an ADC comprised of MAAL-9001 antibody conjugated to the drug-linker MAAA-1162a. There are 4 interchain disulfide bonds that can be reduced to produce cysteine residues which then can react with MAAA-1162a to form

thioether bonds and produce the ADC DS-8201a. The target number of drug-linker coupled to 1 antibody molecule is 8. The drug which is released is the MAAA-1181a moiety.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

The conjugation of the MAAL-9001 and drug-linker occurs at the Daiichi Sankyo Chemical Pharma Co., Ltd. (DSCP), Onahama site in Japan. During the active substance manufacturing process, the MAAL-9001 antibody is conjugated with the MAAA-1162a drug-linker. MAAA-1162a and MAAL-9001 are categorised as active substance intermediates.

The DS-8201a manufacturing process consists of MAAL-9001 thawing) followed by reduction. Reduced MAAL-9001 is incubated with MAAA-1162a for conjugation. After conjugation, the crude MAAA-1162a is purified, and the composition is adjusted to the final formulation. The composition adjusted solution is then filtered into separate bags and frozen for storage and shipment. The manufacturing process is adequately described.

Control of materials

Appropriate specifications are presented for non-compendial materials.

Control of critical steps and intermediates

The IPCs defined for the control strategy are found to be acceptable.

Process validation

Process evaluation

Process evaluation involved the initial identification of CQAs through an evaluation of the Quality Target Product Profile (QTPP) and CQAs of the finished product. This was followed by a preliminary hazard analysis and a risk assessment to identify areas of focus and potential CPPs with impact on CQAs, respectively. Potential CPPs, classified as high risk, were evaluated through process evaluation studies to determine if they had a critical impact on the relevant CQAs. The control strategy is considered acceptable.

Process verification

The commercial manufacturing process was successfully validated. The process validation batches met the validation acceptance criteria supporting that the process is in a valid state.

Shipping qualification studies were performed and verified that the product-temperature is maintained for the duration of shipping.

Manufacturing process development

Overall, the results of the comparability studies support that the quality of DS-8201a throughout the product and process development has been comparable from the early development non-clinical and clinical trials, to the pivotal trial and to the commercial product.

Characterisation

Elucidation of structure

Trastuzumab deruxtecan (DS-8201a active substance) has been thoroughly characterised.

The primary structure of DS-8201a active substance and the drug-linker conjugation sites were confirmed by a peptide mapping technique.

The secondary structure was verified by confirmation of the expected disulphide bond configuration of the IgG1 subclass antibody by peptide mapping under non-reducing conditions.

The charge heterogeneity of DS-8201a was evaluated by cation exchange chromatography (CEX-HPLC), imaged capillary isoelectric focusing (icIEF) and capillary zone electrophoresis (CZE).

The size heterogeneity of DS-8201a active substance was investigated and it was found that DS-8201a is predominantly a monomer in solution with trace amounts of HMWS and LMWS.

The distribution profile of drug-linker on DS-8201a active substance was characterised by 3 methods: RP-HPLC, hydrophobic interaction chromatography (HI-HPLC) and non-reduced CE-SDS (nrCE-SDS). The average DAR of DS-8201a active substance was determined by RP-HPLC and HI-HPLC to be 7.8.

The secondary structure was elucidated using far UV circular dichroism (CD) spectroscopy. The tertiary structure was elucidated using near UV CD spectroscopy. The folding state of the conjugated MAAL-9001 was deduced from its thermal stability using Differential Scanning Calorimetry (DSC) and the results indicate that the tertiary structure of the MAAL-9001 is maintained through the drug-linker conjugation process.

Biological characterisation

The biological characterisation is found comprehensive and support the putative mechanism of action (MoA). The major MoA of the DS-8201a active substance is antitumor activity through HER2 binding and cytotoxic activity of the conjugated drug MAAA-1162a, which is cleaved and the MAAA-1181a released after internalization and leads to apoptosis of the target tumour cells via the inhibition of topoisomerase I. The DS-8201a active substance has the same amino acid sequences as trastuzumab, which targets HER-expressing tumour cells. DS-8201a active substance exhibits ADCC activity and HER2-mediated Akt phosphorylation inhibition, but no complement dependent cytotoxicity (CDC).

Overall the binding activity studies demonstrate that the DS-8201a active substance, after undergoing the conjugation process that attaches the drug-linker, retains most of the structural features of MAAL-9001.

Impurities

Product-related impurities

HMWS, LMWS and unconjugated DS-8201a active substance are considered product-related impurities. HMWS

HMWS and LMWS are present in MAAL-9001 and are carried over to DS-8201a active substance.

Product-related substances

The charge variants of DS-8201a active substance are classified as product-related substances. The APG and BPG in MAAL-9001 are carried over to the DS-8201a active substance.

Process-related impurities

The process-related impurities are tested according to the specifications and are considered sufficiently controlled.

Extractables/Leachables

A risk assessment for the single-use polymeric components used in the manufacture and storage of the active substance was conducted. The results demonstrate that single-use polymeric components used in

active substance manufacture and storage have low or no risk of leachables on product safety and quality.

Specification

The specification for trastuzumab deruxtecan (DS-8201a) active substance performed at release and for stability assessment are provided in and includes control of identity, purity and impurities, potency and other general tests.

The release specifications include general tests (appearance (colour and clarity), osmolality pH), test for identity, purity and impurity tests, CZE, SE-HPLC, CE-SDS) tests for protein content (UV) and potency as well as tests for safety (endotoxin and bioburden). Overall, the parameters included in the active substance specification are found adequate to control the quality of the active substance.

The acceptance criteria for the active substance specification parameters are found appropriate.

Analytical procedures

The analytical procedures are described in sufficient details in method overviews and information on the reference standards and controls are included where relevant. System suitability criteria are specified where relevant and the system suitability test ranges have been confirmed during validation of the methods. The Applicant has provided validation reports for the non-compendial methods. The methods for release of DS-8201a have been validated in line with ICH Q2, and it has been clarified that suitability of the methods has been adequately demonstrated. The suitability of the test for bioburden and test for endotoxin performed according to Ph. Eur. have been demonstrated.

Batch analysis

Data for DS-8201a batches manufactured through clinical development and for the commercial product have been provided.

Data for all batches show that data is comparable across production scales and sites. All batches met the acceptance criteria.

Reference standard

A standard approach with two tier reference standards is in place. A primary reference standard and a secondary reference standard is established and has been qualified. Qualification included DS-8201a active substance release methods as well as additional characterisation.

The Applicant has provided the history of the previous DS-8201a reference standards and has documented the link between the current reference standard and the initial material used for toxicology and clinical studies. Detailed information on the qualification and assessment against the primary reference standard of the secondary reference standard has been provided. Information on the generation and storage of future primary- and secondary reference standards, is given by referring to the description of the procedures used for the preparation of the current primary- and secondary reference standards.

Container closure

The primary container closure system for DS-8201a is a single-use bag-in-shell system. The bag is the same as those used for the MAAL-9001 storage.

Stability

The proposed shelf life is considered supported by the long-term stability data and the stability studies are performed in accordance with current guidelines.

Active substance stability studies have been performed under long-term and accelerated storage condition, as well as at stress conditions.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the finished product

Trastuzumab deruxtecan 100 mg finished product is a sterile lyophilised powder for concentrate for solution for infusion, supplied as single-use vials. Each carton contains 1 vial.

Trastuzumab deruxtecan is formulated with well-known compendial excipients: sucrose, L-Histidine, L-Histidine hydrochloride monohydrate and polysorbate 80.

Prior to use, the finished product is reconstituted with 5 mL of water for injections to provide a solution with a concentration of 20 mg/mL trastuzumab deruxtecan, in 25mM histidine buffer that includes 90 mg/mL sucrose and 0.03% (w/v) of polysorbate 80 at pH 5.5. The reconstituted solution is a sterile solution and is then diluted in an infusion bag containing 5% dextrose (glucose) for dosing via intravenous infusion.

The primary container closure system is a Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper, and a polypropylene/aluminium yellow flip off crimp cap.

There are no overages.

Pharmaceutical development

The formulation development was guided by the QTPP and based on prior knowledge regarding the stabilisation of lyophilised monoclonal antibodies and antibody-drug conjugate products. CQAs were identified based on the QTPP. The rationale for the identified CQAs has been provided. The rationale for assigning the parameters as CQAs is based on the influence of the individual CQA on safety and/or efficacy and stability of the finished product.

The formulation development has been thoroughly described and the rationale for the selection of the formulation has been adequately addressed and justified. The manufacturing process development is described in detail and found to be comprehensive.

A comprehensive set of studies is presented for each step in the manufacturing process. The knowledge gained during process development studies was used to develop the control strategy Overall the approach taken for the control strategy is considered acceptable. A summary of the critical IPCs has been provided. The definition of the approach to non-conformances for IPCs is acceptable.

DS-8201a is light-sensitive and an amber vial was selected for the container of the finished product in order to prevent light-induced photo-degradation. No incompatibility between the amber vials and the finished product was observed. The selection of the amber glass vial as a control measure to minimise photo-degradation is supported by the registration stability studies.

The integrity of the container closure system to prevent microbial contamination has been adequately examined. Further, the sterility of the finished product is assured by the validated aseptic manufacturing process.

An IV compatibility study was conducted using a representative range of administration materials including commonly used in-line filters. In addition to the physical and chemical compatibility study, an in-use study to assess the sterility maintenance and a microbial challenge penetration study was also conducted. It is agreed that these studies support storage at 2°C to 8°C for no more than 24 hours for reconstituted and diluted product as stated in the SmPC.

Overall, the pharmaceutical development of the finished product is described in sufficient details and is acceptable.

Manufacture of the product and process controls

Manufacture

Trastuzumab deruxtecan (DS-8201a) finished product is manufactured, tested, stored, labelled and packaged in accordance with EU GMP.

The manufacturing process includes active substance thawing and compounding, sterile filtration, aseptic filling, lyophilisation and capping. The pooled, fully formulated finished product solution is sterilised using sterile filters. For the lyophilisation process, the freezing, primary drying, and secondary drying steps are performed consecutively. The manufacturing process does not include any isolated process intermediates.

Throughout the manufacturing process, measures are taken to protect DS-8201a from light exposure, since it is a critical parameter for the purity of the active substance. The microbial quality is assessed during finished product manufacturing by IPC testing for bacterial endotoxins (compounding step), bioburden (prior to sterile filtration) and filter integrity (post filtration). Filter integrity testing is performed pre- as well as post-filtration. In addition to the IPCs related to microbial control, the fill volume is part of the routine IPCs for each batch. Processing and hold times limits for the manufacture of finished product has been provided in the detailed description of the manufacturing process.

The manufacturing process is well described and considered acceptable. Flow charts of the manufacturing process steps, including IPCs have been provided and a narrative description of each step is given. The IPCs and CPPs are considered acceptable and sufficient to ensure the quality and consistency of each manufacturing step.

Process validation

Process validation (PPQ) was performed and three PPQ batches were manufactured.

All the PPQ tests met the acceptance criteria and it is agreed that the validated process is reproducible, consistent, and under control.

Sterilisation and depyrogenation of the filling equipment and components used in the finished product manufacturing process has been validated and are re-qualified periodically. The equipment used for sterilisation and depyrogenation of the filling equipment and container closure components of finished product were qualified. The sterilisation-in-place (SIP) of the lyophiliser was validated with all acceptance criteria being met.

Routine revalidation of media fills for all vial formats, interventions and challenging conditions were covered. For confirmation of the container closure system used for commercial manufacturing of the

finished product, additional product-specific media fills were conducted. As a result, the aseptic procedure for the manufacturing of the finished product was qualified.

Filter validation has been performed, demonstrating the consistent *B. diminuta* retention capability of the sterilising-grade filter.

To ensure finished product quality, a study was performed focusing on leachables coming from the manufacturing equipment. The manufacturing process of the finished product did not generate leachables of safety concern to patients. In addition, from these results, it was confirmed that no leachables are present above the safety limit or the AET.

The presented finished product manufacturing process, the proposed manufacturing control strategy for the manufacturing process and the performed process validation are considered acceptable.

Product specification

The specification for the finished product includes control of identity, purity and impurity, potency and other general tests.

A comprehensive control strategy has been developed to ensure the quality of the final finished product.

The release specifications for the finished product includes general tests (appearance before reconstruction and after reconstruction (color and clarity), osmolality, pH, water content, reconstitution time), tests for identity , purity and impurity tests test for protein content (UV) and potency as well as tests for safety(visible particles, subvisible particulate matter, endotoxin and test for sterility). The acceptance criteria for the finished product specification parameters are considered appropriate.

The potential presence of elemental impurities in the active substance and finished product has been assessed on a risk-based approach in line with the ICH Q3D guideline for elemental impurities. The risk of carryover of elemental impurities is considered negligible and no additional control is required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed(as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures

The analytical procedures for the finished product are adequately described. The procedures are either specific to the finished product or identical to the active substance. Validation reports were provided.

Batch analysis

Data for all batches show that data is comparable across production scales and comparable between the formulations and strengths. All batches met the acceptance criteria in place at the time of release.

Reference materials

A DS-8201a reference standard is used for release and stability testing of DS-8201a finished product for the purpose of identity and potency. The same primary and secondary reference standards for the active substance are used as the reference standards for DS-8201a finished product testing.

Container closure

The primary container closure of DS-8201a finished product is Type I amber glass 10 mL vials sealed with a 20 mm fluoro-resin laminated butyl rubber stopper and crimped with a 20 mm polypropylene/ aluminium flip-off cap with a plastic flip-off disk. The container closure integrity has been adequately examined, and the sterilisation and depyrogenation for the container closure components has been validated as part of the process validation.

A leachables study was performed on the finished product container closure system. The data presented supports the Applicant's conclusion that the DS-8201a finished product would not generate leachables of concern for safety to the patient and, in addition, the potential amount of leachables would not have an impact on the quality of the finished product.

Stability of the product

A 24-month shelf life is proposed for the finished product when stored at 2-8°C in the proposed container closure system (unopened vial). The proposed shelf life is considered supported by the long-term and accelerated registration stability data. The stability studies are performed in accordance with current guidelines.

The finished product registration batches placed into the stability program are considered representative of the material used in non-clinical and clinical studies as well as the material produced by the commercial process.

Overall, the proposed shelf life of 2 years at 2 ºC to 8 ºC (unopened vial) is considered acceptable.

In-use stability studies on the finished product reconstituted in 5 mL water for injections was performed as part of the product development and they support:

- Storage of the reconstituted solution for up to 24 hours at 2 ºC to 8 ºC;

- Storage of the reconstituted solution diluted in infusion bags containing 5% glucose solution at room temperature (≤ 30 °C) for up to 4 hours or in a refrigerator at 2 °C to 8 °C for up to 24 hours. These storage times start from the time of reconstitution.

A photostability study was conducted in accordance with ICH Q1B on one registration batch. All photostability study results were within the specifications. The lyophilisation of the finished product appears to protect the finished product from light-induced damage, since the DS-8201a finished product seems less light-sensitive than the DS-8201a DS. However, the diluted solution, if not used immediately, should be stored protected from light.

Adventitious agents

MAAL-9001

Raw materials.

No raw materials of animal- or human origin are used during the manufacture of the MAAL-9001 antibody active substance. The bag, used as container closure for MAAL-900, contains additives derived from tallow.

A risk assessment has been conducted evaluating the risk of transmitting TSE or adventitious viruses from these raw materials or from the container closure system. Based on the processes used for manufacture of the raw materials/tallow-derived additives, the stage at which the specific material has

been used, and of the origin of the animal-derived material (species and geographical), it is concluded that the TSE- or adventitious virus-related risk associated with MAAL-9001 is negligible.

Cell banks

The master, working, and limit-of-in-vitro-age (LIVCA) cell banks have been tested according to ICH Q5A and Q5D for absence of non-viral (mycoplasma, bacteria, fungi) and viral adventitious agents, and endogenous retroviruses. The testing verified the absence of adventitious agents and endogenous viruses, except for type A- and C- retrovirus-like particles, known to be present in the CHO cells.

Bulk harvest

Bulk harvest is routinely tested for the bioburden level and the absence of mycoplasma and adventitious viruses (IPCs). The bioburden and mycoplasma testing are conducted according to Ph. Eur. Testing for viral contaminants is conducted using a 28 days *in vitro* assay for adventitious viruses with MRC-5, Vero, CHO, and 324K cells as detector cells. Results have been provided from three commercial scale batches, verifying the absence of mycoplasma, bioburden, and viral contamination.

Viral clearance studies

The viral clearance capacity of the MAAL-9001 purification process was evaluated by conducting viral clearance studies, using qualified scale down models in accordance with ICH Q5A. The scale down procedure is considered acceptable and the scale down models are representative of the commercial scale. The studies conducted at worse-case values were included where applicable. FMEA was employed to identify the CPPs for viral clearance capability based upon organisation experience, viral clearance, characterisation of development experiments for the MAAL-9001 manufacturing process and from experience with similar biological products. The parameters selected by FMEA for performing virus clearance studies are considered relevant and appropriate.

Four model viruses were used for the virus validation, including murine leukemia virus (MLV), reovirus 3 (REO3), pseudorabies virus (PRV), and mouse minute virus (MMV). The selected model viruses represent a wide range of particle size, genome-type, and degree of resistance to physico-chemical treatments.

Based on the cumulative log reduction obtained for MLV, a safety factor has been determined and is considered a low and acceptable risk.

Conclusion

Overall, the risk of contamination of MAAL-9001 with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of viral contaminants in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity demonstrated for the MAAL-9001 purification process.

Trastuzumab deruxtecan active substance (DS-8201a)

No animal- or human-derived materials are used in the manufacture of the DS8201a active substance, consisting of the MAAL-9001 antibody, for which adventitious agents safety evaluation is described above, conjugated to the chemical drug-linker, MAAA-1162a. Tests for bioburden are routinely performed during manufacture of the active substance. No additional risk of contamination by adventitious agents is conferred by the DS8201a manufacturing process.

Finished product

No animal- or human-derived materials are used for formulation of the trastuzumab-deruxtecan finished product. No additional risk of contamination by adventitious agents is conferred by the finished product manufacturing process.

Overall Conclusion

Enhertu is considered safe for commercial purposes with regards to of risk of contamination with non-viral or viral adventitious agents.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Enhertu is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Enhertu is considered approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Trastuzumab deruxtecan is an antibody drug conjugate, where 8 drug moieties are linked via a peptide linker to cysteine residues on the trastuzumab antibody. The drug linker will be cleaved and will release the deruxtecan moiety which has membrane permeability, e.g. it will permeate the cell membrane and have effect inside the cell, and it may even affect neighbouring cells, hence a bystander effect has been shown. Deruxtecan is a topoisomerase I inhibitor, and DNA damage and apoptosis are observed. Trastuzumab, the antibody part of the ADC, will also have pharmacological activity, hence the ADC show both ADCC as well as drug mediated cellular toxicity.

The nonclinical profile for the ADC, DS-8201a, and the released drug, MAAA-1181a, has been characterized through pharmacology, pharmacokinetic, and toxicology studies. The in vivo studies were primarily conducted via intravenous injection in mice, rats, and monkeys, as this is the intended route of administration in humans. Safety pharmacology and toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) regulations and were consistent with the Organisation for Economic Co-operation and Development (OECD) standards in effect at the time. A nonclinical testing strategy for DS-8201a was developed based on the product characteristics and existing regulatory guidelines in the US, the EU, and Japan, including the Food and Drug Administration guidance "*Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*" (November 1995),

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3(R2), ICH S6(R1), and ICH S9.

MAAL-9001 is produced in Chinese hamster ovary (CHO) cells transfected with MAAL-9001 DNA sequence. Two MAAL-9001 producing cell lines have been established for the development of DS-8201a. The MAAL-9001 producing cell line was used to support preclinical studies and early stage of development. The second MAAL-9001 producing cell line is used for early and late stage of development and for commercial manufacture. MAAL-9001 manufacturing processes (mAb Process-1 and mAb Process-2) are developed for each of MAAL-9001 producing cell lines.

In nonclinical sections, MAAL-9001 and DS-8201a used in nonclinical studies are named as follows:

MAAL-9001 produced by mAb Process-1 is referred to as MAAL-9001 (Process 1) and MAAL-9001 produced by mAb Process-2 is referred to as MAAL-9001 (Process 2).

DS-8201a manufactured using MAAL-9001 (Process 1) is referred to as DS-8201a (Process 1). DS-8201a manufactured using MAAL-9001 (Process 2) is referred to as DS-8201a (Process 2).

Unless otherwise stated in this section, DS-8201a refers to DS-8201a (Process 1) and MAAL-9001 refers to MAAL-9001 (Process 1).

2.3.2. Pharmacology

Primary pharmacodynamic studies

IN VITRO

Binding activity and specificity of DS-8201a to human HER2:

The binding activity of DS-8201a and MAAL-9001, the antibody component of DS-8201a, to human HER family (epidermal growth factor receptor, HER2, HER3, and HER4) and HER2 ortholog (mouse, rat, and cynomolgus monkey) proteins was evaluated by enzyme-linked immunosorbent assay (ELISA).

DS-8201a and MAAL-9001 specifically bound to both human HER2 and cynomolgus monkey HER2, but not to other human HER family or other HER2 ortholog proteins. The dissociation constant (Kd) values of DS-8201a and MAAL-9001 for human HER2 protein were 7.33 and 7.84 ng/mL, respectively. The Kd values of DS-8201a and MAAL-9001 for cynomolgus monkey HER2 protein were 7.46 and 7.48 ng/mL, respectively.

The results indicate that DS-8201a and MAAL-9001 exhibit specific binding activity to both human and cynomolgus monkey HER2 and the impact of drug conjugation on the binding activity is minimal.

HER2-specific cell growth inhibitory activity of DS-8201a in human cancer cells:

In order to evaluate the cell growth inhibitory activity and specificity of DS-8201a, 5 human cancer cell lines were used: the lung adenocarcinoma cell line Calu-3, the gastric carcinoma cell line NCI-N87, the breast adenocarcinoma cell lines SK-BR-3 and MDA-MB-468, and the breast cancer cell line KPL-4. Each cell line was treated with DS-8201a, MAAL-9001, or MAAA-9001b, an ADC with the same drug-linker as DS-8201a in which MAAL-9001 has been replaced with a human IgG1 isotype control, at concentrations from 0.64 ng/mL to 10,000 ng/mL. Cell viability was evaluated 6 days after incubation by detection of adenosine triphosphate. The HER2 expression level of each cell line was determined by flow cytometric analysis with fluorescein isothiocyanate-labeled anti-HER2 antibodies or isotype control antibodies.

Human HER2 was expressed on the Calu-3, KPL-4, NCI-N87, and SK-BR-3 cells, but not on the MDA-MB-468 cells. DS-8201a exhibited cell growth inhibitory activity against HER2-positive Calu-3, KPL-4, NCI-N87, and SK-BR-3 cells, but not against HER2-negative MDA-MB-468 cells. On the other hand, MAAA-9001b showed no cell growth inhibitory activity against the cells tested. MAAL-9001 showed cell growth inhibitory activity only against NCI-N87 and SK-BR-3 cells, although not as much as DS-8201a. As a reference, all cell lines were sensitive to the active metabolite, MAAA-1181c.

These results indicate that DS-8201a possesses HER2-specific activity. The activity was higher than that of the anti-HER2 antibody, MAAL-9001, and was observed even in MAAL-9001 insensitive cells except for HER2-negative MDA-MB-468 cells.

Topoisomerase I inhibitory activity of MAAA-1181a:

MAAA-1181a is expected to be released from DS-8201a in the cytoplasm after DS-8201a binds to HER2 and is internalized in tumor cells. Since human topoisomerase I can relax supercoiled DNA, the inhibitory activity of MAAA-1181a against human topoisomerase I was evaluated by a topoisomerase I-mediated DNA relaxation assay using supercoiled DNA as a substrate. Human topoisomerase I is a type IB topoisomerase which can relax positive and negative supercoiled DNA and is an essential enzyme for DNA replication, transcription, and chromatin condensation. The inhibition of topoisomerase I causes cell death.

Recombinant human topoisomerase I was incubated with MAAA-1181a for 5 min. Supercoiled pBR322 DNA was then added and incubated at 37°C for 30 minutes (final concentration of MAAA-1181a: 20,000, 10,000, 5,000, 2,500, 1,250, 625, 312.5, 156.25, and 78.125 nmol/L). After the mixture was electrophoresed on an agarose gel, the amount of the supercoiled DNA was measured. MAAA-1181a inhibited the relaxation of supercoiled DNA caused by human topoisomerase I in a dose-dependent manner. This result indicates that MAAA-1181a has inhibitory activity against human topoisomerase I.

Induction of DNA damage and apoptosis by DS-8201a:

Since it has been reported that topoisomerase I inhibitors induce double-strand DNA breaks and apoptosis, the induction of DNA damage and apoptosis by DS-8201a was evaluated using the human breast cancer cell line KPL-4 in comparison with MAAL-9001 and MAAA-1181a. The KPL-4 cells were treated with DS-8201a, MAAL-9001, or MAAA-1181a. Phosphorylation of Chk1 and histone H2A.X was evaluated as DNA damage markers and cleaved poly(adenosine diphosphate-ribose) polymerase (PARP) as an apoptosis marker by a Western blotting method after 24, 48, and 72 hours.

DS-8201a and MAAA-1181a induced the phosphorylation of Chk1 after 24 hours, the phosphorylation of histone H2A.X after 48 hours, and PARP cleavage after 72 hours, whereas MAAL-9001 induced no major changes in any markers. The results indicate that DS-8201a induced DNA damage and apoptosis in the same manner as MAAA-1181a, suggesting that these changes were caused by the topoisomerase I inhibition of the MAAA-1181a released from DS-8201a.

Inhibitory activity of DS-8201a against intracellular phosphorylation of Akt

MAAL-9001 has the same amino acid sequence as trastuzumab, and DS-8201a is therefore expected to have HER2-mediated Akt phosphorylation inhibitory activity and ADCC activity. In this study, the inhibitory activity of DS-8201a against the intracellular phosphorylation of Akt in human breast adenocarcinoma SK-BR-3 cells was evaluated by ELISA. The SK-BR-3 cells were incubated with DS-8201a at concentrations from 1.524 ng/mL to 10,000 ng/mL. After 24 hours of incubation, phosphorylated Akt (pAkt) and total Akt were measured using a commercially available ELISA kit.

DS-8201a induced the downregulation of intracellular pAkt in the SK-BR-3 cells in a dose-dependent manner and the estimated minimum value of relative pAkt was 17.2%, and the ED50 value was 89.65

ng/mL. Conversely, the treatment of the control IgG ADC, MAAA-9001b, did not induce the distinct downregulation of the intracellular pAkt indicating.

Antibody-dependent cellular cytotoxic activity of DS-8201a using human peripheral blood mononuclear cells (P140118):

The ADCC activities of DS-8201a and MAAL-9001 were evaluated using human peripheral blood mononuclear cells derived from 3 healthy donors as effector cells and human breast cancer SK-BR-3 cells as target cells. The effector cells and the ^{51}Cr-labeled target cells were incubated with DS-8201a or MAAL-9001 at concentrations from 0.001 ng/mL to 10,000 ng/mL and the ADCC activity was measured based on the radioactivity released from the target cells 4 hours after incubation.

DS-8201a and MAAL-9001 exhibited ADCC activity against the SK-BR-3 cells. The 50% effective concentration (EC_{50}) in the 2 donor samples were 3.8 and 5.9 ng/mL for DS-8201a, and 2.1 and 2.7 ng/mL for MAAL-9001, whereas the EC_{50} for the other donor sample could not be calculated due to the low percentage of natural killer (NK) cells.

These results suggest that DS-8201a possesses ADCC activity in the presence of human peripheral blood mononuclear cells, as does MAAL-9001, and that the impact of drug conjugation on ADCC activity is considered minimal.

Antibody-dependent cellular cytotoxic activity of DS-8201a (Process 1 and Process 2) using natural killer cells (B161208):

The ADCC activities of DS-8201a (Process 1) and DS-8201a (Process 2) were evaluated using human CD16-expressing NK cells as effector cells and human breast cancer SK-BR-3 cells as target cells. The effector cells and the ^{51}Cr-labeled target cells were incubated with DS-8201a at concentrations from 0.0508 ng/mL to 1000 ng/mL and the ADCC activity was measured based on the radioactivity released from the target cells 4 hours after incubation. MAAA-9001b was also evaluated as a negative control.

DS-8201a (Process 1) and DS-8201a (Process 2) exhibited ADCC activity against SK-BR-3 cells. The EC_{50} was 10.1 ng/mL for DS-8201a (Process 1) and 18.2 ng/mL for DS-8201a (Process 2). The maximum possible effect (Emax) was 41.8% for DS-8201a (Process 1) and 31.4% for DS-8201a (Process 2).

IN VIVO

Antitumor activity of DS-8201a (Process 1 and Process 2) and its antibody component in HER2-positive breast cancer xenograft model in nude mice (CR16-H0018-R06):

The in vivo efficacy of DS-8201a was evaluated in a mouse xenograft model of HER2-positive breast cancer KPL-4 cells in female CAnN.Cg-Foxn1^{nu}/CrlCrlj mice (nude mice) in a comparison with MAAL-9001. In this study, the efficacies of two lots of DS-8201a as well as MAAL-9001 were compared in order to investigate the impact of the differences in in vitro ADCC activity as shown in study ***B161208***. DS-8201a (Process 1), DS-8201a (Process 2), MAAL-9001 (Process 1), and MAAL-9001 (Process 2) were administered intravenously at a single dose of 10 mg/kg to the mice (n = 12/group) 13 days after inoculation (Day 0). The tumor dimensions and body weight of each mouse were measured twice a week until Day 21. The area under the curve (AUC) of tumor growth inhibition (TGI) against days after administration was calculated for DS-8201a.

DS-8201a (Process 2) at 10 mg/kg significantly inhibited tumor growth by 97.4% compared with the vehicle control group on Day 21 ($P < 0.0001$, Student's t-test). The relative mean AUC of TGI for DS-8201a (Process 2) compared to DS-8201a (Process 1) was 110.8% (95% confidence interval: 98.4% to 123.1%), which indicated that there is no significant difference in efficacy between DS-8201a

(Process 2) and DS-8201a (Process 1). MAAL-9001 (Process 1) and MAAL-9001 (Process 2) inhibited tumor growth by 24.7% and 26.9%, respectively, on Day 21.

These results suggest that the antitumor activity of DS-8201a is mainly derived from the activity of the conjugated drug, MAAA-1181a, and no apparent difference in antitumor activity in vivo was observed between the 2 lots of DS-8201a and MAAL-9001 tested.

Antitumor activity of DS-8201a in a trastuzumab-resistant HER2-positive breast cancer xenograft model in nude mice (CR16-H0018-R23):

The HER2-positive breast cancer cell line JIMT-1 was derived from a trastuzumab-resistant patient and is known to be refractory to T-DM1. In this study, the in vivo efficacy of DS-8201a was evaluated in comparison with that of T-DM1 and MAAL-9002b in a mouse xenograft model of JIMT-1 cells. JIMT-1 cells were inoculated into female CAnN.Cg-Foxn1^{nu}/CrlCrlj mice (nude mice) and DS-8201a, T-DM1, and MAAL-9002b were administered intravenously at a single dose of 3 or 10 mg/kg for DS-8201a and 10 mg/kg for T-DM1 and MAAL-9002b to the mice (n = 10/group) 10 days after inoculation (Day 0). The tumor dimensions and body weight of each mouse were measured twice a week until Day 21.

DS-8201a at 3 and 10 mg/kg, T-DM1 at 10 mg/kg, and MAAL-9002b at 10 mg/kg significantly inhibited tumor growth by 64%, 85%, 35%, and 66%, respectively, compared with the vehicle control on Day 21 ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively, Dunnett's test). Furthermore, DS-8201a at 10 mg/kg showed significantly greater efficacy than T-DM1 and MAAL-9002b ($P < 0.0001$ and $P = 0.0003$, respectively, Student's t-test). The results suggest that DS-8201a is effective even in T-DM1-refractory HER2-positive breast cancer tumors and that the high DAR results in higher efficacy.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted.

Safety pharmacology programme

Two dedicated safety pharmacology studies were performed. A hERG study and an in vivo cynomolgus study with telemetered animals, where cardiovascular, respiratory and CNS endpoints were evaluated.

Safety Pharmacology Study of MAAA-1181a on hERG Channels in hERG Transfected CHO Cells (SBL315-029, GLP study)

The effect of MAAA-1181a on the hERG currents, which are responsible for the rapidly activating component of delayed rectifier potassium current (IKr), was evaluated using the whole-cell patch clamp method. MAAA-1181a monohydrate was applied by perfusion at concentrations of 1, 3, and 10 µmol/L to hERG transfected CHO cells at room temperature (n = 5/concentration). The tail peak currents were used as an indicator of the hERG currents, and the compensated suppression rates of the tail peak currents, corrected for the negative control value, were used to evaluate the test article's effect on the hERG currents. A negative control (physiological saline diluted 188-fold with Tyrode solution), and a known selective IKr blocker, E-4031 at 0.1 µmol/L, as the positive control, were applied to the cells in the same manner as the test article.

The compensated suppression rates of MAAA-1181a at 1, 3, and 10 µmol/L for the tail peak current were −4.24%, 0.42%, and −0.74%, respectively. MAAA-1181a had no statistically significant effect on tail peak currents at any concentrations in comparison with the negative control. E-4031, the positive control, at 0.1 µmol/L produced a statistically significant decrease in tail peak currents in comparison

with the negative control (79.34%). This result indicates that the test system was reliable and suitably sensitive to detect the inhibitory effect of the test article on hERG currents.

In conclusion, under the conditions of this study, MAAA-1181a had no effect on hERG currents at 1, 3, or 10 μmol/L in hERG transfected CHO cells. MAAA-1181a had no effect on hERG channel current at concentrations up to 10 μmol/L (approximately 5000 ng/mL), at which there was a sufficient margin of exposure compared with the Cmax (7.2 ng/mL) of MAAA-1181a in patients administered at 5.4 mg/kg of DS-8201a in the clinical study (Study DS8201-A-U201).

Safety Pharmacology Study of DS-8201a on the Cardiovascular, Respiratory, and Central Nervous Systems in Monkeys (SBL315-061, GLP study)

A safety pharmacology study of DS-8201a on the cardiovascular, respiratory, and central nervous systems was conducted in 8 conscious and unrestrained male cynomolgus monkeys (4 years to 6 years old) using a telemetry system, blood gas analysis, and a functional observational battery method. DS-8201a dissolved in a control article (10 mmol/L histidine buffer [pH 5.8], 10 w/v% trehalose, and 0.02 w/v% polysorbate 20) was intravenously administered at single doses of 30 or 78.8 mg/kg (dose volume, 4 mL/kg; rate of administration, 3 mL/min). The control article was administered to all 8 animals on Day 1 and then the test article was administered to the 30 and 78.8 mg/kg groups (4 animals/group) on Day 22.

Blood pressure (systolic, diastolic, and mean), heart rate, electrocardiogram (ECG) parameters (PR interval, QRS duration, QT interval, and QT interval corrected with Bazett's formula), respiratory rate, blood gas parameters (arterial blood pH, arterial oxygen tension, arterial carbon dioxide tension, and haemoglobin oxygen saturation), intra-abdominal body temperature, presence or absence of arrhythmia, general behaviour and neurobehavioral function were evaluated. Clinical signs, body weight, and food consumption were also evaluated. At 30 and 78.8 mg/kg, there were no test article-related changes in blood pressure, heart rate, any ECG parameter, respiratory rate, any blood gas parameter, intra-abdominal body temperature, or general behaviour or neurobehavioral function. There was no arrhythmia at either dose level. At 30 mg/kg, no abnormalities in clinical signs were observed in any animal. At 78.8 mg/kg, vomiting (including retching) was observed sporadically in 3 animals between approximately 6 and 47.5 hours after the end of administration. Soft stool and/or diarrhoea were observed in 3 animals between 4 and 11 days after administration. Abnormal skin colour (brownish black) was observed in all animals between 9 days after administration and the final observation day. A decrease in food consumption was observed in 2 animals between 1 and 8 days after administration at 30 mg/kg and in 3 animals between 1 and 10 days after administration at 78.8 mg/kg. In 3 animals that were treated with 78.8 mg/kg, a decrease in body weight was also observed 6, 13, and 20 days after administration.

In conclusion, under the conditions of the present study, DS-8201a had no effect on the cardiovascular, respiratory, or central nervous systems at doses of up to 78.8 mg/kg when administered once intravenously to male monkeys.

Cardiovascular endpoints were also included in the repeat dose study (SBL-315-031), where the animals were dosed once weekly for 3 consecutive weeks, at doses of 0, 10, 30 or 78.8 mg/kg. Shortening of PR interval and prolongation of QTc was observed in the 78.8 mg/kg group, and related to treatment with DS-8201a.

MAAA-1181d had no effect on hERG currents at 1, 3, or 10 μM in hERG transfected CHO cells. Also, a safety pharmacology study of DS-8201a was conducted in male cynomolgus monkeys using a telemetry system, blood gas analysis, and a functional observational battery method. DS-8201a had no effect on the cardiovascular, respiratory, or central nervous systems at doses of up to 78.8 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted since this application (see discussion on non - clinical pharmacology).

2.3.3. Pharmacokinetics

The in vivo pharmacokinetic studies with DS-8201a (trastuzumab deruxtecan) were conducted via intravenous (IV) injection, as this is the intended clinical route of administration, to rats and cynomolgus monkeys, which were used for toxicology studies. Tissue distribution was evaluated in monkeys. The in vitro metabolic profile of DS-8201a was evaluated in plasma and in hepatocytes. The in vivo metabolism and excretion of DS-8201a was investigated in plasma, urine and faeces of monkey and the in vivo metabolism and excretion of MAAA-1181a in rats.

Methods of analysis

Ligand binding assays were developed and validated to determine the concentrations of DS-8201a and total antibody (the sum of conjugated and unconjugated antibody) in mouse, rat, and monkey plasma. Electro-chemiluminescence assay (ECLA) methods were developed and validated to determine the anti-DS-8201a antibody (ADA) and anti-MAAL-9001 antibody concentrations in rat and monkey plasma. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were developed and validated to determine the MAAA-1181a concentrations in the samples.

Absorption

A single dose, non-GLP, IV administration study in cynomolgus monkeys were performed. Furthermore, a single dose PK study was performed comparing the two process DS-8201a (Process 1 and 2), which is presented and discussed under the heading "other PK studies".

Pharmacokinetics after Single Intravenous Administration of DS-8201a in Cynomolgus Monkeys (SBL315-043)

The PK of DS-8201a, total antibody, and MAAA-1181a were investigated after single intravenous administration of DS-8201a at doses of 0.1, 0.3, 1, and 3 mg/kg to male fasted cynomolgus monkeys (n = 3/group). The plasma DS-8201a, total antibody, anti-DS-8201a antibody, and MAAA-1181a concentrations were measured pre-dose and at designated time points (0.083, 1, 7 hours, 1, 3, 7, 14, 21, and 28 days post-dose).

The plasma DS-8201a concentrations decreased exponentially after single intravenous administration. The AUC of DS-8201a increased in a greater than dose-proportional manner. The CL (14.0 mL/d/kg to 55.7 mL/d/kg) decreased with the dose ranged from 0.1 mg/kg to 3 mg/kg. The t1/2 and MRTinf were longer at 1 and 3 mg/kg (t1/2, 2.90 and 3.92 day; MRTinf, 2.55 and 3.84 day) than at 0.1 and 0.3 mg/kg (t1/2, 0.641 and 0.686 day; MRTinf, 0.834 and 0.867 day). The Vss (30.6 mL/kg to 55.4 mL/kg) of DS-8201a was close to the plasma volume and no difference was noted between the doses of DS-8201a.

No significant differences were observed in the pharmacokinetic parameters between DS-8201a and total antibody. No anti-DS-8201a antibodies were detected in any animals. All individual MAAA-1181a concentrations were below the LLOQ (0.100 ng/mL) at 0.1 and 0.3 mg/kg. Low plasma concentrations of MAAA-1181a were detected at a few time points at 1 and 3 mg/kg (lower than 0.195 and 0.709 ng/mL, respectively).

Toxicokinetics after Repeated Intravenous Administration of DS-8201a

Rats: Six-week Intermittent Dose Toxicity Study (SBL315-030)

The toxicokinetic (TK) of DS-8201a, total antibody, and MAAA-1181a were evaluated in a GLP-compliant 6-week intermittent dose (once every 3 weeks [q3w]) toxicity study of DS-8201a by intravenous bolus injection.

The toxicokinetic parameters of DS-8201a, total antibody, and MAAA-1181a are summarized in the below table. The C0 and AUC21d values of DS-8201a and total antibody generally increased along with the dose ranged from 20 mg/kg to 197 mg/kg. The Cmax and AUC21d values of MAAA-1181a also generally increased along with the dose ranged from 20 mg/kg to 197 mg/kg. No apparent changes after repeated dosing nor any apparent sex differences were noted in the toxicokinetic parameters. Anti-DS-8201a antibodies were not detected in any animals during the dosing or recovery period.

Toxicokinetic Parameters in the 6-week Intermittent Intravenous Dose Toxicity Study of DS-8201a in Rats

Dose (mg/kg)	**20**		**60**		**197**	
No. of Animals	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
DS-8201a						
C0 (µg/mL)						
Day 1	439 ± 41.6	497 ± 37.7	1400 ± 47.7	1510 ± 174	4300 ± 348	5070 ± 444
Day 22	613 ± 28.3	615 ± 31.7	1740 ± 75.5	1890 ± 130	6410 ± 121	5730 ± 558
AUC21d (µg·d/mL)						
Day 1	1776 ± 64	1869 ± 188	4903 ± 493	4871 ± 542	13,824 ± 1420	15,096 ± 2432
Day 22	2676 ± 226	2339 ± 265	6756 ± 415	7391 ± 536	14,264 ± 4063	19,818 ± 2159
t1/2 (d)						
Day 1	8.07 ± 0.0631	7.61 ± 0.270	8.52 ± 0.827	8.67 ± 1.17	5.78 ± 2.66	6.88 ± 2.54
Day 22	8.47 ± 0.481	7.63 ± 0.660	8.98 ± 1.61	9.56 ± 0.731	5.20 ± 2.44	8.43 ± 1.14
Total antibody						
C0 (µg/mL)						
Day 1	459 ± 48.5	514 ± 22.9	1530 ± 77.6	1470 ± 65.1	4980 ± 262	4700 ± 533
Day 22	611 ± 41.1	632 ± 12.7	2030 ± 191	1780 ± 86.5	6560 ± 475	5970 ± 736
AUC21d (µg·d/mL)						
Day 1	2095 ± 106	2182 ± 156	6017 ± 579	6067 ± 231	17,481 ± 2054	17,036 ± 2396
Day 22	3035 ± 200	2736 ± 358	8069 ± 545	8448 ± 461	17,895 ± 5189	22,533 ± 2460
t1/2 (d)						
Day 1	9.79 ± 0.390	9.76 ± 0.735	10.4 ± 0.337	10.4 ± 1.16	6.12 ± 2.85	7.86 ± 3.12
Day 22	11.0 ± 0.376	9.04 ± 1.01	9.64 ± 1.72	11.7 ± 1.29	5.13 ± 2.41	10.3 ± 2.04
MAAA-1181a						

Dose (mg/kg)	20		60		197	
No. of Animals	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
Cmax (ng/mL)						
Day 1	0.819 ± 0.108	1.21 ± 0.370	2.49 ± 0.351	3.54 ± 1.21	9.89 ± 1.34	15.0 ± 3.57
Day 22	1.41 ± 0.284	1.19 ± 0.362	4.20 ± 0.287	4.36 ± 0.397	13.4 ± 1.06	14.0 ± 4.25
AUC21d (ng·d/mL)						
Day 1	2.88 ± 0.287	2.45 ± 0.657	8.57 ± 0.456	6.86 ± 0.690	31.9 ± 3.42	28.1 ± 3.17
Day 22	4.68 ± 0.733	3.02 ± 0.515	14.4 ± 0.606	10.0 ± 1.24	40.3 ± 9.87	32.4 ± 3.09
t1/2 (d)						
Day 1	4.24 ± 0.506	3.16 ± 0.641	3.90 ± 1.30	3.46 ± 0.703	3.57 ± 1.24	5.34 ± 0.430
Day 22	6.64 ± 0.524	5.73 ± 1.95	6.14 ± 0.373	6.90 ± 1.12	3.23 ± 1.56	6.37 ± 1.30

d, day; F, female; M, male; No., number.

Values are expressed as the mean ± standard deviation.

Cynomolgus Monkeys: Six-week Intermittent Dose Toxicity Study (SBL315-031)

The TK of DS-8201a, total antibody, and MAAA-1181a were evaluated in a GLP-compliant 6-week intermittent dose (q3w) toxicity study of DS-8201a by intravenous bolus injection.

The toxicokinetic parameters of DS-8201a, total antibody, and MAAA-1181a are summarized in the table below. The C0 and AUC21d values of DS-8201a and total antibody generally increased along with the dose ranged from 10 mg/kg to 78.8 mg/kg. The Cmax and AUC21d values of MAAA-1181a also generally increased along with the dose ranged from 10 mg/kg to 78.8 mg/kg. No apparent changes after repeated dosing nor any apparent sex differences were noted in the toxicokinetic parameters. Anti-DS-8201a antibodies were not detected in any animals during the dosing or recovery period.

Toxicokinetic Parameters in the 6-week Intermittent Intravenous Dose Toxicity Study of DS-8201a in Cynomolgus Monkeys

Dose (mg/kg)	10		30		78.8	
No. of Animals	**M:3**	**F:3**	**M:5**	**F:5**	**M:5**	**F:5**
DS-8201a						
C0 (µg/mL)						
Day 1	271 ± 38.8	291 ± 9.23	907 ± 128	891 ± 81.2	2600 ± 573	2080 ± 120
Day 22	338 ± 40.1	363 ± 46.4	859 ± 150	699 ± 69.3	2520 ± 156	2190 ± 275
AUC21d (µg·d/mL)						
Day 1	1050 ± 123	1057 ± 216	3611 ± 594	3442 ± 198	9338 ± 1243	7778 ± 1435
Day 22	1096 ± 264	1067 ± 157	4802 ± 1002	3861 ± 534	10,563 ± 774	9471 ± 638[a]
t1/2 (d)						
Day 1	4.96 ± 0.833	5.07 ± 0.904	7.47 ± 0.624	6.59 ± 1.36	7.42 ± 0.814	5.99 ± 0.780
Day 22	5.03 ± 1.63	5.26 ± 1.12	7.01 ± 0.505	6.30 ± 0.474	8.52 ± 1.14	6.32 ± 2.33
Total antibody						
C0 (µg/mL)						

Dose (mg/kg)	10		30		78.8	
No. of Animals	**M:3**	**F:3**	**M:5**	**F:5**	**M:5**	**F:5**
Day 1	268 ± 33.3	267 ± 8.44	1010 ± 73.4	885 ± 86.9	2580 ± 521	2200 ± 127
Day 22	290 ± 35.9	294 ± 28.6	972 ± 176	698 ± 87.7	2120 ± 109	2050 ± 101
AUC21d (µg·d/mL)						
Day 1	1065 ± 90	1087 ± 230	4318 ± 654	3936 ± 198	10,026 ± 1199	8962 ± 1451
Day 22	1152 ± 342	1247 ± 338	5884 ± 1167	3939 ± 481	12,135 ± 794	10,535 ± 901[a]
t1/2 (d)						
Day 1	5.63 ± 1.14	5.67 ± 1.01	8.69 ± 0.910	6.81 ± 3.07	8.48 ± 0.777	6.80 ± 0.841
Day 22	5.53 ± 1.83	5.90 ± 1.45	10.1 ± 1.58	8.50 ± 0.847	9.15 ± 1.13	7.18 ± 2.35
MAAA-1181a						
Cmax (ng/mL)						
Day 1	0.896 ± 0.270	1.25 ± 0.305	3.55 ± 1.36	3.01 ± 0.723	11.0 ± 1.10	16.4 ± 11.6
Day 22	1.14 ± 0.399	0.834 ± 0.0630	3.76 ± 0.633	2.85 ± 0.567	12.8 ± 1.30	13.5 ± 5.95
AUC21d (ng·d/mL)						
Day 1	2.79 ± 0.784	1.93 ± 0.131	9.06 ± 2.13	9.60 ± 2.83	44.9 ± 15.1	73.9 ± 48.2
Day 22	3.22 ± 1.18	1.47 ± 0.258	11.0 ± 2.47	8.39 ± 2.42	39.3 ± 9.34	24.7 ± 3.72
t1/2 (d)						
Day 1	4.38 ± 0.539	3.07 ± 1.85	3.97 ± 1.12	4.58 ± 3.19	4.32 ± 0.638[a]	5.59 ± NC[b]
Day 22	3.13 ± 0.668	1.68 ± 0.403	5.79 ± 2.18	4.77 ± 2.59	5.16 ± 0.941	4.78 ± 1.73

Values are expressed as the mean ± standard deviation; d, day; F, female; M, male; NC, not calculated; No., number.

[a] Calculated from 4 animals; [b] Calculated from 2 animals.

Cynomolgus Monkeys: Three-month Intermittent Dose Toxicity Study of DS-8201a (SBL315-526)

The TK of DS-8201a, total antibody, and MAAA-1181a were evaluated in a GLP-compliant 3-month intermittent dose (q3w) toxicity study of DS-8201a (Process 2) by intravenous bolus injection.

The toxicokinetic parameters of DS 8201a, total antibody, and MAAA 1181a are summarized in the table below. The C0 and AUC21d values of DS-8201a and total antibody generally increased along with the dose ranged from 3 mg/kg to 30 mg/kg. The Cmax and AUC21d values of MAAA-1181a also generally increased along with the dose ranged from 3 mg/kg to 30 mg/kg. No apparent changes after repeated dosing nor any apparent sex differences were noted in the toxicokinetic parameters. Anti-DS-8201a antibodies were not detected in any animals during the dosing period.

Toxicokinetic Parameters in the 3-month Intermittent Intravenous Dose Toxicity Study of DS-8201a (Process 2) in Cynomolgus Monkeys

Dose (mg/kg)	3		10		30	
No. of Animals	**M:4**	**F:4**	**M:4**	**F:4**	**M:6**	**F:6**
DS-8201a						
C0 (µg/mL)						
Day 1	101 ± 9.08	95.3 ± 8.18	295 ± 33.9	339 ± 31.8	877 ± 88.5	899 ± 58.9
Day 64	78.2 ± 15.0	98.4 ± 7.97	320 ± 79.0	352 ± 67.8	898 ± 130	1090 ± 202
AUC21d (µg·d/mL)						

Dose (mg/kg)	3		10		30	
No. of Animals	**M:4**	**F:4**	**M:4**	**F:4**	**M:6**	**F:6**
Day 1	317 ± 26.9	268 ± 31.3	1220 ± 113	1080 ± 125	4090 ± 685	3770 ± 462
Day 64	286 ± 45.3	285 ± 29.1	1390 ± 170	1110 ± 226	5030 ± 771	4910 ± 802
t1/2 (d)						
Day 1	3.95 ± 0.227	3.85 ± 0.183	5.56 ± 0.457	5.13 ± 0.385	7.71 ± 0.666	6.53 ± 0.524
Day 64	4.32 ± 0.579	3.84 ± 0.383	6.08 ± 0.521	5.05 ± 1.07	9.02 ± 1.42	7.40 ± 0.878
Total antibody						
C0 (µg/mL)						
Day 1	113 ± 12.0	96.9 ± 4.83	280 ± 41.3	312 ± 58.2	845 ± 112	886 ± 92.1
Day 64	78.4 ± 12.1	106 ± 11.3	295 ± 59.3	320 ± 60.8	949 ± 122	1090 ± 190
AUC21d (µg·d/mL)						
Day 1	357 ± 31.8	287 ± 36.8	1280 ± 118	1130 ± 141	4300 ± 731	3790 ± 445
Day 64	297 ± 54.8	319 ± 41.0	1450 ± 208	1150 ± 260	5960 ± 1100	5500 ± 1040
t1/2 (d)						
Day 1	4.33 ± 0.340	4.09 ± 0.304	6.25 ± 0.473	5.89 ± 0.587	9.25 ± 1.23	7.95 ± 1.18
Day 64	4.73 ± 0.569	4.18 ± 0.491	7.04 ± 0.649	5.80 ± 1.22	9.56 ± 1.28	8.31 ± 1.25
MAAA-1181a						
Cmax (ng/mL)						
Day 1	0.242 ± 0.0236	0.248 ± 0.106	0.656 ± 0.0912	1.02 ± 0.451	2.71 ± 0.546	3.90 ± 1.11
Day 64	0.223 ± 0.0708	0.186 ± 0.0277	0.842 ± 0.207	1.28 ± 0.659	2.33 ± 0.450	4.86 ± 1.88
AUC21d (ng·d/mL)						
Day 1	0.779 ± 0.122	0.874 ± 0.507	2.52 ± 0.876	2.75 ± 1.40	9.91 ± 2.68	12.0 ± 3.52
Day 64	0.634 ± 0.215	0.294 ± 0.0532	3.06 ± 0.289	2.39 ± 1.05	11.0 ± 2.42	13.5 ± 4.43
t1/2 (d)						
Day 1	NC	NC	3.33 ± 1.11	2.35 ± 0.487	7.15 ± 1.85	4.07 ± 1.42
Day 64	NC	NC	3.61 ± 0.545	2.36 ± 0.963	6.15 ± 1.78	3.72 ± 1.49

Values are expressed as the mean ± standard deviation; d, day; F, female; M, male; NC, not calculated; No., number.

MAAA-1181a Toxicokinetics after Repeated Intravenous Doses

Rats: Four-week Intermittent Dose Toxicity Study of MAAA-1181a (SBL315-026)

The TK of MAAA-1181a were evaluated in a GLP-compliant intermittent dose (once weekly) toxicity study of MAAA-1181a by intravenous bolus injection.

The toxicokinetic parameters of MAAA 1181a are summarized in the table below. The C0 and AUC1d values of MAAA-1181a generally increased along with the dose ranged from 3 mg.kg to 30 mg/kg. No apparent changes after repeated dosing nor any apparent sex differences were noted in the toxicokinetic parameters.

Toxicokinetic Parameters in the 4-week Intermittent Intravenous Dose Toxicity Study of MAAA-1181a in Rats

Dose (mg/kg)	3		10		30	
No. of Animals	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
C0 (ng/mL)						
Day 1	2910 ± 546	1440 ± 363	14,600 ± 3290	7430 ± 3190	65,100 ± 12,700	43,800 ± 8420
Day 29	4420 ± 1340	2610 ± 1140	13,600 ± 2450	12,100 ± 4840	59,600 ± 12,800	70,200 ± 19,000
AUC1d (ng·d/mL)						
Day 1	27.8 ± 3.08	16.6 ± 3.09	122 ± 28.8	66.9 ± 19.6	536 ± 96.5	396 ± 58.0
Day 29	42.2 ± 12.6	28.9 ± 12.0	134 ± 19.6	108 ± 39.1	520 ± 81.1	596 ± 136
t1/2 (d)						
Day 1	0.0373 ± 0.00621	0.0250 ± 0.0155	0.0518 ± 0.0438	0.0440 ± 0.0283	0.112 ± 0.0454	0.0639 ± 0.0458
Day 29	0.0361± 0.00632	0.0350 ± 0.00549	0.0609 ± 0.0567	0.0312 ± 0.00216	0.121 ± 0.0335	0.0907 ± 0.0102

Values are expressed as the mean ± standard deviation; d, day; F, female; M, male; No., number.

Cynomolgus Monkeys: Four-week Intermittent Dose Toxicity Study of MAAA-1181a (SBL315-032)

The TK of MAAA-1181a were evaluated in a GLP-compliant intermittent dose toxicity (once weekly) study of MAAA-1181a by intravenous bolus injection.

The toxicokinetic parameters of MAAA 1181a are summarized in table below. The C0 and AUC1d values of MAAA-1181a generally increased along with the dose ranged from 1 mg.kg to 12 mg/kg.

Toxicokinetic Parameters in the 4-week Intermittent Intravenous Dose Toxicity Study of MAAA-1181a in Cynomolgus Monkeys

Dose (mg/kg)	1		3		12	
No. of Animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:5**	**F:5**
C0 (ng/mL)						
Day 1	1560 ± 464	1310 ± 340	8350 ± 1330	5020 ± 1280	36,600 ± 4050	22,800 ± 5470
Day 22	1860 ± 974	1480 ± 789	6730 ± 1470	10,600 ± 5700	52,100 ± 6220[a]	46,900 ± 20,800
AUC1d (ng·d/mL)						
Day 1	18.0 ± 4.12	13.3 ± 2.48	79.1 ± 13.2	47.7 ± 7.50	349 ± 64.2	212 ± 43.0
Day 22	20.2 ± 7.64	15.7 ± 6.34	68.2 ± 13.6	95.2 ± 55.9	473 ± 20.7[a]	384 ± 170[a]
t1/2 (d)						
Day 1	0.0571 ± 0.0319	0.0384 ± 0.00248	0.161 ± 0.00944	0.165 ± 0.0254	0.174 ± 0.0263	0.167 ± 0.0425
Day 22	0.107 ± 0.0592	0.0390 ± 0.000578	0.176 ± 0.0626	0.152 ± 0.0671	0.180 ± 0.0534[a]	0.123± 0.0279

[a] Calculated from 4 animals; Values are expressed as the mean ± standard deviation; d, day; F, female; M, male; No., number;

MAAL-9001 Toxicokinetics after Repeated Intravenous Doses

Rats and Cynomolgus Monkeys: Six-week Intermittent Dose Toxicity Studies of MAAL-9001 (SBL315-144 and SBL315-143)

The TK of MAAL-9001 were evaluated in GLP-compliant 6-week intermittent dose (q3w) toxicity studies of MAAL-9001 (Process 1) in rats and cynomolgus monkeys by intravenous bolus injection.

The toxicokinetic parameters of MAAL 9001 in rats and cynomolgus monkeys are summarized in table below. No apparent changes after repeated dosing nor any apparent sex differences were noted in the toxicokinetic parameters. Anti-MAAL-9001 antibodies were not detected in any animals in rat study. While anti-MAAL-9001 antibody was detected in 1 female monkey in the 78.8 mg/kg group on Day 43 of dosing, no effects on TK parameters were seen.

Toxicokinetic Parameters in the 6-week Intermittent Intravenous Dose Toxicity Studies of MAAL-9001 in Rats and Monkeys

Animal	**Rat**		**Monkey**	
Dose (mg/kg)	**197**		**78.8**	
No. of Animals	**M:4**	**F:4**	**M:3**	**F:3**
C0 (µg/mL)				
Day 1	5520 ± 378	4510 ± 624	2310 ± 301	2510 ± 187
Day 22	6910 ± 541	5340 ± 486	2720 ± 337	2540 ± 130
AUC21d (µg·d/mL)				
Day 1	22,801 ± 1795	19,412 ± 2311	17,568 ± 2210	15,362 ± 1524
Day 22	28,321 ± 2429	23,573 ± 2190	23,609 ± 3451	19,199 ± 2190
t1/2 (d)				
Day 1	9.28 ± 2.72	10.8 ± 0.985	13.6 ± 3.49	10.1 ± 1.37
Day 22	10.7 ± 0.863	10.2 ± 0.883	15.8 ± 3.28	9.86 ± 2.32

Values are expressed as the mean ± standard deviation; d, day; F, female; M, male; No., number.

Distribution

Tissue distribution was examined in the cynomolgus monkey, using autoradioluminography following single dose of ^{3}H-labelled Trastuzumab deruxtecan or ^{14}C-labelled Trastuzumab deruxtecan, of which the drug component MAAA-1181a was ^{14}C labelled. Tissue distribution was evaluated 1 and 14 days after administration by whole-body autoradioluminography.

The radioactivity was located mainly to the blood, and well perfused organs. The only organ with a higher radioactivity score was the large intestine, after administration of ^{14}C-labelles trastuzumab deruxtecan. No apparent retention in any organs was observed, as the radioactivity had decreased in all tissues from 1 to 14 days post dose. In vitro blood cell distribution of the drug moiety of the ADC (MAAA-1181a) as well as the plasma protein binging were examined. The blood cell distribution ratios of ^{14}C-MAAA-1181a radioactivity ranged from 31.6% to 33.8% in mice, 27.8% to 32.7% in rats, 36.4% to 39.7% in monkeys, and 13.0% to 17.7% in humans. The ratio of the concentration of radioactivity in blood to that in plasma was 0.82 to 0.85 in mice, 0.81 to 0.87 in rats, 0.92 to 0.95 in monkeys, and 0.59 to 0.62 in humans. The mean plasma protein binding ratios ranged from 90.3% to 92.5% in mice, 94.2% to 96.7% in rats, 86.5% to 89.1% in monkeys, and 96.8% to 98.0% in humans.

Metabolism

In vitro metabolite profiling was performed. The theoretical release rate of the drug moiety of the ADC was examined in mouse, rat, monkey and human plasma as well as PBS+1%BSA, and it was shown

that the release rates were comparable between doses at 10 and 100 µg/mL, and similar across the species tested as well. the highest release of the drug moiety was 3.9 %, observed in the monkey at a dose of 10 µg/mL.

In vitro metabolism of trastuzumab deruxtecan was examined in rat, monkey and human hepatocytes. No human specific metabolites were detected. 6 metabolite peaks were identified in all species. The most abundant metabolite was unchanged MAAA-1181a, detected at only 0.1% of the total amount of free and conjugated drug. Hence, the applicant concluded that trastuzumab deruxtecan is metabolic stable in the in vitro cryopreserved hepatocyte incubation system. This is accepted. The rat and monkey are considered appropriate for characterising the toxicity of trastuzumab deruxtecan, and the drug moiety of the ADC.

The in vivo metabolism of DS 8201a was investigated in one male cynomolgus monkey. After a single intravenous administration of 14C DS 8201a (6.4 mg/kg), the majority of label was found to be conjugated to the antibody in plasma. Only 14C-MAAA 1181a radioactivity was found to be present in plasma but as <1%. Also, in urine and faeces only one major labelled peak was found across the time periods up to 144h, which was identified as 14C-MAAA-1181a.

Metabolic profiling of a mass balance study in rats using 14C-labelled MAAA 1181a (1 mg/kg) showed that one main (>1%) labelled peak (86% - 89% of total radioactivity) was detected in urine, faeces, and bile (0 - 48h). Metabolic profiling showed that the radioactive component was MAAA-1181a and it was present in urine, faeces, and bile as 23%, 61% and 63%, respectively, of the dose after a single IV administration. In faeces one other peak >1% (1.1%) was detected but not identified. This indicates that metabolism of MAAA-1181a is low and mainly excreted as unchanged MAAA 1181a in rat.

Excretion

The excretion of trastuzumab deruxtecan and the drug moiety was examined in monkeys following single IV administration of 14C labelled ADC or drug moiety alone. With respect to both the ADC and the drug moiety, the major route of excretion was faeces, with approximately 60 to 70% of the recovered radioactivity detected in the faeces, and only approximately 20 to 30% excreted in urine. Negligible amounts were recovered in the expired air.

A study was also performed in bile cannulated rats, administered 14C-labelled deruxtecan (MAAA-1181a). Here it was shown that the bile was the primary route of excretion (71.6% of the excreted radioactivity recovered in bile), with only 21.9% in urine, and 2.7% in feces. In normal rats 70% was found in faeces and 27% in urine at 168h after dosing. MAAA-1181a was the most abundant component of radioactivity. Elimination of MAAA-1181a was found to be fast as at the 0 - 4h time period bile excretion was almost maximal.

In vitro pharmacokinetic drug interactions have been studied using human biomaterials and are described in the clinical part of this MAA.

Other PK studies

Pharmacokinetics after Single Intravenous Administration of DS-8201a (Process 1) or DS-8201a (Process 2) to Cynomolgus Monkeys (SBL315-376 and SBL315-532):

The PK of DS-8201a, total antibody, and MAAA-1181a were investigated after single intravenous administration of DS-8201a (Process 1 [Lot: HA104-U]) or DS-8201a (Process 2 [Lot: HA202]) at 8.0 mg/kg to male fasted cynomolgus monkeys (n = 12/group). The plasma DS-8201a, total antibody, anti-DS-8201a antibody, and MAAA-1181a concentrations were measured pre-dose and at designated time points (0.083, 1, 7 hours, 1, 3, 7, 14, and 21 days post-dose).

The geometric mean ratios of DS-8201a (Process 2)/DS-8201a (Process 1) for the Cmax, AUCinf, and AUC21d of DS-8201a were 0.865 (90% confidence interval [CI]: 0.809 to 0.925), 0.779 (90% CI: 0.700 to 0.867), and 0.784 (90% CI: 0.709 to 0.867), respectively. Anti-DS-8201a antibodies for both drug substances were not detected through 21 days after administration in any animals.

No significant differences were observed between the kinetic parameters (Cmax, AUC) of the two processes, at dose levels of 8.0 mg/kg.

2.3.4. Toxicology

All toxicology studies were conducted in compliance with GLP regulations and were consistent with the OECD standards in effect at the time. The toxicity of trastuzumab deruxtecan, the drug moiety alone as well as the antibody moiety alone were examined in the nonclinical toxicity program. Rat and cynomolgus monkey were chosen by the Applicant as the nonclinical species.

Single dose toxicity

No single dose toxicity studies of DS-8201a have been conducted in accordance with the ICH M3(R2), since the acute toxicity information is available from the repeated dose toxicity studies. In a 6-week intermittent dose (q3w) toxicity study in rats, skin trauma and/or crust was observed in a female at 20 mg/kg and in both sexes at ≥60 mg/kg, and sparse fur and/or loss of fur in both sexes at 197 mg/kg from Day 8 of dosing. Decreased food consumption was observed in males and females at 197 mg/kg on Day 2 of dosing, and decreased body weight was observed on Day 3 or later. There were no deaths or moribund animals throughout the study, and the approximate lethal dose for a single administration in rats was determined to be >197 mg/kg. In a 6-week intermittent dose (q3w) toxicity study in cynomolgus monkeys, diarrhea was observed from Day 8 of dosing at 78.8 mg/kg. Decreased food consumption was observed in 1 male and 1 female from Day 2, followed by decreased body weight. After two doses of 78.8 mg/kg, 1 female was prematurely euthanized on Day 26 due to the deteriorated condition resulted from decreased body weight and food consumption as well as bone marrow toxicity and intestinal toxicity. However, there were no serious toxic findings leading to death or moribundity after the first dose. Based on the above results, the approximate lethal dose for a single administration in cynomolgus monkeys was determined to be >78.8 mg/kg.

Repeat dose toxicity

Repeat-dose studies were performed in rats and monkeys. Studies with trastuzumab deruxtecan, as well as studies where MAAA-181a was administered alone, and studies with administration of MAAL-9001 alone were also performed. Intermittent dosing regimens were employed. The pivotal studies were performed in accordance to GLP (below table).

Study ID	Species/ Sex/ Number/ Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Rats					
SBL315-030 GLP	SD rat Main study 15 M/F TK 4 M/F	0, 20, 60, 197 mg/kg/day Intermittent iv dosing Q3W	6 weeks (3 dosing administrations Day 1, 22 43) 9 weeks recovery	STD10 > 197 mg/kg	≥20 mg/kg decrease in reticulocyte ratio (M) ≥60 mg/kg decreases in leukocyte, lymphocyte, basophil, and neutrophil counts M: a decrease in eosinophil and an increase in platelet count F: decrease in large unstained cell count Incisor tooth abnormalities 197 mg/kg: decrease in large unstained cell count(M+F) decrease in monocyte count Decreased body weight, food consumption. No spermatids Lower testes and epididymis weight, and thymus weight (F) High level summary: target organs/tissues of DS-8201a were intestines, lymphatic/ hematopoietic organs, kidneys, testes, skin, and teeth. Recovery of histopathological changes observed, except testes and teeth.
Monkey					

					≥10 mg/kg: Increased ALAT, ASAT, single cell necrosis of crypt cells in small and large intestine ≥30 mg/kg: single cell necrosis in the hair follicles in the skin and at the injection sites M: decreased number of round spermatids in Stage V-VI seminiferous tubule in the testes 78.8 mg/kg, moribundity: 1 F Day 26, Clinical condition deteriorated due to decreased body weight, food consumption, bone marrow toxicity, intestinal toxicity and and critical pulmonary toxicity (e.g. interstitial inflammation and/or alveolar edema) diarrhea, abnormal skin color (blackish brown decreased erythrocyte count, hemoglobin concentration, hematocrit, decreased erythroblasts and myelocytes in the bone marrow; single cell necrosis of the crypt epithelial cells in the duodenum; tubular basophilia, proliferation of the tubular epithelium, anisokaryosis in the proximal tubules, hyaline/cellular casts, hyaline material and cellular infiltration in the interstitium in the kidneys; single cell necrosis in the hair follicles, and epidermal thickening and pigmentation in the skin and at the injection sites Surviving animals in high dose group, presented with similar signs to the female described above.
SBL315-031 GLP	Cynomolgus monkey Main study 3 M/F Recovery 2 M/F (only mid and high dose groups)	0, 10, 30, 78.8 mg/kg/day Intermittent iv dosing Q3W	6 weeks (3 dosing administrations Day 1, 22 43) 9 weeks recovery	HNSTD 30 mg/kg	

					≥10 mg/kg blood chemistry, increases in aspartate transaminase, lactate dehydrogenase, and creatine kinase single cell necrosis of the crypt epithelial cells in the small and large intestines
SBL315-553 GLP	Cynomolgus monkey 3 M/F	**Process 2** 0, 10, 30 mg/kg/day Intermittent iv dosing Q3W	6 weeks (3 dosing administrations Day 1, 22 43)	HNSTD 30 mg/kg	30 mg/kg hematology, decreases in erythrocyte count, hematocrit value, and hemoglobin concentration single cell necrosis in the hair follicle in the skin and at the injection sites; decreased erythroblasts in the sternal bone marrow

					≥3 mg/kg single cell necrosis of crypt epithelial cells in the small and large intestines ≥10 mg/kg single cell necrosis in the hair follicles in the skin 30 mg/kg abnormal skin color (blackish brown) decrease in reticulocyte ratio Increased ASAT, Lactate dehydrogenase, creatine kinase black foci in the skin, white foci in the lungs, decreased erythroblasts and brown pigment deposition in the macrophages in the sternal bone marrow, aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation in the lungs, anisokaryosis in the proximal tubules in the kidneys, and epidermal pigmentation in the skin, single cell necrosis in the hair follicles at the injection sites, decreased myelocytes in the sternal bone marrow, brown pigment deposition in the Kupffer cells/hepatocytes/bile canaliculus in the liver (the pigment in the liver was negative with Hall's method), brown pigment deposition in the macrophages in the spleen, and decreased round spermatid in Stage V-VI seminiferous tubules in the testes Recovery observed for most findings, except anisokaryosis in the proximal tubules in the kidneys, and epidermal pigmentation in the skin, very slight changes limited to aggregation of foamy alveolar macrophages in the lungs
SBL315-526 GLP	Cynomolgus monkey Main study 3 M/F Recovery 2 M/F	**Process 2** 0, 3, 10, or 30 mg/kg Intermittent iv dosing Q3W 3 months recovery	Days 1, 22, 43, 64, and 85	HNSTD 30 mg/kg	

In the studies with trastuzumab deruxtecan, the rodent study and one monkey study were performed with process 1 material, whereas the 2 additional cynomolgus monkey studies were performed with process 2 material.

The highest non-severely toxic dose of trastuzumab deruxtecan was established at 197 mg/kg in rats (non-binding species), and 30 mg/kg in cynomolgus monkey (78 mg/kg resulted in moribundity in one

female, and the changes observed for this female resulting in euthanasia on Day 26 of the study, were also seen in the remaining animals in the high dose group). The subsequent studies were performed with 30 mg/kg as the high dose level, and this dose was tolerated. The target organs and tissues were intestines; lymphatic/haematopoietic system, lungs (cynomolgus monkey only), kidneys, skin, testes, incisor teeth (rat only). Two studies were performed with intermittent dosing (q1w, 5 administrations) of the drug moiety alone (MAAA-1181a), in rat and cynomolgus monkey respectively. The toxicities observed were similar compared to the findings in the repeat dose toxicity studies with trastuzumab deruxtecan, except additional ocular toxicity (rat and NHP) as well as heart and liver toxicity (NHP only), but no pulmonary, renal, skin and testicular toxicity were seen with MAAA-1181a alone. The ocular toxicity, cardiotoxicity and livertoxicity were observed at exposure multiples of 14-fold the human AUC (based on cynomolgus monkey exposure following 12 mg/kg dose). Based on Cmax, the safety margins are well in excess of any clinical relevance, 6900-fold human Cmax. The liver toxicity was observed at exposure multiples of 14-fold the human AUC. Based on Cmax, the safety margins are well in excess of any clinical relevance, 6900-fold human Cmax.

Toxicities observed in cynomolgus monkeys after administration of the free drug deruxtecan were associated with much higher deruxtecan plasma exposure levels than when the ADC was administered. The apparent higher sensitivity after ADC administration as well as the occurrence of additional toxicities (lung, kidney, skin and testis) is likely explained by the different plasma/tissue concentration-time profiles for deruxtecan. After administration of the ADC, deruxtecan plasma levels are lower, but present over extended periods of times, whereas after administration of free drug, deruxtecan is cleared from the plasma in a short period of time.

In order to characterise the toxicity of the antibody moiety of trastuzumab deruxtecan (MAAL-9001), two repeat dose studies were performed (one in rats and one in monkeys. In 6-week intermittent dose toxicity studies of MAAL-9001, MAAL-9001 was administered intravenously (q3w) to rats at 0 and 197 mg/kg (SBL315-144) and to cynomolgus monkeys at 0 and 78.8 mg/kg (SBL315-143). In these toxicity studies, no test article-related toxic changes were observed. The no observed adverse effect level (NOAEL) was considered to be the high dose level in both species; 197 mg/kg in rats and 78.8 mg/kg in cynomolgus monkeys, respectively.

Comparative exposure for the toxicities observed in the repeat-dose toxicity studies is presented in the below table.

Margins of Exposure for DS-8201a, Total Antibody, and MAAA-1181a Based on Systemic Exposure (AUC) at DS-8201a Therapeutic Dose in Humans and the NOAEL or Toxic Dose for Target Organ Toxicities in Rats and Monkeys

Type of study/target toxicity	Species	Dose/ NOAEL or Toxic Dose (mg/kg)	Sex	DS-8201a		Total Antibody		MAAA-1181a	
				AUC21d (µg·d/mL)	MOE	AUC21d (µg·d/mL)	MOE	AUC21d (ng·d/mL)	MOE
Clinical trial[a]	Humans	5.4	NA	559	NA	720	NA	30.5	NA
Intestinal toxicity	Rats	20	M	2676	4.8	3035	4.2	4.68	0.15
			F	2339	4.2	2736	3.8	3.02	0.099
	Monkeys	3	M	286	0.51	297	0.41	0.634	0.021
			F	285	0.51	319	0.44	0.294	0.0096
Lymphatic/ hematopoietic organ toxicity	Rats	20	M	2676	4.8	3035	4.2	4.68	0.15
			F	2339	4.2	2736	3.8	3.02	0.099
	Monkeys	10[1]	M	1390	2.5	1450	2.0	3.06	0.10
			F	1110	2.0	1150	1.6	2.39	0.078

		30	M	5030	9.0	5960	8.3	11.0	0.36
			F	4910	8.8	5500	7.6	13.5	0.44
Pulmonary toxicity	Rats	197[1]	M	14264	26	17895	25	40.3	1.3
			F	19818	35	22533	31	32.4	1.1
	Monkeys	10[1]	M	1390	2.5	1450	2.0	3.06	0.10
			F	1110	2.0	1150	1.6	2.39	0.078
		30	M	5030	9.0	5960	8.3	11.0	0.36
			F	4910	8.8	5500	7.6	13.5	0.44
Renal toxicity	Rats	20[1]	M	2676	4.8	3035	4.2	4.68	0.15
			F	2339	4.2	2736	3.8	3.02	0.099
		60	M	6756	12	8069	11	14.4	0.47
			F	7391	13	8448	12	10.0	0.33
	Monkeys	10[1]	M	1390	2.5	1450	2.0	3.06	0.10
			F	1110	2.0	1150	1.6	2.39	0.078
		30	M	5030	9.0	5960	8.3	11.0	0.36
			F	4910	8.8	5500	7.6	13.5	0.44
Skin toxicity	Rats	20	M	2676	4.8	3035	4.2	4.68	0.15
			F	2339	4.2	2736	3.8	3.02	0.099
	Monkeys	3[1]	M	286	0.51	297	0.41	0.634	0.021
			F	285	0.51	319	0.44	0.294	0.0096
		10	M	1390	2.5	1450	2.0	3.06	0.10
			F	1110	2.0	1150	1.6	2.39	0.078
Testicular toxicity	Rats	20	M	2676	4.8	3035	4.2	4.68	0.15
			F	2339	4.2	2736	3.8	3.02	0.099
	Monkeys	10[1]	M	1390	2.5	1450	2.0	3.06	0.10
			F	1110	2.0	1150	1.6	2.39	0.078
		30	M	5030	9.0	5960	8.3	11.0	0.36
			F	4910	8.8	5500	7.6	13.5	0.44

1. NOAEL was underlined. AUC21d, area under the concentration-time curve up to 21 days at Cycle 1 in human and at the steady state in animals; F, female; M, male, MOE, margin of exposure; NA, not applicable; NOAEL, no observed adverse effect level. [a] Study No. DS8201-A-U201

Genotoxicity

Three GLP compliant genotoxicity studies were performed with the drug moiety (MAAA-1181a) of the antibody-drug conjugate. Please see summary table below, presenting the study details and results.

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria SBL315-617 GLP	Salmonella strains TA100, TA1535, TA98, and TA1537) and *Escherichia coli* strain WP2*uvrA*	313 µg to 5000 µg per plate (calculated as MAAA-1181a) +/- S9	Negative
Gene mutations in mammalian cells SBL315-618 GLP	CHO-cells, HGPRT-locus	For 6 hours of treatment with 18 hour recovery: 0.05, 0.1, 0.2, and 0.4 µg/mL - S9 0.05, 0.1, 0.2, 0.4, and 1 µg/mL + S9 For 24 h continous treatment:	MAAA-1181a did not increase the number of cells with numerical chromosome aberrations in any treatment condition. However, MAAA-1181a increased the number of cells with structural chromosome aberrations in a dose-dependent manner in all treatment conditions. In conclusion, MAAA-1181a was considered to have the potential

		0.0125, 0.025, 0.05, 0.1, and 0.2 µg/mL for 24 H +/- S9	to induce structural chromosome aberrations in this test system.
Chromosomal aberrations in vivo SBL-315-756 GLP	Rat, micronuclei in bone marrow M Crl:CD(SD)	Iv administration of 0, 0.025, 0.05, 0.1, and 0.2 mg/kg (calculated as MAAA-1181a)	A statistically significant increase in the number of MNIEs was observed at ≥0.05 mg/kg when compared with the negative control group. No statistically significant increase in the proportion of immature erythrocytes observed.

MNIE: micronucleated immature erythrocytes

MAAA-1181a was negative in the bacterial reverse mutation test (SBL315-617), but was found to be positive in the in vitro mammalian chromosome aberration test (SBL315-618) as well as causing an increased number of micronucleated immature erythrocytes (SBL315-756). No increase in the proportion of immature erythrocytes was observed. The exposure level in male rats was 27.8 ng*d/mL, where the clinical plasma exposure level following the recommended human dose, is 30.5 ng*d/mL.

Carcinogenicity

No carcinogenicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No fertility and early embryonic development to implantation studies, effects on pre and postnatal development, including maternal function studies or embryo-fetal developmental toxicity studies have been submitted (see discussion on non-clinical aspects).

Effects on the reproductive system following the intravenous administration of DS-8201a were evaluated in intermittent dose toxicity studies in rats and cynomolgus monkeys. In the 6-week intermittent dose toxicity study in rats, small-sized testes and epididymides accompanying reduced organ weights were observed at 197 mg/kg. Histopathological findings in rats included spermatid retention at 20 and 60 mg/kg, and tubular degeneration/atrophy in the testes accompanied by secondary changes of luminal cell debris and reduced sperm in the epididymides at 197 mg/kg. In the 6-week and 3-month intermittent dose toxicity study in cynomolgus monkeys, decreased number of round spermatids in the Stage V-VI seminiferous tubule in the testes was observed at ≥30 mg/kg.

Toxicology studies in rats and monkeys with DS-8201a or MAAA-1181a indicated toxic effects to rapidly dividing cells (lymphatic/hematopoietic organ, intestines, or testes) (see above).

Toxicokinetic data

Please see the pharmacokinetic section.

Local Tolerance

No standalone local tolerance studies have been performed. Local tolerance endpoints were included in the repeated dose toxicity studies.

Other toxicity studies

Tissue Cross-reactivity Study of DS-8201a with Human Tissues (20064734, GLP Study)

The potential tissue cross-reactivity of DS-8201a was evaluated using a normal human tissue panel (38 tissues). DS-8201a or a human IgG1κ (isotype control article) was applied to a full panel of normal human tissues from at least 3 separate individuals at 2 concentrations (1 and 10 µg/mL) and immunohistochemically detected using a biotinylated anti-human IgG precomplex method. An NCI-N87 (human gastric cancer) cell xenograft was used as a positive control sample and an MDA-MB-468 (human breast adenocarcinoma) cell xenograft was used as a negative control sample.

Specific DS-8201a staining was observed in the cytoplasm and/or cell membrane of syncytiotrophoblasts and decidual cells in the placenta at 1 µg/mL or more. Specific staining was also observed in the cytoplasm of epithelial cells in multiple human tissues including the breast, cervix, colon, fallopian tube, kidney, ocular lens fibers, pancreas, parathyroid, pituitary, prostate, salivary gland, skin, small intestine, stomach, thymus, thyroid, tonsil, ureter, urinary bladder, and uterus-endometrium. However, the biological relevance of cytoplasmic staining is low because the antibody is not able to access to the cytoplasmic compartment directly in vivo.

Tissue Cross-reactivity Study of DS-8201a with Cynomolgus Monkey Tissues (20069107, GLP Study)

The potential tissue cross-reactivity of DS-8201a was evaluated using selected cynomolgus monkey tissues (bone marrow, brain, heart, intestines, kidney, liver, lung, skin, spleen, and testis). DS-8201a or a human IgG1κ (isotype control article) was applied to the cynomolgus monkey tissues from 3 separate individuals at 2 concentrations (1 and 10 µg/mL) and immunohistochemically detected using a biotinylated anti-human IgG precomplex method. An NCI-N87 cell xenograft was used as a positive control sample and an MDA-MB-468 cell xenograft was used as a negative control sample.

Neither membranous nor cytoplasmic staining was noted in the cynomolgus monkey tissues tested. No staining on the cell membrane in the selected cynomolgus monkey tissues was consistent with the results obtained for the corresponding human tissues.

Intermittent Dose Toxicity Study in Rats Treated Intravenously with MAAA-1181a Monohydrate Once Weekly for 4 Weeks Followed by a 4-week Recovery Period (SBL315-026, GLP Study)

MAAA-1181a monohydrate was intravenously administered intermittently once weekly for 4 weeks (Days 1, 8, 15, 22, and 29 of dosing, 5 times in total) to Crl:CD(SD) rats (10 animals/sex/group) at dose levels of 0 (vehicle: physiological saline), 3, 10, and 30 mg/kg (calculated as MAAA-1181a). Additional animals (5 animals/sex) were treated at dose levels of 0 and 30 mg/kg for 4 weeks and used to assess the reversibility of the toxic changes after a 4-week recovery period. An additional satellite group of 4 animals of each sex was established for TK assessment of MAAA-1181a

There was no test article-related death or moribundity, and no test article-related toxic changes were noted in clinical signs, ophthalmology, urinalysis, or necropsy at any dose level during the dosing or recovery period.

In both sexes, the following changes were noted at ≥3 mg/kg: transient suppression of body weight gain and low food consumption; decreased erythroid parameters (erythrocyte count, hemoglobin concentration, hematocrit value, and reticulocyte ratio); decreased white blood cell parameters (leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts); and high levels in serum glucose. Histopathological findings included decreased erythroblasts and myelocytes in the bone marrow; single cell necrosis in the lymphocytes in the thymus with decreased organ weight;

atrophy of the follicles in the submandibular lymph nodes and/or ileac Peyer's patches; single cell necrosis of the crypt epithelial cells in the small and large intestines, and in the corneal epithelium; and atrophy of the villi in the duodenum.

Additional changes at 30 mg/kg included: atrophy of the thymus in both sexes; and regeneration of the crypt epithelial cells with luminal dilatation in the cecum in a male.

By the end of the 4-week recovery period, the changes observed during the dosing period showed reversibility.

Under the conditions of this study, the target organs/tissues of MAAA-1181a included intestines, lymphatic/hematopoietic system and cornea. The STD_{10} was determined to be greater than 30 mg/kg because the changes were not severe to induce a deteriorated condition, moribundity, or death.

Intermittent Dose Toxicity Study in Monkeys Treated Intravenously with MAAA-1181a Monohydrate Once Weekly for 4 Weeks Followed by a 4-week Recovery Period (SBL315-032, GLP Study)

MAAA-1181a monohydrate was intravenously administered once weekly (Days 1, 8, 15, 22, and 29 of dosing, 5 times in total) to cynomolgus monkeys (3 animals/sex/group) at a dose level of 0 (vehicle: physiological saline), 1, 3, or 12 mg/kg. Additional animals (2 animals/sex) were treated with MAAA-1181a at a dose level of 12 mg/kg for 4 weeks and used to assess the reversibility of the toxic changes after a 4-week recovery period. TK assessments were conducted for MAAA-1181a.

In the 12 mg/kg group, 1 male was euthanized due to moribundity on Day 12 of dosing and 1 female died on Day 23 of dosing. Clinical observations in these animals included vomiting, diarrhea, lateral position, hypothermia, pale oral mucosa, and/or suppression of touch response. Additionally, decreased body weight and food consumption and/or no consumption of food were noted. The abnormal findings were observed in hematology (decreased in hematocrit value and lymphocyte count), and blood chemistry (increases in aspartate transaminase and alanine transaminase; decreases in sodium and chloride).

The following histopathological changes were observed in these animals: degeneration/necrosis of cardiac myocytes in the heart (only in the male), decreased erythroblasts and myelocytes in the bone marrow, atrophy of the follicles and the periarterial lymphatic sheath in the spleen, atrophy of the follicles in the mesenteric lymph nodes and ileac Peyer's patches, single cell necrosis, focal necrosis, and increased mitosis of hepatocytes, bile thrombus and dilatation of the bile canaliculus, brown pigment deposition in Kupffer cells in the liver**,** and regeneration of the crypt epithelial cells, single cell necrosis of the crypt epithelial cells and/or dilatation of crypt in the small and large intestines. The cause of moribundity was considered related to the animal's deteriorated clinical condition resulted from decreased body weight and/or food consumption as well as lesions of the intestine and bone marrow.

In the surviving animals, the following changes that were similar to those noted in the animals that died prematurely were noted: decreases in reticulocyte ratio, atrophy of the follicles in the spleen, mesenteric lymph nodes, and ileac Peyer's patches, and single cell necrosis of lymphocytes in the thymus at ≥1 mg/kg; vomiting, decreases in body weight, and increases in aspartate transaminase at ≥3 mg/kg. At 12 mg/kg, abnormal stool, increases in alanine transaminase, single cell necrosis in the hepatocytes, and single cell necrosis of the crypt epithelial cells in the small intestine were observed. Additional changes in the animals in the 12 mg/kg group included decreases in erythrocyte parameters (erythrocyte count, hemoglobin concentration, and hematocrit value) and lymphocyte count, an increase in platelet count, prolongation and shortening of activated partial thromboplastin time, increases in inorganic phosphorus and potassium, and single cell necrosis in the corneal epithelium.

No test article-related abnormalities were noted in urinalysis in any group.

The test article-related changes noted during the dosing period showed recovery by the end of the recovery period.

Under the conditions of this study, the target organs/tissues of MAAA-1181a included the heart, bone marrow, lymphatic organs, liver, intestines, and cornea. The HNSTD was determined to be 3 mg/kg in both sexes based on the moribundity or death observed at 12 mg/kg.

Antigenicity

No standalone studies were performed. Antidrug-antibody (ADA) analysis was included in the pivotal toxicity studies. No ADA were detected in the rat study (SBL315-030). In the monkey studies, only pre-dose samples in a few animals in two of the four studies showed detectable ADA (one male in study SBL315-031, 3 animals in Study SBL315-526). No other animals were positive for ADA during the studies.

Phototoxicity

MAAA-1181a was found to be phototoxic under the conditions of the in vitro 3T3 NRU assay, with a mean photo effect value of 0.432. However, in the subsequent in vivo study, in pigmented rats, administered doses of 0, 1 or 3 mg/kg MAAA-1181a intravenously, the drug did not show any phototoxic potential. The high dose group, provided a safety margin to the clinical Cmax, of 13-fold (90.5 ng/mL in rats, compared to 7.2 ng/mL In clinical study DS8201-A-U201). Therefore, the negative in vivo study result is considered to be sufficient to overrule the in vitro positive result.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is an antibody-drug conjugate (ADC) composed of an anti-HER2 antibody, MAAL-9001, and a topoisomerase I inhibitor, MAAA-1181a, bound together by a peptide-based cleavable linker with a drug-to-antibody ratio (DAR) of approximately 8. The antibody- and linker are of biological origin, and is expected to be metabolised in the body, and the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, these two moieties are not expected to pose a risk to the environment.

With regards to the drug-part of the ADC, MAAA-1181a is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of Enhertu.

Calculation of $PEC_{surface\ water}$

Enhertu is dosed at 5.4 mg/kg body weight once every three weeks. MAAA-1181a released after application is 2.5% of the dose and calculated as:

On average, the target number of drug-linker (MAAA-1162a [drug + linker molecule]) to 1 antibody molecule is 8. The molecular weight of MAAA-1162a is 1034.05 and the molecular weight of the MAAL-9001 is approximately 150,000 Da. Therefore, the total molecular weight of trastuzumab deruxtecan is approximately 158,000 Da. On average 8 molecules of the active drug (MAAA-1181a at 493.484 Da) are present on each molecule (8 × 493.484 = 3947.872 Da), thus MAAA-1181a represents approximately 2.5% of the total dose of trastuzumab deruxtecan (3947.872 ÷ 158 000 = 2.5%). On the basis of the average body weight of a European adult of 70.8 kg (Walpole et al., 2012) a dose of 9.56 mg/patient/day (5.4 x 70.8 x 0.025) is calculated for the default phase I PEC calculation.

$$PEC_{SW} = \frac{DOSEai \cdot F_{pen}}{WASTEWinhab \cdot DILUTION}$$

*DOSE*ai = 9.56 (mg patient^{-1} d^{-1})
F_{pen} = 0.01 (patient inh^{-1})
*WASTEW*inhab = 200 (L inh^{-1} d^{-1})
DILUTION = 10 (–)

The unrefined phase I PEC is 0.0478 µg/L.

Refinement of F_{pen}

The applicant has indicated that based on posology, the drug is dosed once every three weeks, the PECsw would be below the action limit 0.01 µg/L but has performed an F_{pen} refinement based on prevalence.

The highest breast cancer rate is reported for Belgium with a 191.8 per 100 000 females (Ferlay et al., 2018). Assuming a 1:1 male: female ratio, the prevalence for the total population is 95.9 per 100 000. In addition, HER2-positive breast cancers have been demonstrated to account for 15-20% of all breast cancer sub-types (Wolff et al., 2013). On the basis of this the F_{pen} is calculated as 95.9/100 000 x 0.2 = 0.000192. With this refined F_{pen} the PEC_{sw} is calculated as 0.00092 µg/L.

Summary of main study results

Substance (INN/Invented Name): MAAA-1181a (drug part of trastuzumab deruxtecan)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log DOW = 1.924 @ pH 5 Log DOW = 1.799 @ pH 7 Log DOW = 1.280 @ pH 9	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Result	not B
	BCF	Log DOW = 1.924 @ pH 5 Log DOW = 1.799 @ pH 7 Log DOW = 1.280 @ pH 9	not B
Persistence	DT50 or ready biodegradability	-	P/not P
Toxicity	NOEC or CMR	-	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	If Fpen=0.01 0.048 (default) If Fpen=0.000288 (refined)	0.0014µg/L	< 0.01 threshold (when the refined Fpen is used) Phase II assessment is not required
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	*S* = 7.52 mg/L	

2.3.6. Discussion on non-clinical aspects

The mechanism of action of Enhertu, as a HER2-targeted antibody-drug conjugate, which after binding to HER2 undergoes internalization and intracellular linker cleavage of the deruxtecan part by lysosomal enzymes, that are upregulated in cancer cells, causing DNA damage and apoptotic cell death, has been demonstrated to a high extent in vitro. However, the process of linker cleavage is written in less detail. Okamoto et al (2020) showed the results of the exposure of the tissues of KPL-4 tumour-bearing mice to released DXd (deruxtecan, MAAA-1181a) after a single iv administration of T-DXd (Enhertu) or non-targeted control ADC. This indicates the proof of principal; the majority of MAAA-1181a (ca. 80%) is delivered in the tumor. This means that ca. 20% of MAAA-1181a is exposed to other tissues in this model, but is relatively quickly removed from the body (t1/2 was fond 1.35 h). However, a detailed process of cleavage and the observed discrepancies in some animal studies related to the DAR and HER2 occupation could not be explained. Altogether, it is clear that there is very likely some exposure to free MAAA-1181a in the human system, which should be taken into account in the toxicological characterization of the product.

Results in patient-derived xenograft (PDX) models of breast cancer suggest that DS-8201a is effective even in T-DM1 refractory HER2-expressing breast cancer tumours due to the drug-linker system with a different mechanism of action. However, it is unexpected that DS-8201a has a clear, although not significant, lesser effect than MAAL-9002b which has a two times lower drug-to-antibody ratio (DAR) in the HER2-positive CTG-0708 model. This is not seen in the HER2-low model. Furthermore, when the HER2-positive and HER2-low xenografts are compared, it is noted that DS-8201a has a more robust antitumor activity in the HER2-low model. This is also unexpected, since the antibody part of DS-8201a binds specifically to HER2.

In the HER2-positive breast cancer cell line JIMT-1, derived from a trastuzumab-resistant patient and known to be refractory to T-DM1, DS-8201a at 3 and 10 mg/kg, T-DM1 at 10 mg/kg, and MAAL-9002b at 10 mg/kg significantly inhibited tumour growth by 64%, 85%, 35%, and 66%, respectively. So, in this model the high DAR of DS-8201a results in higher efficacy, because MAAL-9002b showed a lower effect than DS-8201a.

No secondary pharmacodynamic studies have been conducted. However, according to ICH S9, understanding the secondary pharmacodynamic properties of a pharmaceutical could contribute to the assessment of safety for humans, and those properties might be investigated as appropriate. The Applicant considers secondary pharmacodynamic studies not necessary, because sufficient information is known from the other studies and of other topoisomerase inhibitors as well. However, MAAA-1181a is a new active substance, and probably, there is some exposure to the human system. It would be informative to know whether MAAA-1181a can bind to other targets, which could explain secondary or toxic effects observed, or predict other secondary or toxic effects not seen thus far in animal studies or clinical trials. Therefore, the Applicant is recommended to perform a secondary pharmacodynamic study post-marketing.

No pharmacodynamic drug interactions studies have been conducted since this application is for use of trastuzumab deruxtecan as monotherapy.

Pharmacokinetics

The in vivo pharmacokinetic studies with DS-8201a (trastuzumab deruxtecan) were conducted via intravenous (IV) injection, as this is the intended route of administration in humans, in rats and cynomolgus monkeys, which were used for toxicology studies. From the pharmacokinetic point of view, the cynomolgus monkey was the most relevant species for non-clinical efficacy and safety studies.

Absorption, tissue distribution and excretion were consistent with what is known for monoclonal antibodies. The drug part of DS-8201a, the topoisomerase I inhibitor MAAA-1181a, was found in plasma of rats or monkeys but as <1% and, given its pharmacokinetic behaviour, its clearance is suggested to be dependent on release from the conjugate. The excretion of MAAA-1181a was found to be mainly via the biliary/faecal route as unchanged MAAA-1181a.

Toxicology

In animals, toxicities were observed in lymphatic and haematopoietic organs, intestines, kidneys, lungs, testes and skin following the administration of trastuzumab deruxtecan at exposure levels of the topoisomerase I inhibitor (DXd) below clinical plasma exposure. In these animals, antibody-drug conjugate (ADC) exposure levels were similar or above clinical plasma exposure.

Overall, the toxicology programme revealed that trastuzumab deruxtecan was tolerated in both rats and cynomolgus monkey at clinically relevant exposures as well as at higher exposures. Most of the toxicities observed, could be attributed to the drug moiety (deruxtecan, MAAA-1181a). Target organs and tissues of toxicity were identified to be intestines, lymphatic/haematopoietic system, lungs (cynomolgus monkey only), kidneys, skin, testes, incisor teeth (rat only). When the drug moiety MAAA-1181a was administered alone; ocular toxicity, liver toxicity and cardiotoxicity were observed, at exposure multiples of 14-fold the human AUC (based on cynomolgus monkey) (see SmPC section 5.3).

The observed toxicities in non-clinical studies after administration of DS-8201a are explained as the consequence of the presence of free deruxtecan. Nevertheless, the presence of HER2 in parenchymal cells of the lung may have an important role in the processes leading to inflammatory changes and interstitial lung toxicity, however, the precise mechanisms are unclear.

Considering that toxicity is likely related to continuous exposure to deruxtecan after treatment with trastuzumab deruxtecan, and clinical deruxtecan plasma exposures exceed plasma exposures in animals at the NOAEL, the observed toxicities in cynomolgus monkeys are potential safety concerns (see also Clinical Safety section). Intestinal, lymphatic/haematopoietic, pulmonary, skin, renal and testicular toxicity have been addressed in the RMP.

During development, the production of the antibody moiety was changed, and a Process 1 and Process 2 antibody and subsequent ADC was examined. Both comparative PK studies were performed, some of the in vivo studies were performed with process 2 ADC, as well as two of the pivotal toxicity studies in cynomolgus monkey. Hence, the change in production of the antibody moiety is considered to be sufficiently characterised and Process 2 is sufficiently well described and tested from a nonclinical point of view.

DXd was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an *in vitro* Chinese hamster lung chromosome aberration assay and was not mutagenic in an *in vitro* bacterial reverse mutation assay. The positive signal in the in vivo and in vitro mammalian cell assays, is considered to be clinically relevant. Genotoxicity to mammalian cells is a known characteristic of topoisomerase I inhibitors.

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan. This is, according to the ICH S9 guideline, not needed for advanced cancer indications, which the current MAA proposed indication indeed is considered to be.

Dedicated fertility studies have not been conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan may impair male reproductive function and fertility.

There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and DXd were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity. The absence of reproductive and developmental toxicity studies is in line with ICH S9, because MAAA-1181a is genotoxic and targets rapidly dividing cells. Moreover, trastuzumab was shown to cause developmental toxicity. It is therefore very likely that DS-8201a will also cause embryo-foetal damage in the clinic. This is further mentioned in the RMP (as important identified risk) and SmPC. Specifically, in SmPC section 4.6, the effective contraception is recommended for at least 7 months in treated females and at least 4 months in treated males. The times specified are based on the half-life of trastuzumab of 5.7 days, and consequently the washout period for males and females after cessation of therapy with trastuzumab deruxtecan were specified to a period of 4 months (5 half-lives plus 3 months) and a period of 7 months (5 half-lives plus 6 months), respectively.

For breastfeeding, the washout of 7 months was suggested, however, a shorter period of only 5 half-lives should actually be sufficient. However, as the product information of previously approved products (trastuzumab (t½ 13-27 days) or trastuzumab emtansine (t½ 4 days)), suggest 7 months waiting period, the same wording is used in the present product. Furthermore, an additional precautionary wording and recommendation on counselling on sperm storage prior to initiating treatment has been included in section 4.6 of the SmPC. This is based on a further discussion on the findings on sperm in rat and cynomolgus monkey was presented. When comparing DS-8201a plasma levels, the non-recovering findings in rats were observed at approximately 26-fold the MHRD, whereas at lower doses (9-fold MHRD), the findings were less severe and mostly appeared reversible. However, when deruxtecan plasma levels are compared testicular toxicity was observed in animals at plasma levels below human therapeutic plasma levels.

Environmental risk assessment

The Environmental assessment report provided by the applicant consisted of a justification for performing ERA assessment for the drug moiety of the ADC, as the antibody and linker are of biological origin, and expected to be metabolised to peptides and amino acids in the body. This is supported. With regards to the drug-part of the ADC, MAAA-1181a is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of Enhertu. Furthermore, the refining the Fpen resulted in a PECsurfacewater below the trigger value, and the LogKow was also below the limit of 4.5. Due to this, no further environmental studies were performed. This is supported.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that trastuzumab deruxtecan show anti-tumour activity against both HER2 positive and HER2 low cancer models. The pharmacokinetic programme was considered sufficient. Toxicology studies showed that trastuzumab deruxtecan was tolerated in both rats and cynomolgus at clinically relevant as well as higher exposures.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Included in the Application

Study Number, Phase, Status	**DCO**	**Study Title Total Number of Subjects (Location in Module 5)**	**Test Products, Dosage Regimen**
DS8201-A-J101 (Study J101) Phase 1, Completed[a]	*Primary efficacy analysis (CSR DCO):* 01 Feb 2019 *Update DCO*: 01 Aug 2019	Phase 1, two-part, multicenter, nonrandomized, open-label, multiple dose FIH study of DS-8201a, in subjects with advanced solid malignant tumors N = 292 subjects (including 118 subjects with metastatic HER2-positive breast cancer in Part 1 and Part 2a of the study: 51 assigned to 5.4 mg/kg [ie, the target dose] and 67 assigned to 6.4 mg/kg)	*Trastuzumab deruxtecan* IV infusion Q3W *Part 1, Dose Escalation* (27 subjects) 0.8 mg/kg, 1.6 mg/kg, 3.2 mg/kg, 5.4 mg/kg, 6.4 mg/kg, 8.0 mg/kg *Part 2, Dose Expansion* (262 subjects) 5.4 mg/kg, 6.4 mg/kg
DS8201-A-J102 (Study J102), Phase 1, Completed[a]	05 Dec 2018	Phase 1, multicenter, open-label, multiple-dose study of DS-8201a to assess the effect on the QT interval and PK in subjects with HER2-expressing metastatic and/or unresectable breast cancer N = 51 subjects	*Trastuzumab deruxtecan* 6.4 mg/kg IV infusion Q3W
DS8201-A-A103 (Study A103), Phase 1, Completed[a]	14 Sep 2018	Phase 1, multicenter, open-label study of DS-8201a to assess safety and PK in subjects with HER2-positive advanced and/or refractory gastric, GEJ adenocarcinoma, or breast cancer N = 12 subjects	*Trastuzumab deruxtecan* 6.4 mg/kg IV infusion Q3W

Study Number, Phase, Status	DCO	Study Title Total Number of Subjects (Location in Module 5)	Test Products, Dosage Regimen
DS8201-A-A104 (Study A104), Phase 1, Completed[a]	26 Sep 2018	A Phase 1, multicenter, open-label, single-sequence crossover study to evaluate DDI potential of OATP1B/CYP3A inhibitor on the PK of DS-8201a in subjects with HER2-expressing advanced solid malignant tumors N = 40 subjects	*Cohort 1:* Trastuzumab deruxtecan, 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:* Trastuzumab deruxtecan, 5.4 mg/kg IV infusion 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
DS8201-A-U201 (Study U201) Phase 2, Completed[a]	*Primary efficacy analysis (CSR DCO):* 21 Mar 2019 *Update DCO*: 01 Aug 2019	A Phase 2, multicenter, open-label study of DS-8201a, an anti-HER2-ADC for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1 N = 253 subjects with metastatic HER2-positive breast cancer (including 184 subjects assigned to 5.4 mg/kg in Part 1 [50 subjects], Part 2a [130 subjects], and Part 2b [4 subjects])	*Trastuzumab deruxtecan* IV infusion Q3W *Part 1 PK Stage* (65 subjects): 5.4 mg/kg, 6.4 mg/kg, 7.4 mg/kg *Part 1 Dose Finding Stage* (54 subjects): 5.4 mg/kg, 6.4 mg/kg *Parts 2a and 2b* (134 subjects): 5.4 mg/kg
DS8201-A-U301 (Study U301) Phase 3 Ongoing	Projected: first quarter 2022 for PFS*	A Phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody-drug conjugate, vs. treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1 (DESTINY-Breast02) N = ~600 subjects planned/ 329 randomized as of 13 Mar 2020; last subject enrolled expected in Feb 2021	*Trastuzumab deruxtecan* 5.4 mg/kg IV infusion Q3W or *Investigator's choice comparator:* Trastuzumab 8 mg/kg IV loading dose on the first day of treatment followed by 6 mg/kg every 21 days and capecitabine 1250 mg/m^2 administered orally BID approximately 12 hours apart on Days 1 to 14 of a 21-day schedule or Lapatinib 1250 mg administered orally daily and capecitabine 1000 mg/m^2 administered orally BID approximately 12 hours

Study Number, Phase, Status	DCO	Study Title Total Number of Subjects (Location in Module 5)	Test Products, Dosage Regimen
			apart on Days 1 to 14 of a 21-day schedule
DS8201-A-U302 (Study U302) Phase 3 Ongoing		A Phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody-drug conjugate, vs. trastuzumab emtansine (T-DM1) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane (DESTINY-Breast03) N = ~500 subjects planned/ 410 randomized as of 13 Mar 2020; last subject enrolled expected in May 2020	*Trastuzumab deruxtecan* 5.4 mg/kg IV infusion Q3W or *T-DM1* IV infusion Q3W administered according to the approved local label
DS8201-A-U303 (Study U303) Phase 3 Ongoing	*	A Phase 3, multicenter, randomized, open-label, active-controlled trial of DS-8201a, an anti-HER2-antibody drug conjugate (ADC), vs. treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects (DESTINY-Breast04) N = ~540 subjects planned/ 214 randomized as of 13 Mar 2020; last subject enrolled expected in Apr 2021	*Trastuzumab deruxtecan* 5.4 mg/kg IV infusion Q3W or (2:1 ratio [trastuzumab deruxtecan: physician's choice]) *Physician's choice comparator:* 1 of the following drugs administered according to the approved local label: capecitabine; eribulin; gemcitabine; paclitaxel; or nab-paclitaxel

ADC = antibody-drug conjugate; BID = twice daily; CSR = clinical study report; CYP = cytochrome P450; DCO = data cutoff; DDI = drug-drug interaction; DS-8201a = product code for trastuzumab deruxtecan; FIH = first in human; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IV = intravenous; OATP = organic anion transporting peptide; PK = pharmacokinetic; Q3W = every 3 weeks; QD = once daily; T-DM1 = trastuzumab emtansine; vs. = versus
*Event-driven study; the projected date may change
[a]A study was defined as completed if the analyses for the primary objective had been performed.

2.4.2. Pharmacokinetics

Overall, results from 5 studies are presented in the Clinical pharmacology section: four Phase 1 clinical studies in subjects with breast cancer and other solid malignant tumors and one Phase 2 clinical study in breast cancer subjects as well as a popPK analysis and exposure-response analysis.

The intended commercial drug product (Lyo-DP) was used in the Phase 2 study (Study DS8201-A-U201) and in Studies DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104. Two other drug products were used in development: frozen liquid drug product (FL-DP) 1 and FL-DP2. FL-DP1 was used in Study DS8201-A-J101 and FL-DP2 was used in Studies DS8201-A-J101 and DS8201-A-U201. The transition from FL-DP1 to FL-DP2 included changes to the manufacturing process for drug substance

and drug-linker, and cell line and process change for mAb; the only difference between the formulations of FL-DP2 and Lyo-DP is that FL-DP2 was supplied frozen and Lyo-DP is lyophilized.

Analytical methods

Three drug product (DP) dosage forms of trastuzumab deruxtecan have been used across the clinical development program: the first two DPs were frozen-liquid DPs (FL-DP) and the last one is lyophilized powder drug product (Lyo-DP) which is the to-be-marketed formulation of trastuzumab deruxtecan. Three analytes were measured in the development program: trastuzumab deruxtecan (the intact ADC), total anti-HER2 antibody, and MAAA-1181a (the topoisomerase I inhibitor).

PK properties of FL-DP1, FL-DP2, and Lyo-DP formulations of trastuzumab deruxtecan were compared using data from two clinical studies.

The analytical comparability program to establish the comparability of trastuzumab deruxtecan DS manufactured by DS Process-1 and DS Process-2a included an evaluation of both MAAL-9001, which involved a cell line change, and of the changes in D-L manufacturing process.

The impact of the dosage form change from FL-DP2 to Lyo-DP on the quality of trastuzumab deruxtecan DP was evaluated by an analytical comparability exercise, and no differences that may potentially impact on the efficacy and/or safety were observed.

Bioanalysis was conducted to determine the serum concentrations of three moieties associated with trastuzumab deruxtecan: concentrations of the intact drug, trastuzumab deruxtecan; concentrations of total anti-HER2 antibody were determined in an assay that detected the sum of MAAL-9001 and trastuzumab deruxtecan; and concentrations of the released payload, MAAA-1181a. Antidrug antibodies (ADAs) against trastuzumab deruxtecan were also determined.

The bioanalytical methods utilized electrochemiluminescence (ECL) assays for trastuzumab deruxtecan, total anti-HER2 antibody, and anti-trastuzumab deruxtecan antibodies, and liquid chromatography coupled with tandem mass spectrometry detection (LC-MS/MS) for MAAA-1181a.

An assay measuring concentrations of intact trastuzumab deruxtecan in human serum, using an ECL method, was developed and validated at CRO PPD. Trastuzumab deruxtecan was analyzed over the nominal concentration range of 0.400 to 25.6 µg/mL.

An assay measuring concentrations of total anti-HER2 antibody in human serum using an ECL method was developed and validated at CRO PPD. Total anti-HER2 antibody was analyzed over the nominal concentration range of 0.400 to 25.6 µg/mL.

An assay measuring MAAA-1181a (topoisomerase inhibitor component of DS-8201a) concentrations in human serum using a stable-labelled internal standard was developed utilizing protein precipitation and quantification using LC-MS/MS. MAAA-1181a was analyzed over the nominal concentration range of 10.0 to 2000 pg/mL.

An assay to detect and confirm anti-trastuzumab deruxtecan antibodies (anti-DS-8201a antibodies) in human serum using an ECL method in a multi-tiered approach was developed and validated.

Biomarker analysis was performed by measurement of HER-2/neu in serum. The ADVIA Centaur® HER-2/neu assay (Siemens ADVIA Centaur HER-2/neu [H2n]) was a fully automated Food and Drug Administration-approved, 2-site sandwich immunoassay that used direct, chemiluminescent technology.

PopPK analysis

The popPK analysis was composed of two models: intact DS-8201a model and released drug (MAAA-1181a) model. Data from 5 studies were included in the model development.

The PK of intact DS-8201a was described by a two-compartment model with linear elimination. Clearance was estimated to be 0.421 L/day; central and peripheral volumes of distribution were estimated to be 2.77 and 5.16 L respectively. However, non-compartmental analyses comparing cycle 3 with cycle 1 suggested time-varying pharmacokinetics of intact DS-8201a the elimination half-life was longer in cycle 3 compared to cycle 1. A time varying clearance has been described regularly for antibodies in oncology setting (Wilkins et al. 2019, Liu et al. 2017, Li et al. 2017). The popPK model of trastuzumab deruxtecan did not include time-varying clearance**.** The Applicant provided new information about the incorporation of time independent CL in the PopPK. In this analysis, Applicant detailed the time-varying clearance of MAAA-1181a and time-independent clearance of trastuzumab deruxtecan by VPC plots and residual plots stratified by cycle. The conclusion of the applicant are not fully supported; the VPC plots and the residual plots stratified by cycle indicated that the clearance of MAAA-1181a is underestimated in the first cycle and that the model predicted the pharmacokinetics of MAAA-1181a better at the third cycle although the variability is overestimated. For both trastuzumab deruxtecan as well as MAAA-1181a, in the first cycle the initial clearance during the first 4 days is underestimated which is not apparent at the third cycle. It may be hypothesized that effect of baseline tumour size has more impact on the clearance of trastuzumab deruxtecan the first few days after the first administration compared to repeated administration of trastuzumab deruxtecan. The PK of the released drug is described by a time-varying one-compartment model, with intact DS-8201a as an input. Clearance was estimated to be 19.9 L/h, a volume of distribution 17 L/m2, and a release rate of 0.0167 h. The variability was overestimated, and shrinkage of clearance was rather high, i.e. 37.8% in the final model of MAAA-1181a compared to 25.4% in the base model**.**

Table 1 Parameters of the final released drug model

Parameter	**Final Released Drug Model (run416)**					**Bootstrap Analysis[3]**	
	Estimate		**Between-subject Variability**			**Estimate**	
	Typical Value	**RSE[1] (%)**	**Magnitude (%CV)**	**RSE[1] (%)**	**Shrinkage[2,3] (%)**	**Typical Value**	**95% CI**
Released drug clearance (CL_{drug}, L/h)	19.2	4.41	25.4	6.31	37.8	19.1	17.8, 20.4
Released drug volume of distribution (Vdrug, L)	Fixed 17*BSA	-	42.0	4.64	19.9	Fixed 17*BSA	-
Release rate (Krel, 1/h)	0.0159	4.42	37.6	4.56	16.0	0.0159	0.0146, 0.0172
Fraction of Krel when Cycle>1	0.830	1.62	22.9	4.01	17.5	0.829	0.803, 0.859
Cycle effect on Krel	-0.137	5.23	-	-	-	-0.137	-0.160, -0.114
Ritonavir on CL_{drug}	-0.113	13.9	-	-	-	-0.112	-0.236, -0.0177

Itraconazole on CL_{drug}	-0.103	19.0	-	-	-	-0.104	-0.159, -0.0535
AST on CL_{drug}	-0.219	14.5	-	-	-	-0.221	-0.290, -0.150
Total bilirubin on CL_{drug}	-0.207	18.4	-	-	-	-0.209	-0.294, -0.128
Body weight on CL_{drug}	0.440	18.9	-	-	-	0.448	0.299, 0.576
Age on V_{drug}	0.562	16.8	-	-	-	0.558	0.377, 0.750
FL-DP2 formulation on Vdrug	0.255	28.0	-	-	-	0.258	0.115, 0.392
FL-DP1 formulation on Vdrug	-0.212	20.4	-	-	-	-0.215	-0.289, -0.124
Residual variability[4]							
Proportional residual error SD	0.279	0.483	-	-	-	0.279	0.272, 0.288
Between-subject variability							
Variance of CL_{drug}	0.0647	12.6	-	-	-	0.0623	0.0340, 0.102
Variance of V_{drug}	0.176	9.28	-	-	-	0.175	0.141, 0.211
Variance of K_{rel}	0.142	9.13	-	-	-	0.142	0.116, 0.175
Variance of fraction of K_{rel} when Cycle>1	0.0524	8.01	-	-	-	0.0525	0.0438, 0.0635

AST = aspartate aminotransferase; BSA = body surface area; CI = confidence interval; CV = coefficient of variation; FL-DP1 = frozen liquid drug product 1; FL-DP2 = frozen liquid drug product 2; SD = standard deviation; SE=standard error; RSE = relative standard error. 1. RSE of parameter estimate are calculated as 100×(SE/typical value); RSE of between-subject variability magnitude are presented on %CV scale and approximated as 100×(SE/variance estimate)/2. 2. Shrinkage (%) is calculated as 100×(1 - variance of posthoc/estimated variance). 3. 200 bootstrapped datasets were used. 4. Overall residual variability shrinkage was estimated to be 8.74%.

Figure 2 : Structural model

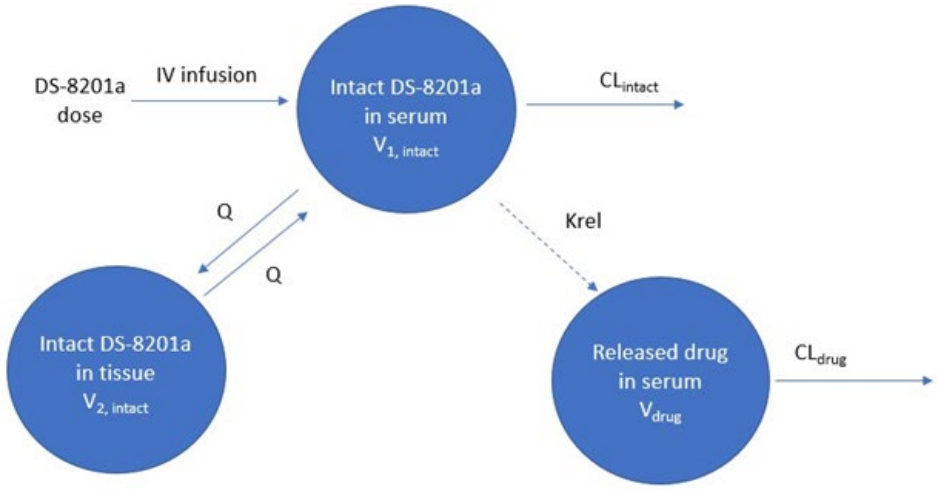


Figure 3: Goodness-of-fit diagnostics of the final intact DS-8201a model

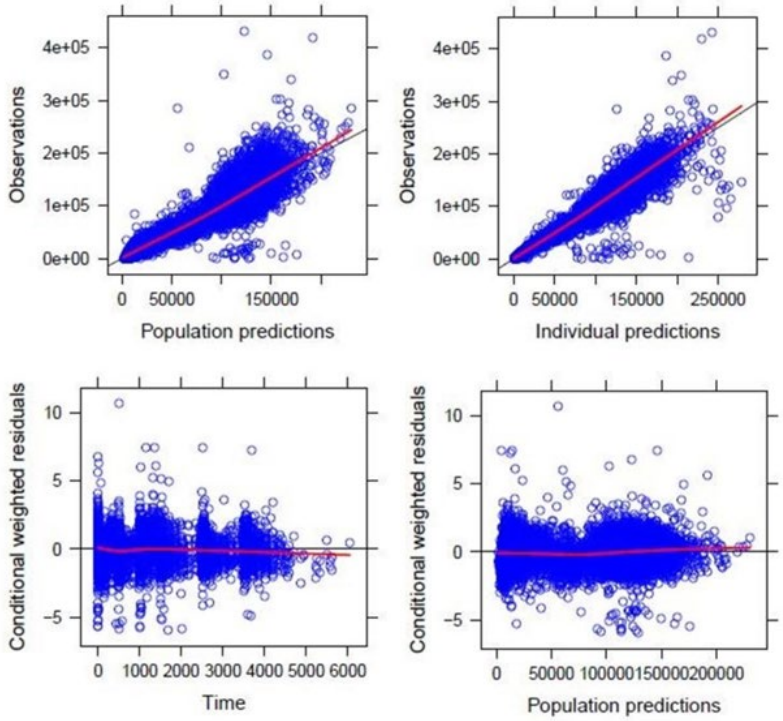
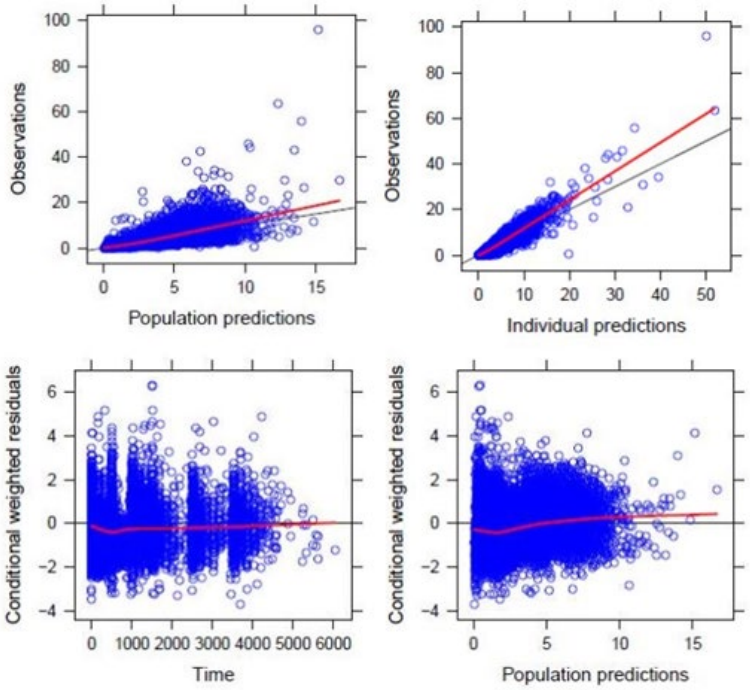


Figure 4: Goodness-of-fit diagnostics of the final released drug model



The blue dots represent observations, the black line represents the identity line, and the red curve represents the loess smoothers

Absorption

Based on non-compartmental analysis from 5 studies (DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, and DS8201-A-U201) Tmax of DS8201a was approximately 2 hours, whereas Tmax of the MAAA-1181a was approximately 6.8 hours.

Bioavailability

The dose of MAAA-1181a (released drug) was unknown, as the drug was not directly administered. In the popPK analysis, each 1000 mg of DS-8201a was modelled to release 3.33 mg of MAAA-1181a upon deconjugation (the ratio of approximately 500/150000 is according to molecular weight). DX-8951f has a molecular weight of 568 g/mol, and trastuzumab has a molecular weight of 146000 g/mol. Additionally, the drug-to-antibody ratio (DAR) for DS-8201a is approximately 8.

Bioequivalence

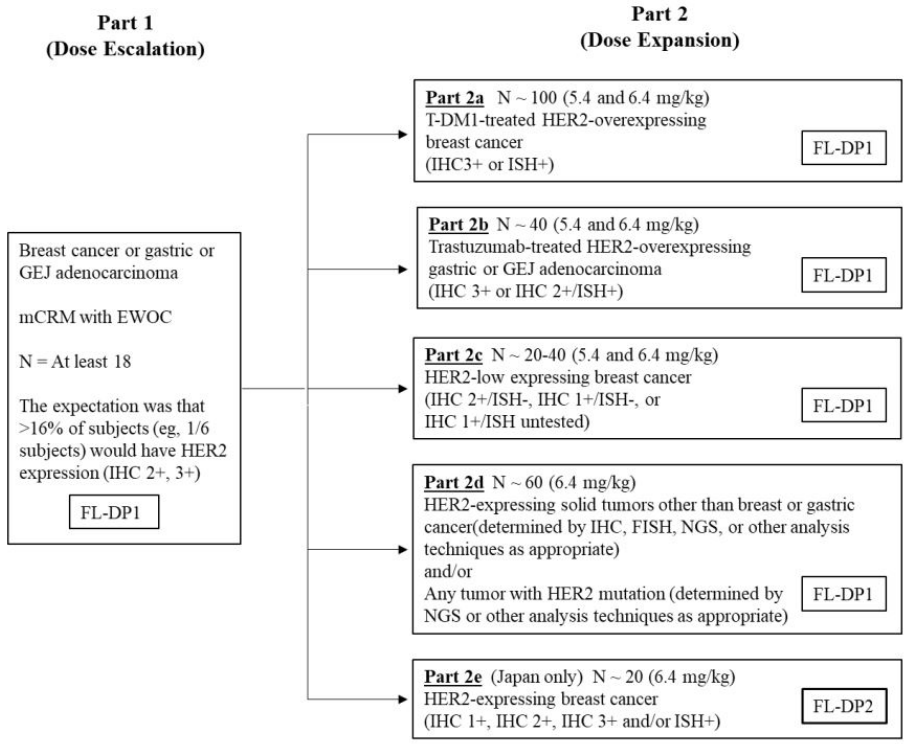
No dedicated bioequivalence studies were conducted. Three drug products were used during the clinical development process: **FL-DP1** (DS-8201a for injection 50 mg/2.5 mL used in Study DS8201-A-J101), **FL-DP2** (DS-8201a for injection 100 mg/5 mL used in studies DS8201-A-J101 and DS8201-A-U201) and **Lyo-DP** (intended commercial drug product used in studies DS8201-A-U201, DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104).

PK comparison of **FL-DP1** and **FL-DP2** was performed in clinical **Study DS8201-A-J101,** while PK comparison after administration of **FL-DP2** and **Lyo-DP** was conducted in **Study DS8201-A-U201**. In addition, the effects of different drug products were evaluated in PopPK analysis.

A **PK comparison** across formulations and DPs was also performed **using integrated data** from subjects with HER2-expressing advanced or metastatic breast cancer across Study DS8201 A J101 (Parts 2a, 2c, and 2e) and Study DS8201 A U201.

Study DS8201-A-J101

This was a Phase 1, 2-part (Dose Escalation followed by Dose Expansion), multicenter, nonrandomized, open-label, multiple-dose, first-in-human study of DS-8201a. Study design schema is presented below. Two types of DS-8201a drug product, FL-DP1 and FL-DP2, were used in this study.
FL-DP1 drug product was used for the Dose Escalation phase and for Dose Expansion Parts 2a, 2b, 2c, and 2d, whereas FL-DP2 drug product was used for Dose Expansion Part 2e. PK analysis set included all subjects who received at least one dose of DS-8201a and had measurable serum concentrations of DS-8201a.



EWOC = escalation with overdose control; FL-DP1 = DS-8201a for Injection 50 mg/2.5 mL; FL-DP2 = DS-8201a for Injection 100 mg/5 mL; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization (fluorescent [FISH] or dual color [DISH]); mCRM = modified continuous reassessment method; NGS = next-generation sequencing; T-DM1 = trastuzumab emtansine

Table 2: Pharmacokinetic Sampling Time Points

Day	Sample times
Day 1	Before infusion (– 8 hours) Within 15 minutes after end of infusion; 2 hours after the start of administration (± 15 minutes); 4 hours after the start of administration (± 15 minutes); 7 hours after the start of administration (± 15 minutes)

Day 2	24 hours after the start of administration (± 2 hours)
Day 4	72 hours after the start of administration (± 2 hours for Part 1, ± 1 day for Part 2)
Day 8	7 days after the start of administration (± 1 day)
Day 15	14 days after the start of administration (± 1 day)
Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of administration (± 2 days)

Based on Protocol DS8201-A-J101 Version 11.0, 25 Jan 2018

Table 3: Pharmacokinetic Parameters of Serum DS-8201a, Total Anti-HER2 Antibody, and MAAA-1181a Following the First Dose at 6.4 mg/kg of FL-DP1 (HER2-positive or HER2-low Breast Cancer without Part 2e) or FL-DP2 (Part 2e) Product (PK Analysis Set)

Drug Product	Pharmacokinetic Parameter													
	Cmax (µg/mL)		Tmax (h)		AUClast (µg d/mL)		AUCinf (µg d/mL)		t1/2 (d)		CL (mL/d/kg)		Vss (mL/kg)	
	N	Mean (SD)	N	Median (Min, Max)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Trastuzumab Deruxtecan														
FL-DP1	74	167 (48.2)	74	2.04 (1.50, 7.05)	74	771 (218)	71	842 (240)	71	6.04 (1.25)	71	8.43 (3.18)	71	62.7 (13.6)
FL-DP2	21	155 (21.4)	21	2.05 (1.62, 7.23)	21	693 (102)	21	753 (118)	21	5.46 (1.02)	21	8.74 (1.59)	21	63.4 (8.95)
Total Anti-HER2 Antibody														
FL-DP1	74	160 (52.1)	74	2.07 (1.50, 505)	74	963 (382)	72	1150 (582)	72	7.39 (2.49)	NA		NA	
FL-DP2	21	152 (27.0)	21	2.00 (1.53, 6.78)	21	826 (158)	21	947 (218)	21	6.63 (1.40)	NA		NA	
MAAA-1181a														
FL-DP1	74	10.2 (4.32)[a]	74	6.81 (3.75, 71.8)	74	41.5 (13.8)[b]	67	43.9 (14.1)[b]	67	5.57 (1.07)	NA		NA	
FL-DP2	21	14.4 (5.50)[a]	21	6.92 (3.92, 7.23)	21	46.6 (16.3)[b]	19	49.2 (17.5)[b]	19	5.34 (1.22)	NA		NA	

AUClast = area under the concentration-time curve from time 0 to the time of the last measureable concentration; AUCinf = area under the concentration-time curve from time 0 to infinity; CL = total body clearance; Cmax = maximum serum concentration; d = day; FL-DP1 = trastuzumab deruxtecan frozen-liquid drug product 1 for injection 50 mg/2.5 mL; FL-DP2 = trastuzumab deruxtecan frozen-liquid drug product 2 for injection 100 mg/5 mL; h = hour; HER2 = human epidermal growth factor receptor 2; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation; t1/2 = terminal elimination half-life; Tmax = time to Cmax; Vss = volume of distribution at steady state

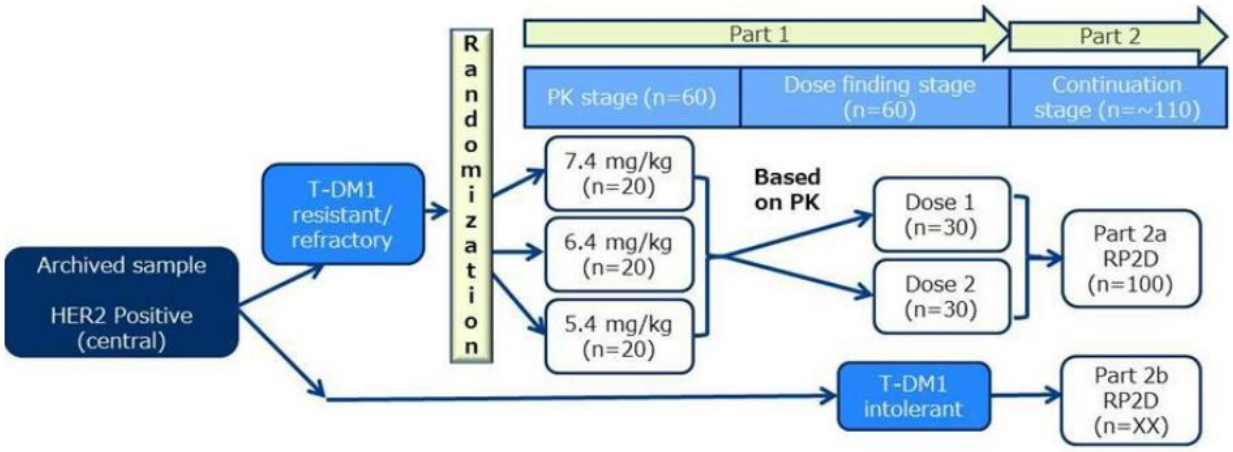
[a] Units are ng/mL.

[b] Units are ng·d/mL.

Study DS8201-A-U201

This was a phase 2, open-label, multicenter, 2-part study designed to justify the recommended dose of DS-8201a and investigate the safety and efficacy in subjects with unresectable and/or metastatic HER2-positive BC previously treated with T-DM1. Study DS8201-A-U201 design is presented in the figure below. Two DP were used during the study **FL-DP2** and **Lyo-DP.**

Figure 5: DS8201-A-U201 Study Design



HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetics; RP2D = recommended Phase 2 dose; T-DM1 = trastuzumab emtansine.

The **FL-DP2** DP was used in all subjects randomized in Part 1 PK stage (ie, 22 subjects in the 5.4 mg/kg dose, 22 subjects in the 6.4 mg/kg dose, and 21 subjects in the 7.4 mg/kg dose cohorts) and Part 1 Dose Finding stage (ie, 28 subjects in the 5.4 mg/kg dose and 28 subjects in the 6.4 mg/kg dose cohorts). In Part 2 (5.4 mg/kg dose), 108 subjects received the **Lyo-DP** product and 26 subjects received the FL-DP2 product. The **PK comparison** between FL-DP2 and Lyo-DP was conducted using **RP2D**, which was determined to be **5.4mg/kg**. The PK comparison was done using Pharmacokinetic (PK) Analysis Set, which was determined as all subjects enrolled in Part 1 or Part 2 who received at least 1 dose of study drug and had measurable serum concentrations of DS-8201a. The PK sampling time points used for the PK comparison are presented in the below tables.

Table 4: Blood Sampling for Pharmacokinetic Analysis in Part 1 Pharmacokinetic Stage

Cycle	Day	Sampling Time Point (Acceptable Ranges)
Cycle 1	Day 1	Before infusion (– 8 hours) End of infusion: within 15 minutes after end of infusion 2 hours after the start of drug administration (± 15 minutes) 4 hours after the start of drug administration (± 15 minutes) 7 hours after the start of drug administration (± 15 minutes)
	Day 2	24 hours after the start of drug administration (± 2 hours)
	Day 4	72 hours after the start of drug administration (± 2 hours)
	Day 8	7 days after the start of drug administration (± 1 day)
	Day 15	14 days after the start of drug administration (± 1 day)
	Day 22	If the schedule on Day 1 of the next cycle was delayed for 3 days or more, including if the subject could not continue onto the next cycle, blood samples were to be collected 21 days after the start of drug administration (± 2 days)

Table 5: Blood Sampling for Pharmacokinetic Analysis in Part 1 Dose Finding Stage and Part 2

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	Before infusion (–8 hours) End of infusion: within 15 minutes after end of infusion 4 hours after the start of drug administration (± 15 minutes) 7 hours after the start of drug administration (± 15 minutes)
	Day 8	7 days after the start of drug administration (± 1 day)
	Day 15	14 days after the start of drug administration (± 1 day)
	Day 22	If the schedule on Day 1 of the next cycle was delayed for 3 days or more, including if the subject could not continue onto the next cycle, blood samples were to be collected 21 days after the start of drug administration (± 2 days)

PK comparison results. After administration of 5.4 mg/kg of FL-DP2 or Lyo-DP, according to the MAA, the geometric mean ratios for Cmax and AUC21d were close to 100% and 90% CIs for the ratios of the geometric means included 100%. The results of PK comparison are presented in the below table.

Table 6: Comparison of Pharmacokinetic Parameters of DS-8201a, Total Anti-HER2-Antibody, and MAAA-1181a Between Lyo-DP and FL-DP2 for Overall 5.4 mg/kg Dose at Cycle 1 (Pharmacokinetic Analysis Set)

Analyte	PK Parameter	Geometric Means		Percentage Geometric Mean Ratio of Lyo-DP / FL-DP2 (%)	90% CI for Percentage Geometric Mean Ratio (%)
		Lyo-DP (n = 108)	FL-DP2 (n = 76)		
Trastuzumab deruxtecan (N = 184)	Cmax (µg/mL)	119.1	118.8	100.28	92.90, 108.25
	AUClast (µg·d/mL)	514.6	504.7	101.97	92.59, 112.30
	AUC21d (µg·d/mL)	558.9	548.5	101.88	93.48, 111.04
Total anti-HER2 antibody (N = 184)	Cmax (µg/mL)	121.8	117.3	103.89	96.30, 112.08
	AUClast (µg·d/mL)	649.7	607.0	107.04	94.84, 120.81
	AUC21d (µg·d/mL)	719.8	682.7	105.58	93.48, 119.24
MAAA-1181a (N = 184)	Cmax (ng/mL)	7.20	6.32	113.78	97.72, 132.49
	AUClast (ng·d/mL)	28.79	25.86	111.35	99.02, 125.22
	AUC21d (ng·d/mL)	30.54	29.39	103.91	85.55, 126.19

Distribution

Intact DS-8201a

From the popPK model Vc of DS-8201a was 2.77L, Vp was 5.16L. Identified covariates on volume of distribution in the popPK model was sex and country (Japan, non-Japan). According to the model, male subjects had approx. 19% higher Vc, whereas subjects from Japan had a approx. 26% lower Vp.

MAAA-1181a (Released drug)

According to MAA, the volume (V) of the released drug was not estimable from the current data, as a result it was fixed to 17 L/m2 (literature documented volume of distribution of exatecan mesylate DX-8951f) multiplied by individual body surface area. Data from popPK indicate that V was greater in older subjects and in subjects receiving FL-DP2 (by approx. 26% in comparison with the Lyo-DP formulation). V was lower in subjects receiving FL-DP1 (by approx. 21% in comparison with the Lyo-DP formulation).

Protein binding

Based on in vitro data, the binding of MAAA-1181a to human plasma proteins was 96.8% to 98.0% across the concentration range of 10 ng/mL to 100 ng/mL.

Blood to plasma ratio

Blood to plasma ratio of MAAA-1181a was also evaluated in vitro, the ratio was 0.59 to 0.62 across the concentration range of 10 ng/mL to 100 ng/mL, suggesting that MAAA-1181a distributes easily into red blood cells.

Transporters

Based on in vitro data, the MAAA-1181a is a substrate of P-glycoprotein, MATE2-K, OATP1B1 and OATP1B3, BCRP, MRP 1.

Elimination

Based on PopPK analysis the clearance of DS-8201a was estimated to be 0.421 L/d, whereas the clearance of MAAA-1181a was 19 L/h. Based on non-compartmental analysis across studies, the apparent terminal elimination half-life of DS-8201a ranged from 2.2 days to 7.3 days across the 0.8 mg/kg to 8.0 mg/kg dose range, half-life for the 5.4mg/kg dose was 6.03 days. The apparent terminal elimination half-life of MAAA-1181a ranged from 2.5 days to 6.45 days across the 0.8 mg/kg to 8.0 mg/kg dose range, half-life for the 5.4mg/kg dose was 6.11 days.

Excretion

The routes and patterns of excretion were not specially investigated in humans. The available data is from studies with animals. This data indicates that after IV administration of 14C-labeled MAAA-1181a to rats the major excretion pathway of radioactivity was faeces via the biliary route and MAAA-1181a was the most abundant component of radioactivity in urine, faeces, and bile. After single IV administration of 14C-labelled trastuzumab deruxtecan (6.4 mg/kg) to monkeys, radioactivity was predominantly excreted into faeces and MAAA-1181a was the most abundant component in urine and faeces

Metabolism

Experiments with CYP-expressing microsomes showed that CYP1A2, CYP2D6, CYP3A4, and CYP3A5 were involved in the metabolism of MAAA-1181a. In the experiments using human liver microsomes with the specific CYP inhibitors, the inhibition rates were -1.3% for CYP1A2, 3.7% for CYP2B6, 16.3% for CYP2C8, -2.9% for CYP2C9, 6.0% for CYP2C19, 8.9% for CYP2D6, and 94.9% for CYP3A4/5. As a result, CYP3A4 is the primary CYP isoform involved in the metabolism of MAAA-1181a.

Dose proportionality and time dependencies

Dose proportionality

There were no clinical studies designed specifically to evaluate single doses of trastuzumab deruxtecan in human subjects. Dose proportionality of 3 analytes was assessed in a Study DS8201-A-J101. The estimation of the slope of the dose proportionality analysis was approximately 1 for both the 0.8-8.0 mg/kg group and the ≥3.2 mg/kg group for DS-8201a and total anti-HER2 antibody. DS-8201a Cmax was dose proportional across the dose range of 0.8 to 8.0 mg/kg. AUClast demonstrated greater-than dose- proportional increases across the wide dose range of 0.8 to 8.0 mg/kg but increased dose proportionally at doses at or above 3.2 mg/kg.

Table 7: Dose Proportionality of Total Anti-HER2 Antibody Analysis of Pharmacokinetic Parameters of DS-8201a Dose Escalation (PK Analysis Set)

Parameter	Dose			
	0.8-8.0 mg/kg		3.2 mg/kg or More	
	Estimation	95% CI	Estimation	95% CI
Cmax (µg/mL)				
Intercept	3.16	(3.02, 3.30)	2.86	(2.48, 3.24)
Slope	0.971	(0.880, 1.06)	1.14	(0.924, 1.35)
AUClast (µg•d/mL)				
Intercept	4.40	(4.05, 4.75)	3.92	(3.32, 4.51)
Slope	1.23	(1.01, 1.46)	1.50	(1.16, 1.83)
AUCtau (µg•d/mL)				
Intercept	4.46	(4.13, 4.79)	3.93	(3.35, 4.52)
Slope	1.20	(0.986, 1.41)	1.49	(1.16, 1.82)

AUClast = area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration; AUCtau = area under the concentration-versus-time curve during the dosing interval; AUCinf = area under the concentration-versus-time curve, from time 0 to infinity; AUCtau = area under the concentration-versus-time curve during the dosing interval; CI = confidence interval; Cmax = maximum (peak) observed serum concentration

Data cut-off date: 01 Feb 2019

Estimate of (95% CI) of the slope for AUClast for total anti-HER2 antibody was 1.23 (1.01, 1.46) for the 0.8-8.0 mg/kg dose range and 1.50 (1.16, 1.83) for the ≥3.2 mg/kg dose range, which suggest greater than the dose-proportional increase for both dose groups (Table 2.1.6.1). Estimation (95% CI) of the slope for AUClast for MAAA-1181 was 0.507 (-0.0255, 1.04) for the ≥ 3.2 mg/kg dose range, due to the constant exposure over 5.4 mg/kg (below table).

Table 8: Dose Proportionality of MAAA-1181a Analysis of Pharmacokinetic Parameters of DS-8201a Dose Escalation (PK Analysis Set)

Parameter	Dose			
	0.8-8.0 mg/kg		3.2 mg/kg or More	
	Estimation	95% CI	Estimation	95% CI
Cmax (ng/mL)				
Intercept	0.275	(-0.0803, 0.631)	1.33	(0.201, 2.46)
Slope	0.993	(0.767, 1.22)	0.411	(-0.225, 1.05)
AUClast (ng•d/mL)				
Intercept	1.78	(1.49, 2.08)	2.61	(1.66, 3.56)
Slope	0.962	(0.777, 1.15)	0.507	(-0.0255, 1.04)
AUCtau (ng•d/mL)				
Intercept	1.79	(1.50, 2.08)	2.60	(1.66, 3.55)
Slope	0.959	(0.774, 1.14)	0.510	(-0.0215, 1.04)

AUClast = area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration; AUCtau = area under the concentration-versus-time curve during the dosing interval; AUCinf = area under the concentration-versus-time curve, from time 0 to infinity; AUCtau = area under the concentration-versus-time curve during the dosing interval; CI = confidence interval; Cmax = maximum (peak) observed serum concentration

Data cut-off date: 01 Feb 2019

Table 9: Summary of Trastuzumab Deruxtecan, MAAA 1181a, and Total Anti HER2 Antibody Serum Pharmacokinetics following the First Dose in Study DS-8201a

PK Parameter, Arithmetic Mean (SD)[a]		Cmax (µg/mL)	Tmax (h)	AUClast (µg·d/mL)	AUCinf (µg·d/mL)	t1/2 (d)	CL (mL/d/kg)	Vss (mL/kg)
Trastuzumab deruxtecan	0.8 mg/kg	22.9 (3.76)	1.95 (1.62-1.98)	51.7 (13.1)	55.0 (11.9)	2.18 (0.671)	15.0 (2.89)	45.0 (8.96)
	1.6 mg/kg	36.2 (4.98)	4.03 (1.87-4.08)	116 (58.7)	121 (58.9)	3.07 (1.22)	16.1 (9.27)	58.3 (10.0)
	3.2 mg/kg	78.2 (16.1)	4.12 (1.95-6.88)	325 (142)	340 (150)	4.23 (1.24)	11.3 (6.52)	56.8 (14.4)
	5.4 mg/kg	127 (17.2)	2.02 (1.87-2.07)	544 (165)	590 (186)	6.03 (0.603)	10.1 (3.90)	75.2 (24.2)
	6.4 mg/kg	181 (33.1)	2.06 (1.50-3.97)	901 (155)	1030 (209)	7.33 (1.64)	6.41 (1.12)	58.6 (11.0)
	8.0 mg/kg	224 (41.0)	1.97 (1.70-6.80)	996 (229)	1100 (259)	6.44 (0.793)	7.60 (1.73)	62.1 (14.0)
Total anti-HER2 antibody	0.8 mg/kg	19.3 (4.30)	1.65 (1.62-1.98)	83.8 (73.4)	93.5 (82.1)	3.49 (2.51)	NA	NA
	1.6 mg/kg	41.2 (12.7)	1.87 (1.67-4.03)	200 (191)	227 (225)	4.35 (2.77)	NA	NA
	3.2 mg/kg	67.5 (13.8)	4.12 (3.97-6.88)	302 (97.8)	313 (102)	3.93 (0.863)	NA	NA
	5.4 mg/kg	116 (13.9)	2.03 (1.87-6.88)	609 (151)	682 (172)	6.78 (2.39)	NA	NA
	6.4 mg/kg	146 (18.9)	3.94 (2.05-6.87)	878 (97.1)	1050 (149)	8.25 (2.16)	NA	NA
	8.0 mg/kg	188 (23.3)	2.07 (1.97-6.83)	1120 (213)	1270 (261)	6.79 (0.821)	NA	NA
		Cmax (n g/mL)	**Tmax (h)**	**AUClast (n g·d/mL)**	**AUCinf (ng·d/mL)**	**t1/2 (d)**		
MAAA-1181a	0.8 mg/kg	1.17 (0.757)	6.77 (6.75-22.25)	4.84 (1.89)	4.89 (1.89)	2.50 (0.579)	NA	NA
	1.6 mg/kg	1.72 (0.193)	6.98 (6.82-24.05)	8.53 (2.15)	8.76 (2.34)	3.48 (1.09)	NA	NA
	3.2 mg/kg	5.69 (0.530)	6.88 (4.00-6.88)	24.0 (7.58)	24.9 (7.98)	4.68 (0.969)	NA	NA

	5.4 mg/kg	10.8 (7.56)	5.38 (3.83-23.75)	40.6 (19.8)	43.6 (21.2)	6.11 (0.811)	NA	NA
	6.4 mg/kg	6.80 (1.72)	6.83 (4.05-7.15)	31.0 (5.11)	34.2 (5.63)	6.28 (1.17)	NA	NA
	8.0 mg/kg	9.65 (2.56)	6.80 (2.07-7.00)	40.3 (5.66)	44.5 (7.03)	6.45 (1.56)	NA	NA

Time dependency

Time dependency of trastuzumab deruxtecan was evaluated in Study DS8201-A-J102 in Cycle 1 and Cycle 3. Following IV administration of DS-8201a at 6.4 mg/kg, the Cmax for MAAA-1181a was reached with a median Tmax of 6.93 hours at Cycle 1 (n = 51) and 6.92 hours at Cycle 3 (n = 37). At Cycle 1, the mean Cmax for MAAA-1181a was 12.6 ng/mL and the mean AUCtau was 39.0 ng•d/mL. At Cycle 3, the mean Cmax for MAAA-1181a was 9.60 ng/mL and the mean AUCtau was 41.5 ng•d/mL; the mean AR for AUCtau at Cycle 3 was 1.09. Steady state was reached at Cycle 3 (see figure below).

Figure 6: Time Courses of Mean Serum Concentrations of DS-8201a, Total Anti-HER2 Antibody, and MAAA-1181a (Linear Scale) (Pharmacokinetic Analysis Set), study DS8201-A J102

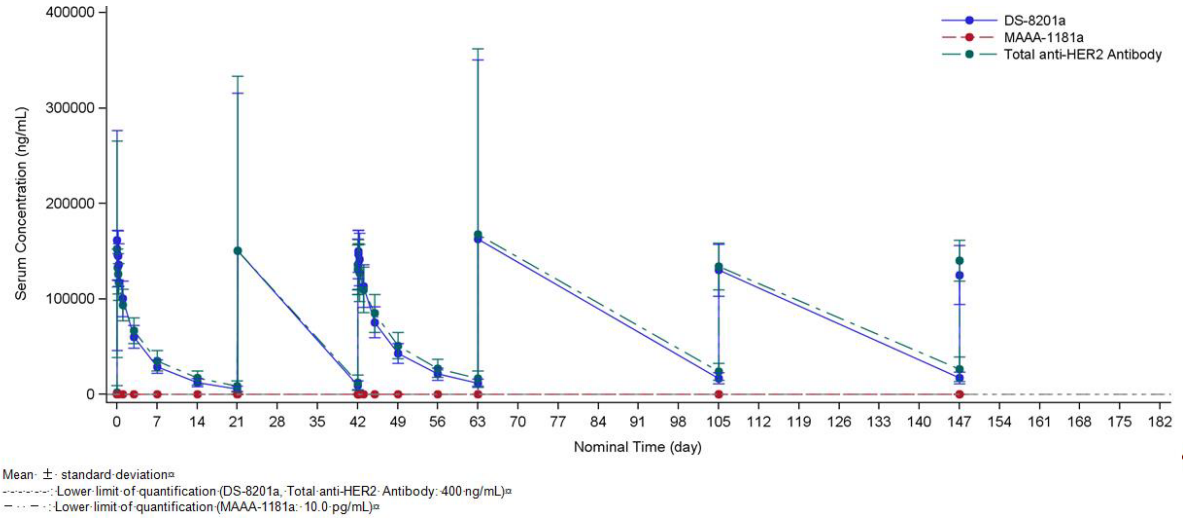
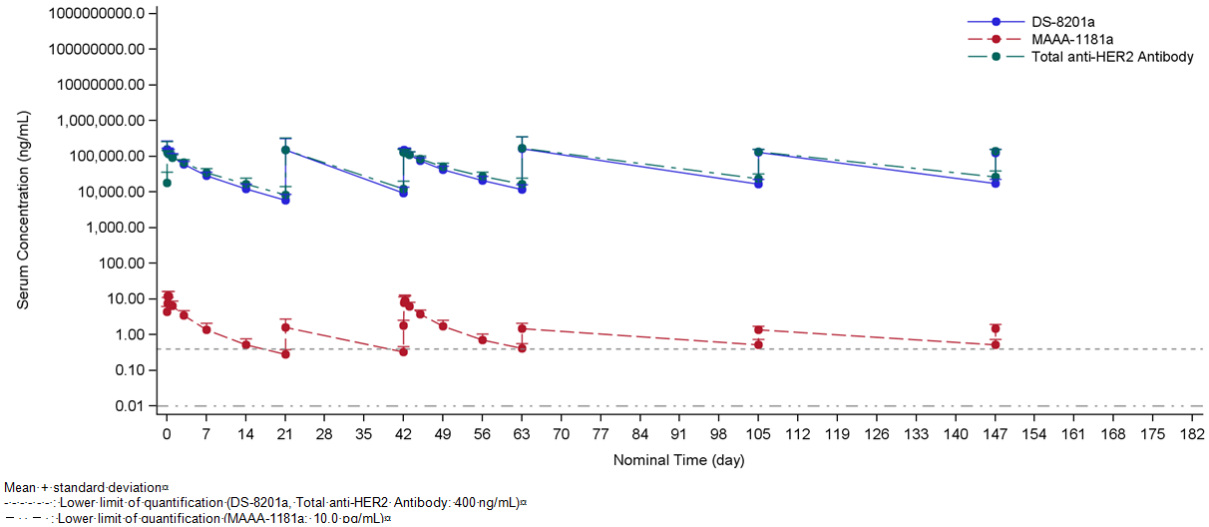


Figure 7: Time Courses of Mean Serum Concentrations of DS-8201a, Total Anti-HER2 Antibody, and MAAA-1181a (Semi-logarithmic Scale) (Pharmacokinetic Analysis Set)



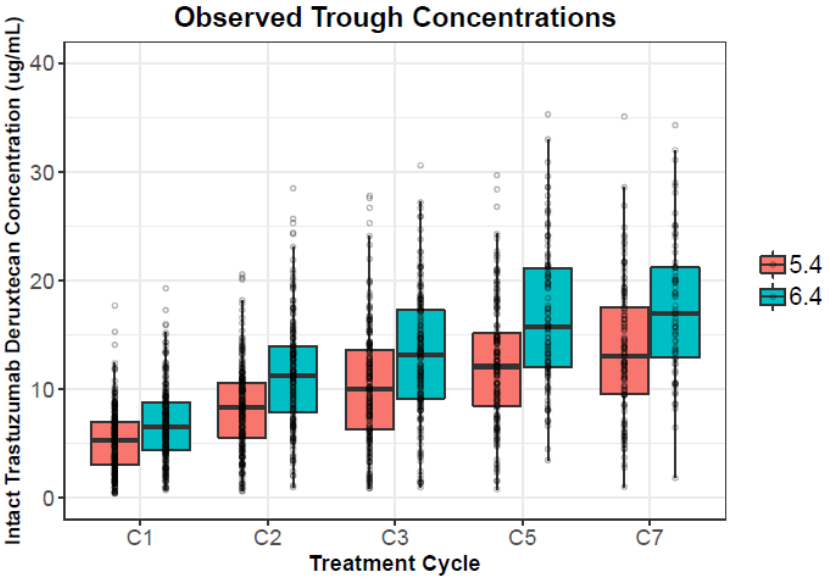
The mean accumulation ratio (AR) for AUCtau at Cycle 3 was 1.35 for trastuzumab deruxtecan, 1.36 for total anti-HER2 antibody, and 1.09 for MAAA-1181a; the accumulation for trastuzumab deruxtecan was consistent with its observed t1/2.

Table 10: Summary of Trastuzumab Deruxtecan, MAAA-1181a, and Total Anti-HER2 Antibody Multiple-Dose Serum Pharmacokinetics in Study DS8201-A-J102, dose 6.4 mg

PK Parameter, Arithmetic Mean (SD)[a]		**Cmax (µg/mL)**	**AUCtau (µg·d/mL)**	**AR (Cycle 3/Cycle 1)**	**Tmax (h)**	**Ctrough (µg/mL)**	**t1/2 (d)**
Trastuzumab deruxtecan	Cycle 1	179 (112)	677 (141)	NA	2.08 (1.55-7.02)	6.03 (2.96)	5.82 (1.11)
	Cycle 3	154 (23.3)	905 (189)	1.35 (0.150)	2.12 (0.70-7.15)	11.8 (4.33)	7.40 (1.48)
Total anti-HER2 antibody	Cycle 1	165 (110)	752 (185)	NA	2.07 (1.48-7.02)	8.61 (5.72)	6.35 (2.01)
	Cycle 3	142 (27.0)	1030 (256)	1.36 (0.219)	2.07 (0.60-7.15)	16.7 (7.97)	8.27 (1.97)
		Cmax (ng/mL)	**AUCtau (ng·d/mL)**	**AR (Cycle 3/Cycle 1)**	**Tmax (h)**	**Ctrough (ng/mL)**	**t1/2 (d)**
MAAA-1181a	Cycle 1	12.6 (4.49)	39.0 (11.2)	NA	6.93 (3.88-191.47)	0.296 (0.128)	5.74 (1.29)
	Cycle 3	9.60 (3.89)	41.5 (13.8)	1.09 (0.194)	6.92 (1.95-70.65)	0.409 (0.150)	6.57 (1.81)

Time to steady state was evaluated using the observed Cmin (trough concentration) data using the PopPK dataset. Based on the observed Cmin by cycle (Figure below) trastuzumab deruxtecan appeared to have reached steady state by Cycle 3.

Figure 8: Observed Trastuzumab Deruxtecan Cmin Values by Dosing Cycle



Cmin = minimum observed serum concentration; IQR = interquartile range.
Note: Individual observed trastuzumab deruxtecan concentrations in the 5.4 mg/kg and 6.4 mg/kg dose groups within the first 8 treatment cycles from the final population PK analysis dataset were used. Some outlying data points with extreme values were excluded to allow better visualization of the observed concentration range in each cycle and dose group. Boxes represent quartiles and whiskers represent 1.5 IQR.

Intra- and inter-individual variability

In the popPK analysis, interindividual variability for DS-8201a clearance was 25.1%, for distribution clearance 30%, for central and peripheral volumes of distribution was 15.8% and 65.6% respectively. Interindividual variability for MAAA-1181a clearance was 25.4%, volume of distribution 42%, release rate 37.6%.

The Applicant was asked to provide data regarding intrasubject variability. The model estimated a proportional residual error (intrasubject variability) of 27.9% (as CV%) for the observed MAAA-1181a concentrations. The proportional residual error (intrasubject variability) was estimated to be 16.3% (as a CV%) for intact trastuzumab deruxtecan.

Special populations

Impaired renal function

The effect of renal impairment on the exposure of DS-8201a and MAAA-1181a was evaluated using CrCL as a covariate in the PopPK analysis. Normal function, mild impairment, moderate impairment, and severe impairment were defined as CrCL (using Cockroft and Gault equation) of ≥90, 60 to 89, 30 to 59, and 15 to 29 mL/min, respectively.

Summary of post-hoc MAAA-1181a exposures in breast cancer subjects with 5.4 mg/kg DS-8201a Q3W dosing, comparison in renal function subgroups is presented in below table. A post hoc comparison of exposures showed approx. 10% lower exposures of MAAA-1181a between subjects with mild renal impairment (N = 206) and subjects with normal renal function (N = 238) (see figure below). Moderate and severe renal impartment showed no apparent change in exposure of MAAA-1181a, although this was based on only 58 subjects (57 subjects with moderate renal impairment and 1

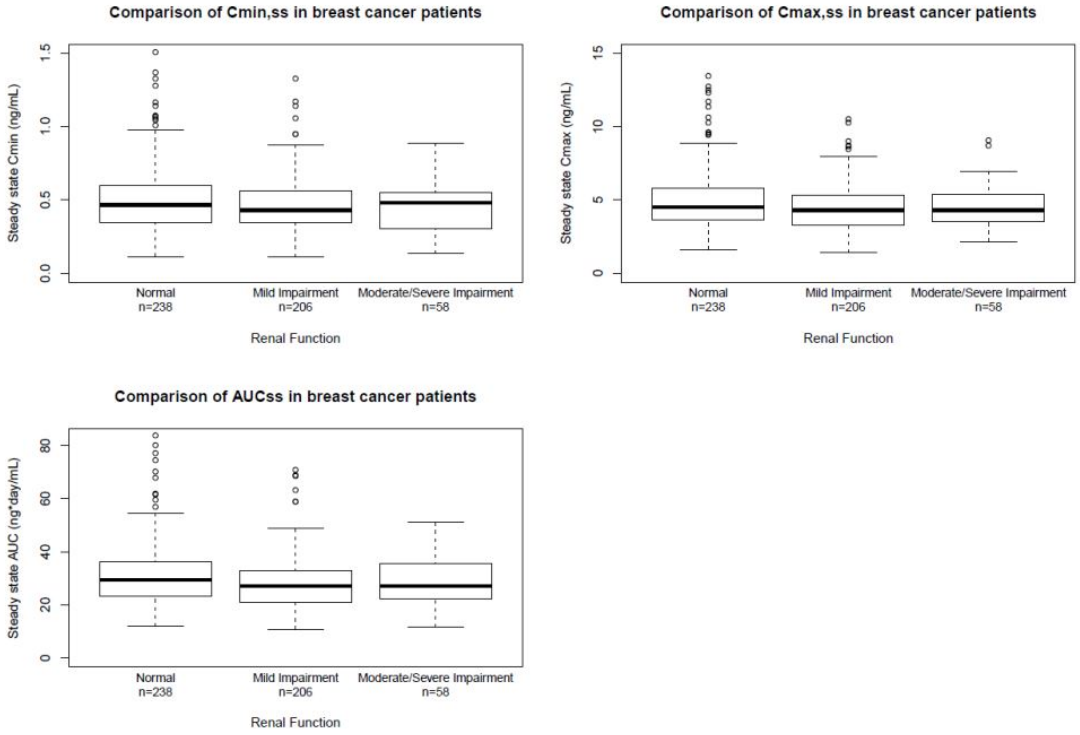
subject with severe renal impairment). The Applicant states that, based on the PopPK analysis, no dose adjustment is recommended for subjects with mild or moderate renal impairment. Limited data preclude a recommendation for subjects with severe renal impairment.

Table 11: Summary of posthoc MAAA-1181a exposures in breast cancer subjects with 5.4 mg/kg DS-8201a Q3W dosing, comparison in renal function subgroups

Exposure Metric	Geometric Mean			Geometric Mean Ratio	
	Normal Renal Function (N=238)	Mild Renal Impairment (N= 206)	Moderate/ Severe Renal Impairment (N= 58)	Mild Renal Impairment vs. Normal Renal Function	Moderate/Severe Renal Impairment vs. Normal Renal Function
Cycle 1 Cmin (ng/mL)	0.334	0.314	0.319	0.942	0.957
Cycle 1 Cmax (ng/mL)	6.88	6.24	6.33	0.908	0.921
Cycle 1 AUC (ng*day/mL)	36.7	33.5	34.5	0.911	0.938
Steady-state Cmin (ng/mL)	0.457	0.436	0.425	0.953	0.930
Steady-state Cmax (ng/mL)	4.66	4.25	4.34	0.911	0.931
Steady-state AUC (ng*day/mL)	29.5	27.2	27.8	0.921	0.942

AUC = area under the concentration-time curve; Cmax = maximum concentration; Cmin = minimum concentration; CrCL = creatinine clearance; FDA = United States Food and Drug Administration; N = number of subjects; Q3W = every 3 weeks.

Figure 9:Boxplots of Steady-State MAAA-1181a Exposures with 5.4 mg/kg Dose, Stratified by Renal Impairment

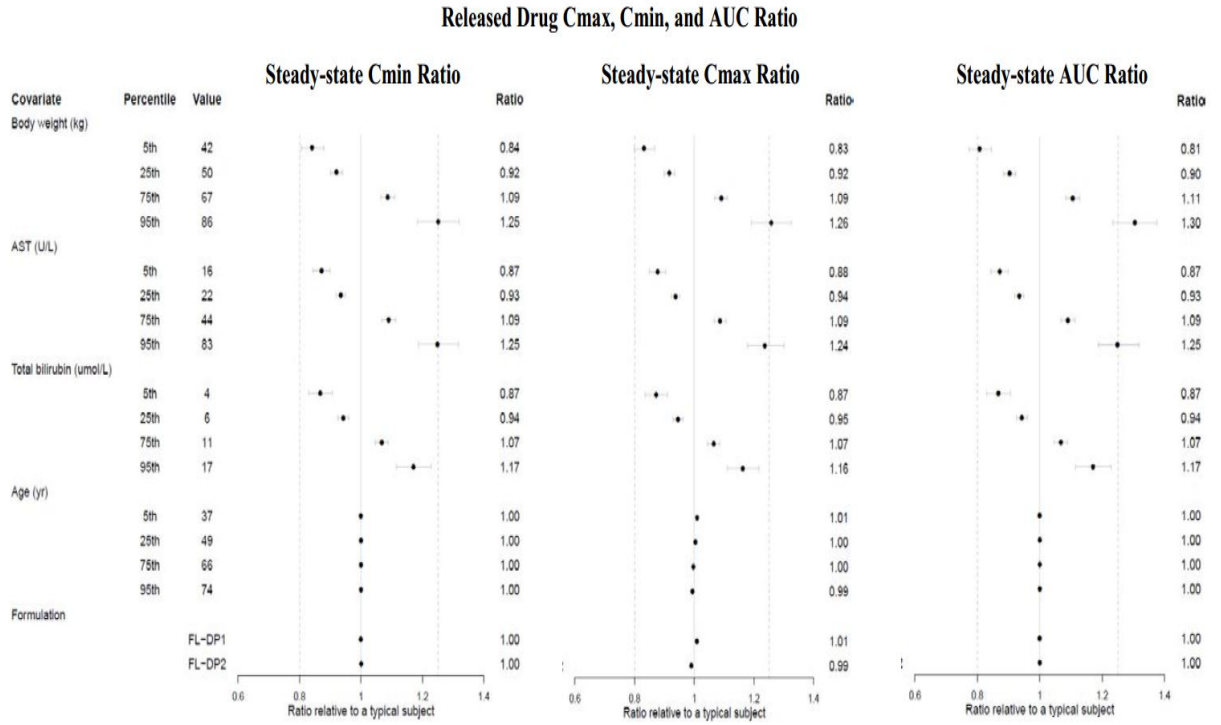


AUCss = area under the concentration-time curve at steady state; Cmax,ss = maximum observed concentration at steady state; Cmin,ss = minimum observed concentration at steady state; CrCL = creatinine clearance; n = number of subjects. Note: Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers.

Impaired hepatic function

Dedicated hepatic impairment study was not conducted. The effect of hepatic impairment was evaluated using hepatic function parameters on clearance and volume of MAAA-1181a in the popPK analysis. Baseline AST and baseline total bilirubin were identified as significant covariates on the clearance of MAAA-1181a. The increase of AST and total bilirubin results in decreased clearance of MAAA-1181a. The effects on clearance resulted in differences in exposure. Subjects with AST of 83 U/L (95th percentile) demonstrated 25% higher MAAA-1181a AUC, 24% higher Cmax and 25% higher Cmin at steady state compared with subjects with the median AST value of 30 U/L (figure 2.1.8.2). Subjects with total bilirubin of 17 µmol/L (95th percentile) demonstrated 17% higher AUC and Cmin, and 16% higher Cmax compared with subjects with the median total bilirubin value of 8 µmol/L (figure below). For both covariates (AST and total bilirubin), values below median resulted in lower exposure of MAAA-1181a. However, the ratios of AUC, Cmin and Cmax remained within the 0.8-1.25 limits (figure below).

Figure 10: Forest plot of covariate effects on released drug (MAAA-1181a) exposure



ST = aspartate aminotransferase; AUC = area under the concentration-time curve; Cmax = maximum concentration; Cmin = minimum concentration; Lyo-DP = lyophilized powder drug product.
Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the estimate and 90% confidence interval, respectively. A typical subject is defined as a 57-year old with body weight 57.8 kg, total bilirubin 8 µmol/L, AST 30 U/L, and administered the Lyo-DP formulation of DS-8201a.

Based on the popPK model, the ratio in exposures between subjects with mild hepatic impairment versus normal hepatic function (based on NCI ODWG criteria which based on total bilirubin and AST) ranged from 1.03 to 1.11 (table below). There were only 1 subject with moderate and 3 subjects with unknown hepatic function. Boxplots of released drug exposure stratified by hepatic function are presented in below figure.

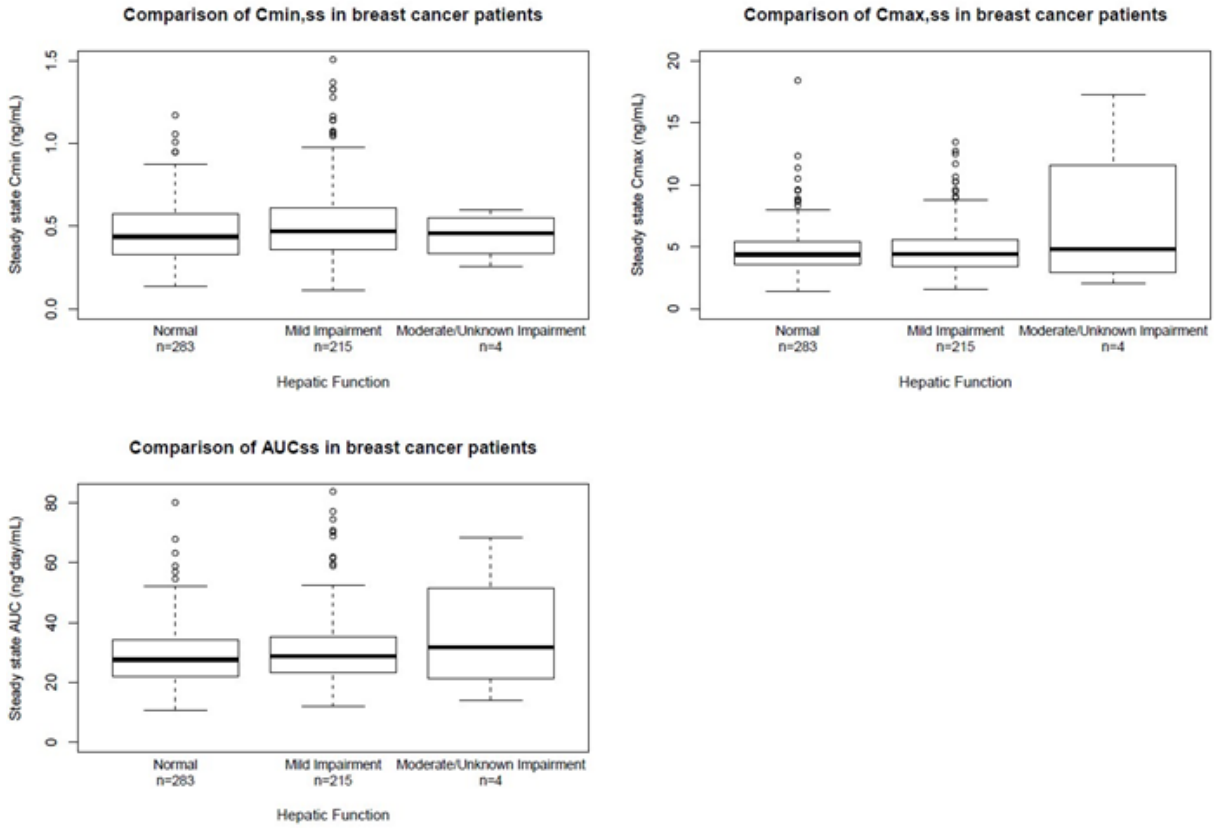
Table 12: Summary of posthoc released drug exposures in breast cancer subjects with 5.4 mg/kg DS-8201a Q3W dosing, comparison in hepatic function subgroups

Exposure Metric	Geometric Mean			Geometric Mean Ratio[1]
	Normal Hepatic Function (N=283)	Mild Hepatic Impairment (N=215)	Moderate/Unknown Hepatic Impairment (N=4)	Mild Hepatic Impairment vs. Normal Hepatic Function
Cycle 1 Cmin (ng/mL)	0.314	0.337	0.347	1.08
Cycle 1 Cmax (ng/mL)	6.49	6.59	7.73	1.02
Cycle 1 AUC (ng*day/mL)	34.2	36.2	40.2	1.06
Steady-state Cmin (ng/mL)	0.425	0.472	0.422	1.11
Steady-state Cmax (ng/mL)	4.40	4.51	5.31	1.03

Steady-state AUC (ng*day/mL)	27.5	29.5	31.3	1.07

AUC = area under the concentration-time curve; Cmax = maximum concentration; Cmin = minimum concentration; N = number of subjects; NCI ODWG = National Cancer Institute Organ Dysfunction Working Group; Q3W = every 3 weeks. 1. Comparison of exposure between moderate/unknown hepatic impairment and normal hepatic function was not performed because of the very limited sample size of breast cancer subjects with moderate/unknown hepatic impairment (N=4). Note: Values were calculated using 15 significant figures but are presented with rounding to 3 significant figures. Hepatic function was categorized using the NCI ODWG criteria.

Figure 11: Boxplots of posthoc steady-state released drug exposure in breast cancer subjects with 5.4 mg/kg DS-8201a Q3W dosing, stratified by hepatic function



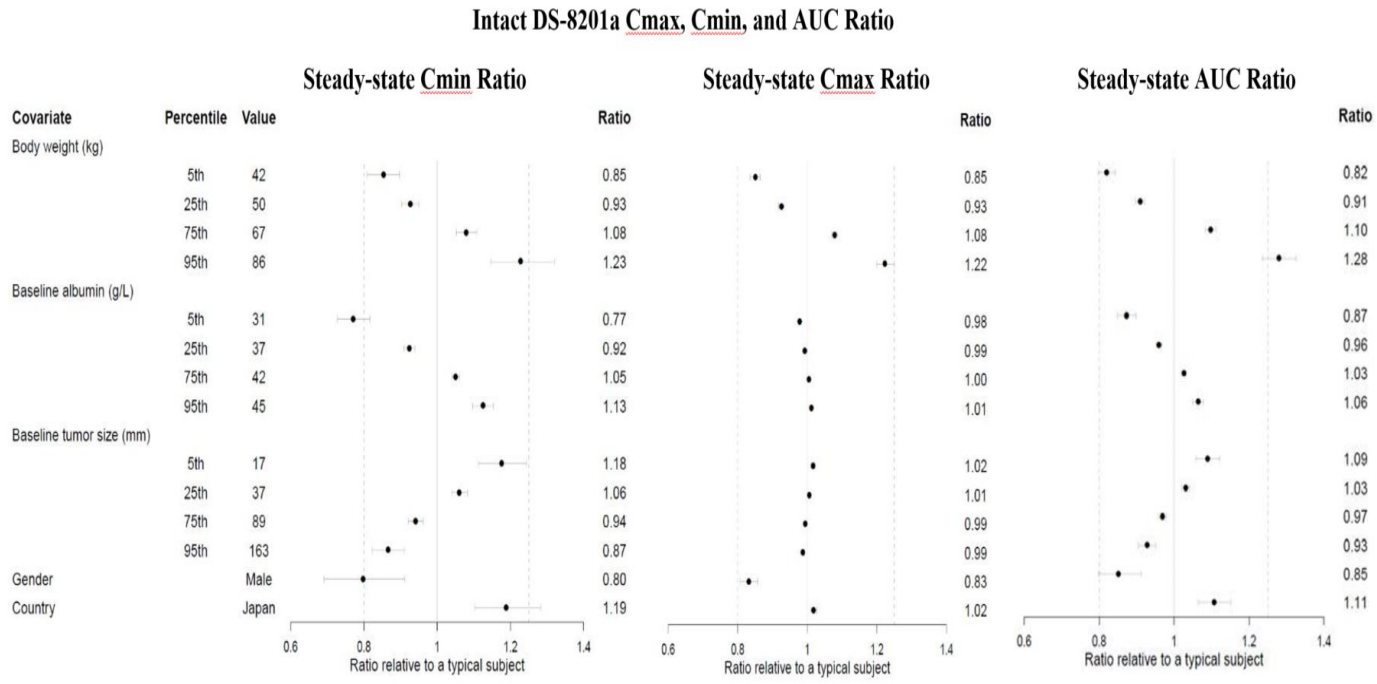
AUCss = area under the concentration-time curve at steady state; Cmax,ss = maximum concentration at steady state; Cmin,ss = minimum concentration at steady state; n = number of subjects; NCI ODWG = National Cancer Institute Organ Dysfunction Working Group; Q3W = every 3 weeks. Note: Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers. Hepatic function was categorized using the NCI ODWG criteria.

Gender

Gender effects on PK of DS-8201a and MAAA-1181a were evaluated in popPK analysis. Sex was identified as a significant covariate for clearance and central volume for DS-8201a. Male subjects had 19.7% higher central volume and 17.4% higher clearance of DS-8201a. This resulted in reduced exposure metrics Cmin, AUC and Cmax compared to typical female subject (see Figure below). However, According to MAA, differences between AUC values were not clinically meaningful as the decrease in AUC at steady state for males was approximately 15% relative to females.

Sex was not identified as significant covariate for any covariates tested for MAA-1181a.

Figure 12: Forest plot of covariate effects on intact DS-8201a exposure



AUC = area under the concentration-time curve; Cmax = maximum concentration; Cmin = minimum concentration. Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the median and 90% confidence interval, respectively. A typical subject is defined as a female from a non-Japan country with body weight 57.8 kg, albumin 40 g/L, and baseline tumor size 57 mm.

Race

The effect of race on exposure was evaluated using the PopPK analysis and was not identified as a significant covariate for either DS-8201a or MAAA-1181a. However, country (Japan versus non-Japan) was also evaluated as a covariate in the PopPK analysis and Japan as a country had a statistically significant effect on the clearance and peripheral volume of DS-8201a. Clearance of DS-8201a decreased with being in Japan (by approx. 9%), and peripheral volume of distribution decreased with being in Japan (by approx. 7%). These effects resulted in increased exposure, but did not correspond to relative changes in exposure outside the 0.8 to 1.25 limits (ratios of 1.11 for AUC and 1.19 for Cmin, see figure 2.1.8.4). Ratio for Cmax was also within the conventional bioequivalence limits (ratio of Cmax was 1.02).

Albumin

Baseline albumin was evaluated as a covariate in the PopPK analysis. Baseline albumin was identified as a significant covariate on the clearance of DS-8201a, indicating decreasing clearance with increasing albumin levels. According to the MAA, the effect of baseline albumin on the exposure of DS-8201a was not considered clinically meaningful as the 90% CIs of the AUC at steady state ratio was within the 0.80 to 1.25 range for both subjects with baseline albumin of 31 g/L (5th percentile) and 45 g/L (95th percentile) compared with subjects with the median value of baseline albumin of 40 g/L (AUC at steady state ratios of 0.87 and 1.06, respectively; see figure 2.1.8.4).

Weight

Body weight was identified as a significant covariate on clearance for DS8201a and MAAA-1181a in the popPK analysis. In both instances the model suggests increasing clearance with increasing body weight. However, despite the fact that the effect of baseline body weight on clearance of DS-8201a and MAAA-1181a suggests increasing clearance with increasing body weight, the overall effect of baseline body weight greater than median is a slight increase in exposure.

According to popPK analysis, subjects with 86 kg (95th percentile) body weight had an approximately 28% increase in **DS8201a** AUC relative to a subject with the median body weight (57.8 kg). Whereas for **MAAA-1181a**, subjects with 86 kg (95th percentile) body weight had an approximately 30% increase in AUC, 26% increase in Cmax and 25% increase in Cmin relative to a subject with the median body weight (57.8 kg). The ratio of Cmin and Cmax for DS8201a and Cmin for MAAA-1181a was in the limits of 0.8-1.25 for all presented percentiles (from 5th to 95th).

Figure 13: Forest Plot of Covariate Effects on DS8201a AUC at Steady State

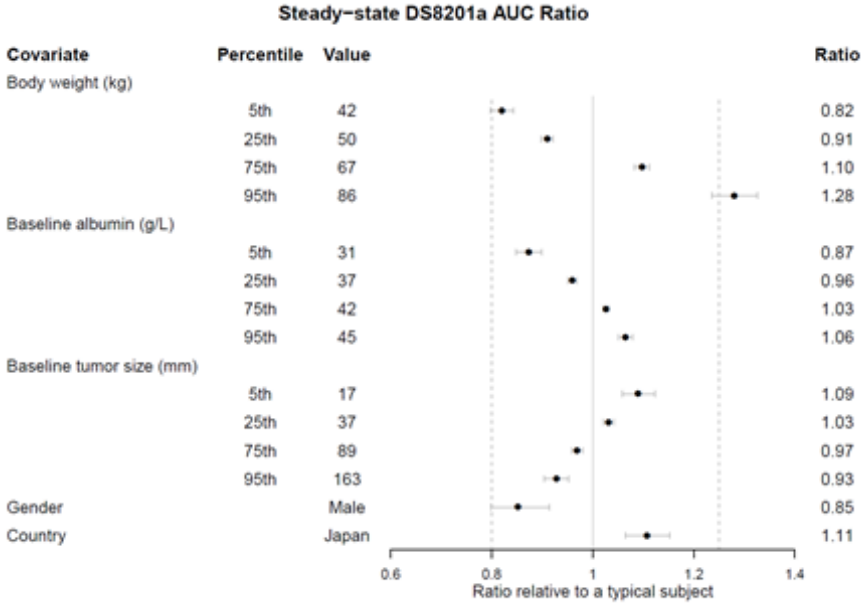
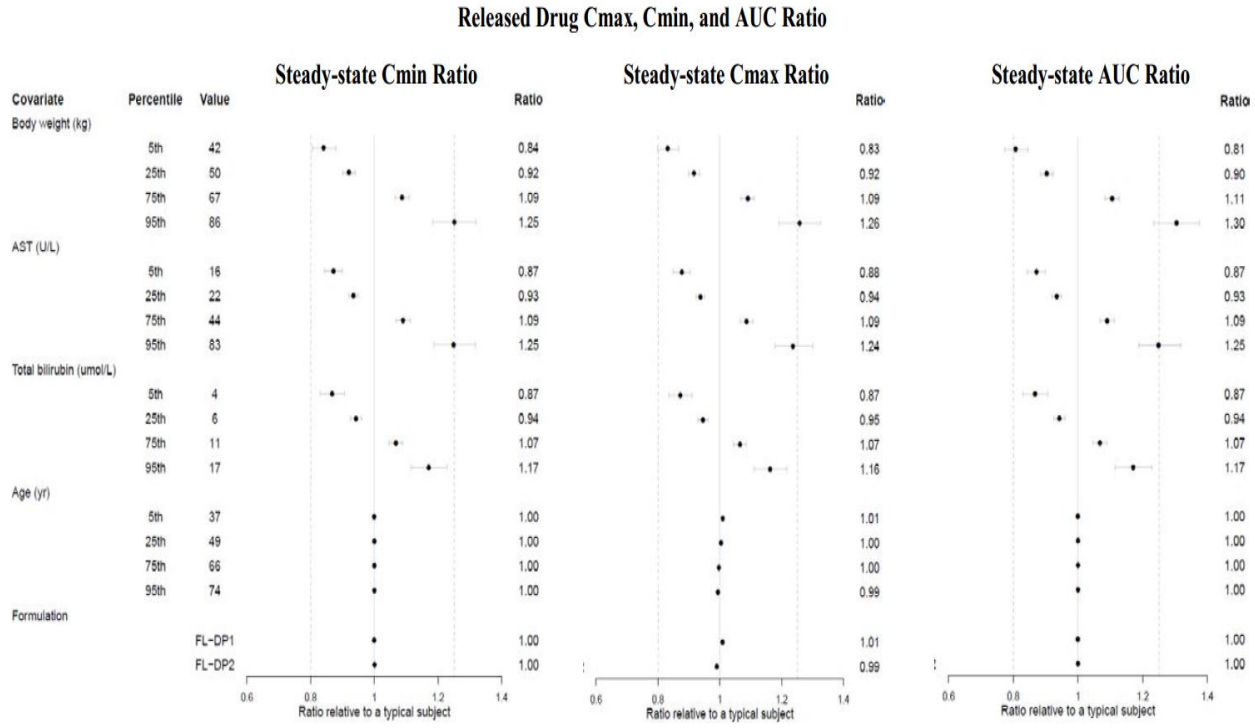


Figure 14 : Forest plot of covariate effects on released drug (MAAA-1181a) exposure



AST = aspartate aminotransferase; AUC = area under the concentration-time curve; Cmax = maximum concentration; Cmin = minimum concentration; Lyo-DP = lyophilized powder drug product.
Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the estimate and 90% confidence interval, respectively. A typical subject is defined as a 57-year old with body weight 57.8 kg, total bilirubin 8 µmol/L, AST 30 U/L, and administered the Lyo-DP formulation of DS-8201a.

Elderly

The effect of age was assessed in the PopPK analysis. Age was identified as a significant covariate for volume of MAAA-1181a. However According to MAA, age did not show a clinically meaningful effect on the AUC of MAAA-1181a as the 90% CI of the AUCss ratio was within the 0.8- to 1.25-fold).

Table 13Table: Elderly enrollment

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials (J102, A103, and A104)	24/103	2/103	0/103
Controlled Trials	N/A	N/A	N/A
Non-Controlled Trials	136/536	24/536	3/536

Pharmacokinetic interaction studies

Study DS8201-A-A104 was a Phase 1, multicenter, open-label, single-sequence crossover study of trastuzumab deruxtecan designed to evaluate DDI potential of ritonavir (dual inhibitor of OATP1B/CYP3A) and itraconazole (strong inhibitor of CYP3A) on trastuzumab deruxtecan and MAAA-1181a in 40 subjects (age 57, range 31-80) with HER2-expressing advanced solid malignant tumors dosed at 5.4 mg/kg.

Cohort 1: Ritonavir was dosed at 200 mg twice a day from Day 17 of Cycle 2 until Day 21 of Cycle 3. Seventeen (17) subjects were enrolled and 5 subjects were excluded from PK statistics because the subjects had missing/incomplete dosing in Cycle 2 and Cycle 3.

Cohort 2: Itraconazole was dosed at 200 mg twice daily on Day 17 of Cycle 2 followed by 200 mg once daily until Day 21 of Cycle 3. Twenty-three (23) subjects were enrolled and 9 subjects were excluded from PK statistical analysis because the subject had missing/incomplete dosing in Cycle 2 and Cycle 3.

AUC0-17d was used as a parameter to evaluate the effect of the inhibitors on the DS-8201a exposure instead of AUC0-21d. This was done to prevent delays to dosing of DS-8201a in Cycle 3 (maintaining 21 day cycle) while also allowing the inhibitors to reach steady state before co-administration. Therefore, ritonavir and itraconazole dosing was initiated on Day 17 of Cycle 2, and AUC of DS-8201a in absence of the inhibitors was calculated prior to the start of administration of the inhibitors. Descriptive statistics of the PK parameters for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a are presented for Cohort 1, Cycles 2 and 3 (without and with ritonavir, respectively), and Cohort 2, Cycles 2 and 3 (without and with itraconazole, respectively) in below table.

Table 14: Drug drug interactions: effect of ritonavir (200 mg BID) and itraconazole (200 mg BID) on the pharmacokinetics of trastuzumab deruxtecan and MAAA-1181a following trastuzumab dderuxtecan 5.4 mg/kg Q3W dosing (study DS8201-A-A104, Mean ±SD, median (range) for Tmax)

Analyte	PK Parameter (Units)	Trastuzumab Deruxtecan + Inhibitor LSM	Trastuzumab Deruxtecan Alone LSM	Ratio (Test/ Reference)	90% CI
Cohort 1 (ritonavir in Cycle 3; Cycle 2 n = 12, Cycle 3 n = 8)					
Trastuzumab deruxtecan	Cmax (µg/mL)	138	131	1.0490	0.9755, 1.1281
	AUC17d (µg·d/mL)	742	623	1.1921	1.1404, 1.2461
MAAA-1181a	Cmax (ng/mL)	8.38	8.49	0.9865	0.8539, 1.1397
	AUC17d (ng·d/mL)	36.6	30.2	1.2151	1.0780, 1.3696
Cohort 2 (itraconazole in Cycle 3; Cycles 2 and 3 n = 14)					
Trastuzumab deruxtecan	Cmax (µg/mL)	140	137	1.0252	0.9631, 1.0913
	AUC17d (µg·d/mL)	685	617	1.1095	1.0732, 1.1470
MAAA-1181a	Cmax (ng/mL)	8.78	8.43	1.0418	0.9167, 1.1839
	AUC17d (ng·d/mL)	33.9	28.8	1.1778	1.1081, 1.2519

ANOVA = analysis of variance; AUC17d = area under the concentration-time curve from time zero to Day 17; CI = confidence interval; Cmax = maximum observed serum concentration; d = day; LSM = least squares mean; n = number of subjects assessed; PK = pharmacokinetic. Source: DS8201-A-A104 CSR, Table 14.4.3.1, Table 14.4.3.2, Table 14.4.3.3, and Table 14.4.3.4.

Concomitant use of ritonavir or itraconazole resulted in minimal increases in exposure of MAAA-1181a, with increases in AUC17d of 22% and 18%, respectively. Concomitant use of ritonavir or itraconazole resulted in minimal increases in exposure of trastuzumab deruxtecan, with increases in AUC17d of 19% and 11%, respectively.

Pharmacokinetics using human biomaterials

MAAA-1181a as victim

Metabolism of MAAA-1181a was evaluated with CYP-expressing microsomes (Report AE-8104-G). This study showed that a metabolite MAAA-1468a was formed by CYP1A2, CYP2D6, CYP3A4, and CYP3A5 were involved in the rapid metabolism of MAAA 1181a. Additional experiments in human liver microsomes with specific inhibitors of CYP enzymes indicated that CYP3A4 is the primary CYP isoform involved in the formation of MAAA-1468a.

The uptake transport of 14C-MAAA-1181a via OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K was examined using cells expressing each transporter in the presence and absence of typical inhibitors (GE-1515-G) or in vesicles MRP1, MRP2, and MRP3 (Report No. DS-23-23Jul2017) or in hepatocytes (Report No. TCRM-DMPK-2015-19). The P-gp- and BCRP-mediated transport of ^{14}C-MAAA-1181a in the presence and absence of typical inhibitors was assessed using Caco-2 cell monolayers. The BSEP-mediated transport of 14C-MAAA-1181a with or without adenosine triphosphate (ATP) was assessed using BSEP-expressing membrane vesicles.

The transport assays using transporter-expressing cell lines revealed that ^{14}C-MAAA-1181a was a substrate for OATP1B1, OATP1B3, and MATE2-K. Michaelis constant (Km) and maximum transport rate values were 13.3 µmol/L and 252 pmol/mg protein/minute, respectively, for OATP1B1, and 19.0 µmol/L and 240 pmol/mg protein/minute, respectively, for MATE2-K. For OATP1B3, the uptake clearance tended to be saturated at a concentration of 0.3 µmol/L or higher, suggesting that the Km was lower than the concentrations tested in this study. Confirmation that MAAA-1181a is a substrate for OATP1B transporters was obtained in hepatocytes. In the presence of rifampicin (150 µmol/L), the uptake of 14C-MAAA-1181a was reduced, resulting in a 2.29- to 3.13-fold reduction in the CLuptake (Report No. TCRM-DMPK-2015-19). MAAA-1181a was a substrate for MRP1 but no marked transport via OAT1, OAT3, OCT1, OCT2, MATE1, MRP2, MRP3 or BSEP was observed. In addition, the P-gp- and BCRP-mediated vectorial transport of 14C-MAAA-1181a across Caco-2 cell monolayers was observed. In conclusion, MAAA-1181a was found to be a substrate for OATP1B1, OATP1B3, MATE2-K, P-gp, BCRP, and MRP-1.

MAAA-1181a as perpetrator

The inhibitory potential of MAAA-1181a on the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A was investigated using human liver microsomes with or without a 30-minute preincubation in the presence of MAAA-1181a at concentrations of 0, 0.05, 0.1, 0.5, 1, 5, 10, and 50 µmol/L.

The IC50 values of MAAA-1181a for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A (testosterone), and CYP3A (midazolam) with and without 30 min preincubation were all estimated to be >50 µmol/L, indicating neither reversible nor time-dependent inhibitory effects of MAAA-1181a on the activities of any of the CYP isoforms.

The inhibitory effects of MAAA-1181a (0.1, 0.3, 1, 3, 10, and 30 µmol/L as MAAA-1181a) on the uptake of typical substrates via human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and

MATE2-K were examined using cells expressing these proteins. The inhibitory effects of MAAA-1181a on P-gp and BCRP were assessed using monolayer culture of Caco-2 cells. In addition, the inhibitory effect of MAAA-1181a on BSEP was assessed using its expressing vesicles. MAAA-1181a inhibited OAT1 and OATP1B1 with IC50 values of 12.7 and 14.4 µmol/L, respectively. MAAA-1181a did not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP (IC50 >30 µmol/L).

Induction potential of MAAA-1181a was investigated with primary cultures of fresh human hepatocytes from 3 donors at concentrations of 0.03, 0.1, 0.3, 1, 3, 10, and 30 µmol/L. After a 72-hour drug exposure, CYP3A4, CYP1A2, and CYP2B6 mRNA levels and enzyme activities (6β-hydroxytestosterone from testosterone for CYP3A4, acetaminophen from phenacetin for CYP1A2, and hydroxybupropion from bupropion for CYP2B6) were measured.

MAAA-1181a, at concentrations of up to 30 µmol/L, did not show any induction potential on mRNA expression or induction of metabolic activity of CYP3A4, CYP1A2, or CYP2B6 in human hepatocytes. In contrast, MAAA-1181a inhibited mRNA expression and metabolic activity of all three enzymes.

2.4.3. Pharmacodynamics

No human PD studies were performed in support of the mechanism of action. Exposure response analysis were performed for efficacy and safety based on the clinical studies DS8201-J101, DS8201-U201, DS8201-J102, DS8201-A103, and DS8201-A104. The effect of trastuzumab deruxtecan on Qt/QTc prolongation was investigated in study DS8201-AJ102.

Primary pharmacology

Not applicable.

Secondary pharmacology

Cardiac effects

Cardiac effects were assessed in the tQT study DS8201-A-J102, a study conducted in Japan to assess the effect of DS-8201a on corrected QT (QTc) interval and its PK in subjects with HER2-expressing metastatic and/or unresectable breast cancer, in which the subjects enrolled (n = 51) received the higher dose (6,4 mg) of DS-8201a as an IV infusion once Q3W on Day 1 of each 21-day cycle.

Four (7.8%) subjects had TEAEs of ECG QT prolonged, all Grade 1, which were considered to be drug-related by the investigators and were not classified as a serious TEAE. None of the subjects required medication and no action was taken with DS-8201a due to the TEAEs. All subjects recovered and continued on study.

The analysis of the QTcF interval over time was the primary analysis for assessment of the effect of DS-8201a on the QTc interval. The results of the analysis indicated that the upper bound of the 90% CI for the mean ΔQTcF was below 10 milliseconds at all time points. A slight increase in the mean QTcF interval was observed for up to 7 hours post-dose in both Cycles 1 and 3. However, no QTcF prolongation was observed on Cycle 1 and Cycle 3 Day 8 and Day 15.

Evaluation the mean change in QTcF interval at the mean Cmax values for DS-8201a and MAAA-1181a (Table below). The values presented in this table were calculated using the observed mean Cmax for each analyte, which was incorporated in the equation for the linear model of concentration vs ΔQTcF for Cycle 1 and Cycle 3. The upper bound of the 90% CI for change in QTcF at the observed mean

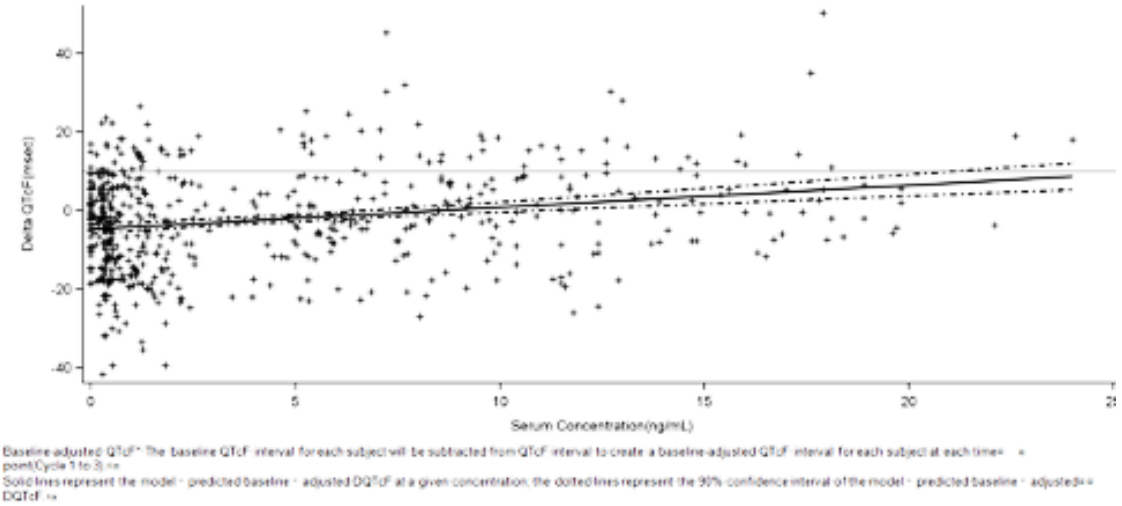
Cmax for each analyte in the linear model of concentration versus change from baseline in mean QTcF in Cycle 1 and Cycle 3 was under 10 milliseconds.

Table 15: Relationship Between Concentration of DS-8201a and MAAA-1181a and QTcF Interval (Cardiac Safety Analysis Set)

QTcF Interval **Maximum Serum Concentration** **Visit**	**DS-8201a (N = 49)**
DS-8201a	
At mean Cmax on Cycle 1 (179 µg/mL)	
ΔQTcF interval estimate	1.3
90% CI	-1.2, 3.8
At mean Cmax on Cycle 3 (154 µg/mL)	
ΔQTcF interval estimate	1.4
90% CI	-1.1, 3.9
MAAA-1181a	
At mean Cmax on Cycle 1 (12.6 ng/mL)	
ΔQTcF interval estimate	2.7
90% CI	0.1, 5.3
At mean Cmax on Cycle 3 (9.6 ng/mL)	
ΔQTcF interval estimate	0.7
90% CI	-1.4, 2.7

Cmax = maximum serum concentration; CI = confidence interval; HR = heart rate QTcF = $QT/(RR)^{1/3}$; if RR was not available, QTcF = $QT/(HR/60)^{1/3}$.
ECGs were collected in triplicate and analyses were based on the average of triplicate results.
The calculation of baseline-adjusted QTcF was done using time-matched baseline.
The estimated value and its 90% CIs were calculated based on the model where concentration and baseline (difference between individual value and mean value) were fixed covariates and measurement time was fixed factor and random effects for the intercept and slope were included.
Cmax in the analysis was calculated using data that were included in the analysis window.
DCO = 05 Dec 2018

Figure 15: Scatter Plot for Relation Between Serum Concentration of MAAA-1181a and ΔQTcF at Cycles 1, 2, and 3 (Cardiac Safety Analysis Set)



Baseline-adjusted QTcF: The baseline QTcF interval for each subject will be subtracted from QTcF interval to create a baseline-adjusted QTcF interval for each subject at each time= = point(Cycle 1 to 3) =>
Solid lines represent the model - predicted baseline - adjusted DQTcF at a given concentration, the dotted lines represent the 90% confidence interval of the model - predicted baseline - adjusted=> DQTcF =>

ΔQTcF, MAAA-1181a = -4.94 + 0.65*concentration

Results from the study indicate that trastuzumab deruxtecan 6.4 mg/kg administration was not associated with a clinically meaningful (change from baseline >10 ms) corrected QT interval by Fridericia's formula (QTcF) prolongation. The upper bound of the 90% CI for change from baseline in QTcF (ΔQTcF) at the observed mean Cmax for each analyte (trastuzumab deruxtecan and MAAA-1181a) in the linear model of concentration versus ΔQTcF for Cycles 1 and 3 was under 10 ms.

Interactions

Possible interaction with OATP1B inhibitors was assessed in the Study A104. No clinically relevant changes in the exposure of trastuzumab deruxtecan was observed.

Genetic differences in PD response

The Applicant has performed PGx in the study A104, however, no analysis was performed due small number of patients included.

Exposure-response analysis

Exposure-efficacy analysis

The exposure-efficacy analysis set included efficacy-evaluable subjects with HER2-positive breast cancer in Studies J101 and U201 that were also included in the population PK analysis.

The exposure-efficacy analysis set comprised 337 HER2-positive breast cancer subjects, including 106 subjects from Study J101 and 231 subjects from Study U201.

Individual post-hoc Bayes estimates of PK parameters of intact DS-8201a and released drug were used to compute exposure metrics after a single dose (maximum concentration [Cmax], minimum concentration [Cmin], area under the concentration-time curve [AUC]) or at steady state (Cmax,

Cmin, AUC), or average concentration to the time of the event (accounting for any dose reductions or dose interruptions).

Exposure-safety analysis

There was a total of 645 subjects who were evaluable for safety. As a sensitivity analysis, the exposure-safety analysis for ILD was repeated amongst subjects from J101 and U201, to confirm robustness of the results.

Individual posthoc Bayes estimates of PK parameters of intact DS-8201a and released drug were used to compute exposure metrics at Cycle 1 (Cmax, Cmin, AUC), steady-state (Cmax, Cmin, AUC), or average concentration to the end of the cycle in which the event occurred (accounting for dose reductions or dose interruptions).

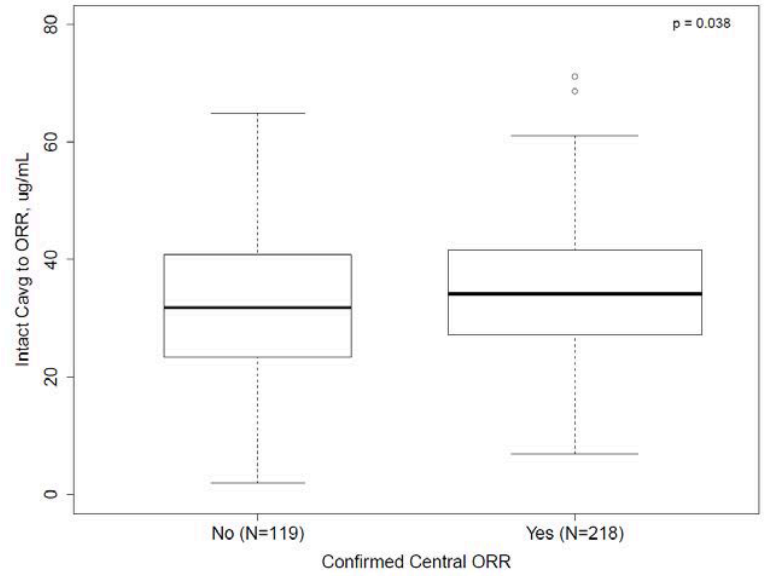
Results

Exposure-Efficacy Analyses

The exposure-efficacy analysis set comprised 337 HER2-positive breast cancer subjects, including 106 subjects from Study J101 and 231 from Study U201.

Below figure shows the distribution of intact DS-8201a average concentration (Cavg) to the time of ORR in subjects with and without confirmed central ORR.

Figure 16: Intact DS-8201a exposure boxplot for confirmed central ORR



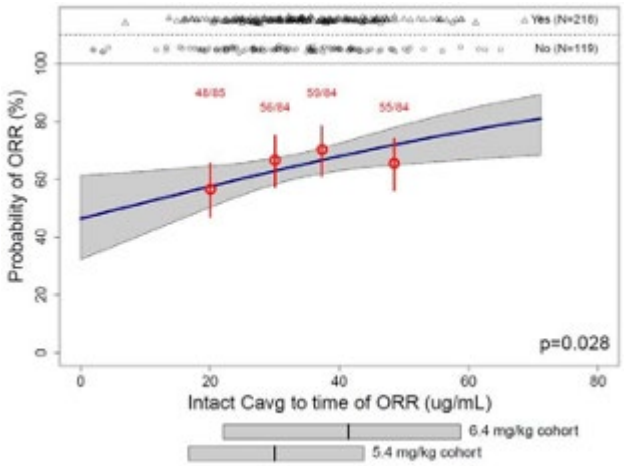
Cavg to ORR = average concentration to time of ORR; Intact = Intact DS-8201a; N = number of subjects; ORR = objective response rate.Note: Thick horizontal line represents median, box ends show the upper and lower quartiles of the data, whiskers show the range of points within 1.5 times the interquartile range, and points are data that lie outside the whiskers (circles). The p-value is for a t-test of differences between means.

Table 16: Observed confirmed central ORR by intact DS-8201a exposure quartiles

Exposure				Observed Confirmed Central ORR
PK Analyte	**Metric**	**Quartile**	**Range**	
Intact DS-8201a	CavgORR (µg/mL)	1	1.91 to 26.6	0.56
		2	26.6 to 33.9	0.67
		3	33.9 to 41.4	0.70
		4	41.4 to 71.1	0.65

CavgORR = average concentration to time of ORR; ORR = objective response rate; PK = pharmacokinetics.

Figure 17: Confirmed central ORR exposure-response plot



Cavg to ORR = average concentration to time of ORR; Intact = intact DS 8201a; N = number of subjects; ORR = objective response rate. Note: Yes and No refer to if subjects experienced or did not experience ORR. Subjects are stratified into exposure quartiles. Red points are mean exposure and ORR rate per quartile. Vertical red bars are 90% CIs of the ORR rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The plot shows data for all dose groups. Horizontal bars below the plot illustrate the 5th, 50th, and 95th percentile of exposures for two selected dose groups of 5.4 and 6.4 mg/kg**.** The p-value is for the slope of the logistic regression fit.

There was a trend towards increased confirmed central ORR with increasing intact DS-8201a exposures but not with released drug exposures. The only relationship that achieved statistical significance was for Cavg to time of ORR (p = 0.028). None of the tested covariates significantly influenced confirmed central ORR.

Table 17: Confirmed central ORR final model parameters

Exposure Metric	Endpoint	Parameter	Estimate	Standard Error
Cavg to ORR	Confirmed central ORR	Intercept	-0.146	0.360
		Slope	0.022	0.010

Cavg to ORR = average concentration to time of ORR; ORR = objective response rate. Source: 2019-07-22-ds8201-ee-v2.r

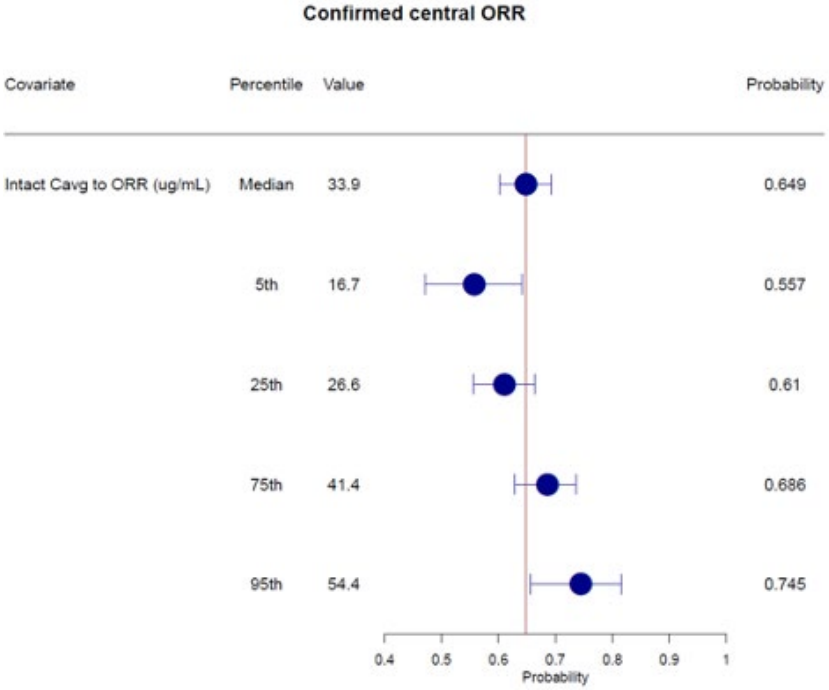
Based on the ER analyses for efficacy, the mean (90% CI) probability of ORR was predicted to be 0.63 (0.55, 0.70) and 0.68 (0.58, 0.76) for the 5.4 mg/kg and 6.4 mg/kg dose groups, respectively (below table).

Table 18: Model-predicted confirmed central ORR at doses of 5.4 and 6.4 mg/kg

DS-8201a Dose	Exposure-Efficacy Model	Model-predicted Confirmed Central ORR	
		Estimate	90% CI
5.4 mg/kg	Cavg to ORR-confirmed central ORR model	0.63	0.55, 0.70
6.4 mg/kg		0.68	0.58, 0.76

Cavg to ORR = average concentration to time of ORR; CI = confidence interval; ORR = objective response rate. Note: Simulations were based on all subjects using subject-specific exposures. The 90% CI was based on model uncertainty and exposure variability. Source: 2019-07-22-ds8201-ee-v2.r

Figure 18: Forest plot of confirmed central ORR probabilities

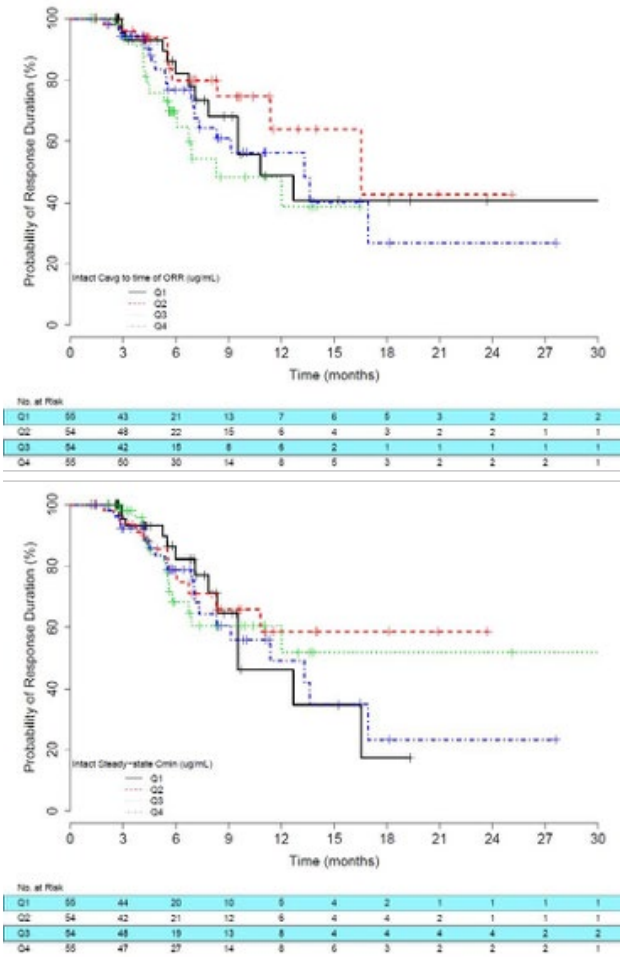


Cavg to ORR = average concentration to time of ORR; Intact = intact DS-8201a; ORR = objective response rate. Note: Dot and horizontal line corresponds to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical subject, and the indicated median exposure.

Table 19: Model-estimated probability for confirmed central ORR by intact DS-8201a exposure percentiles

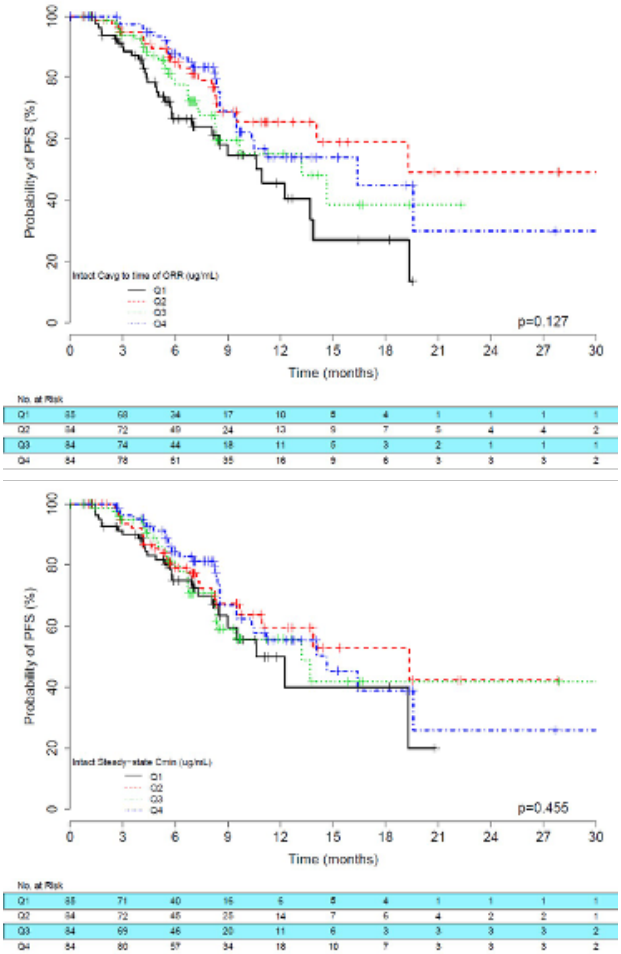
Intact DS--8201a Cavg to ORR Percentile	**Value (µg/mL)**	**Probability of Confirmed Central ORR**	
		Estimate	**90% CI**
Median	33.9	0.65	0.60, 0.69
5th percentile	16.7	0.56	0.47, 0.64
25th percentile	26.6	0.61	0.56, 0.66
75th percentile	41.4	0.69	0.63, 0.74
95th percentile	54.5	0.75	0.66, 0.82

Figure 19: Kaplan-Meier curves for DOR stratified by intact DS-8201a exposure



Cavg = average concentration; Cmin = minimum concentration; DOR = duration of response; Intact = intact DS-8201a; Q = quartile. Note: p-values are not shown as duration of response did not increase with increasing quartiles of exposure.

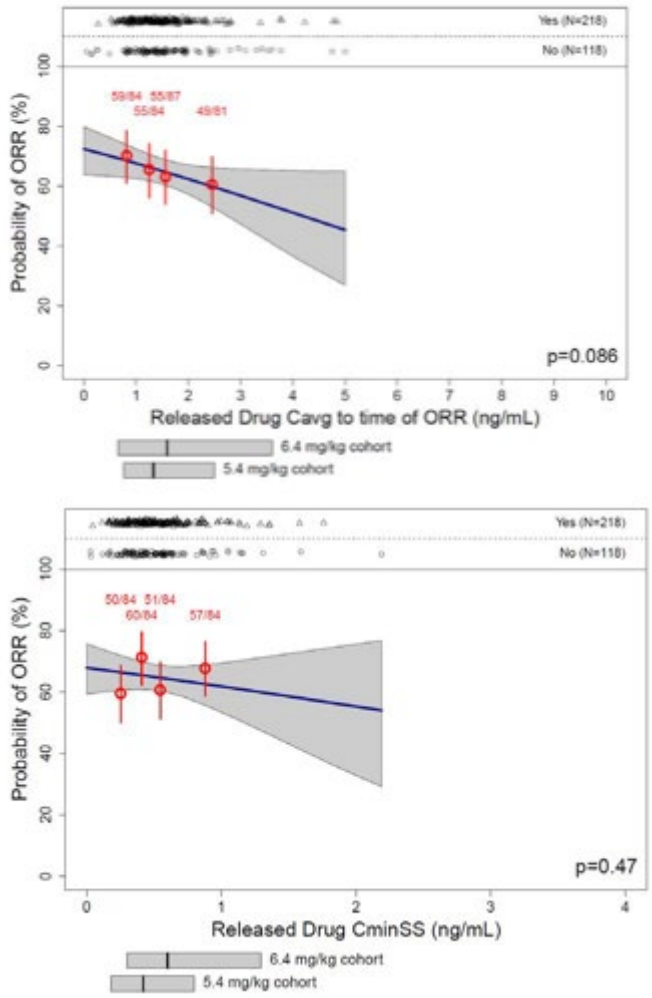
Figure 20: Kaplan-Meier curves for PFS stratified by exposure



Cavg to time of ORR = average concentration to time of objective resopnse rate; Cmin = minimum concentration; Intact = Intact DS-8201a; PFS = progression-free survival; Q = quartile.

For the exposure-efficacy analysis, the Applicant tested the Cmax, Cmin, and AUC after cycle 1 and at steady state for both trastuzumab deruxtecan and MAAA-1181a, in addition to Cav up to the end of the cycle during which event occurred for both trastuzumab deruxtecan and MAAA-1181a, as described. The exposure metric, that demonstrated the most significant relationship with the ORR, was intact Cavg. The was a similar trend for Cmin, but statistical significance was not reached (p = 0.174). Similar trend was observed with released drug Cavg and CminSS.

Figure 21 Confirmed central ORR exposure-response plots



Cavg = average concentration; CI = confidence interval; CminSS = minimum concentration at steady-state;objective response rate; N = number of subjects; ORR = objective response rate. Note: Plot shows probability of ORR versus exposure. Yes and No refer to if subjects experienced or did not experience ORR. Subjects are stratified into exposure quartiles. Red points are mean exposure and ORR rate per quartile. Vertical red bars are 90% CIs of the ORR rate. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The plot shows data for all dose groups. Horizontal bars below the plot illustrate the 5th, 50th, and 95th percentile of exposures for two selected dose groups of 5.4 and 6.4 mg/kg. The pvalue is for the slope of the logistic regression fit.

Complete analyses for E-R-A for efficacy. Exposure parameters used in the ER analysis for efficacy are provided in a selected manner. This approach is not clear and the Applicant should provide ORR data efficacy constructed against Cmax, and AUC metrics for both intact ADC and MAAA-1181a concentrations. None of the tested covariates, including body weight, sex, race, tumor size, and others had statistically significant relationship with the efficacy endpoints.

Exposure-Safety Analyses

The ER analyses for safety were conducted using a combined dataset from 5 clinical studies (DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, and DS8201-U201) and included the following safety endpoints:

(1) discontinuation associated with AEs; (2) dose reduction associated with AEs; (3) dose interruption associated with AEs; (4) AEs of ≥ Grade 3; (5) SAEs; (6) anemia, neutropenia, and thrombocytopenia;

severity grades derived using CTCAE grading criteria; (7) AESIs, ie, ILD/pneumonitis and decreased LVEF; severity grades derived using CTCAE grading criteria.

A number of patient-specific covariates were evaluated for their impact on ER relationship, including country (Japan, non-Japan Asia, non-Japan Other), age, sex, race (Asian, White, African American, other, unknown), HER2 status (positive, negative, unknown), ECOG PS (0 versus 1 or greater), lung metastases (present versus absent), number of prior non-hormonal cancer therapies ≥6, and baseline platelets, hemoglobin, and neutrophils.

Results

LVEF AEs based on AE data were too few for formal exposure-response analysis, so LVEF events based on ECHO data and CTCAE criteria were used instead. Because CTCAE criteria do not define a grade level of one for LVEF reduction, and there were only three events of Grade ≥3, Grade ≥2 by ECHO LVEF decrease was analysed as an endpoint.

A combined race-country covariate was used instead of separate race and country categories to reduce confounding and to capture key differences. In total, there were 310 Asians in Japan, 84 Asians not in Japan, and 245 non-Asians.

All AEs analysed showed an exposure-response relationship.

Table 20: Summary of exposure-response safety analyses

Endpoint	Selected exposure metric	Covariates
Discontinuation associated with AE	Intact DS-8201a steady-state AUC	prior therapies, race-country
Dose reduction associated with AE	Released drug Cavg through event cycle	HER2 status, **body weight**, prior therapies
Dose interruption associated with AE	Released drug Cavg through event cycle	race-country, prior therapies
Any AE, Grade ≥3	Released drug Cavg through event cycle	**body weight**
Any serious AE	Released drug Cavg through event cycle	ECOG PS
Anemia, Any Grade	Released drug Cavg through event cycle	sex, baseline hemoglobin, **body weight**
Anemia, Grade ≥3	Released drug Cavg through event cycle	ECOG PS, baseline hemoglobin, race-country, age
Neutropenia, Any Grade	Released drug Cavg through event cycle	baseline neutrophils, race country, male sex
Neutropenia, Grade ≥3	Released drug Cavg through event cycle	baseline neutrophils, race-country
Thrombocytopenia, Any Grade	Released drug Cavg through event cycle	baseline platelets, race-country
	Released drug Cavg through event cycle	prior therapies, race-country
	Intact DS-8201a steady-state Cmax	–
ILD, Any Grade	Intact DS-8201a steady-state AUC	race-country
ILD, Grade ≥3	Intact DS-8201a steady-state Cmax	–

AE = adverse event; AUC = area under the concentration-time curve; Cavg = average concentration; Cmax = maximum concentration; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction. All exposure relationships were significant ($p<0.05$) in univariate testing and multivariate testing.

Table 21: Summary of model-predicted endpoint rates at 5.4 and 6.4 mg/kg in all subjects

Endpoint	Population	Model-predicted Probability Estimate % (90% CI)		Difference between 6.4 and 5.4 mg/kg DS-8201a
		5.4 mg/kg DS-8201a	6.4 mg/kg DS-8201a	
ORR	All subjects	62.9 (55.4, 69.5)	67.5 (58.4, 76.0)	4.6
DIAE	All subjects	38.0 (35.0, 41.3)	39.9 (36.8, 43.3)	1.9
DISCAE	All subjects	11.3 (9.5, 13.9)	14.4 (12.4, 17.2)	3.1
DRAE	All subjects	20.8 (18.3, 23.8)	25.3 (22.6, 28.7)	4.5
GR3	All subjects	53.7 (50.2, 57.1)	60.6 (57.3, 63.6)	6.9
SERAE	All subjects	18.9 (16.3, 21.6)	21.9 (19.1, 24.9)	3.0
ANMLB	All subjects	90.1 (87.8, 92.0)	92.0 (89.8, 93.6)	1.9
ANM3LB	All subjects	12.3 (10.4, 14.8)	15.7 (13.5, 18.7)	3.4
NTPLB	All subjects	64.4 (61.0, 67.4)	69.1 (65.8, 71.9)	4.7
NTP3LB	All subjects	19.1 (16.8, 21.9)	22.4 (19.9, 25.4)	3.3
TCPLB	All subjects	58.0 (54.7, 61.3)	63.7 (60.5, 66.6)	5.7
TCP3LB	All subjects	7.6 (6.2, 9.6)	10.5 (8.7, 12.9)	2.9
LVEF2CV	All subjects	13.2 (11.1, 15.9)	17.2 (14.6, 20.1)	4.0
ILD-180	All subjects	7.0 (5.2, 7.8)	8.6 (6.9, 9.6)	1.6
ILD-360	All subjects	14.0 (11.5, 15.6)	17.0 (14.8, 19.2)	3.0
ILD3-180	All subjects	1.9 (1.3, 2.6)	3.2 (2.0, 4.0)	1.3
ILD3-360	All subjects	2.4 (1.7, 3.2)	4.0 (2.6, 5.1)	1.6

AE = adverse event; ANMLB = any anemia based on laboratory data; ANM3LB = Grade ≥3 anemia based on laboratory data; CI = confidence interval; DIAE = dose interruption associated with AE; DISCAE = discontinuation associated with AE; DRAE = dose reduction associated with AE; GR3 = Grade ≥3 AE; ILD-180, ILD-360 = Any Grade ILD AE at 180 days or 360 days; ILD3-180, ILD3-360 = Grade ≥3 ILD AE at 180 days or 360 days;
LVEF2CV = left ventricular ejection fraction decrease Grade ≥2 determined by echocardiogram; NTPLB = Grade ≥1 neutropenia AE based on laboratory data; NTP3LB = Grade ≥3 neutropenia AE based on laboratory data; ORR = objective response rate; SERAE = serious adverse events; TCPLB = Grade ≥1 thrombocytopenia AE based on laboratory data; TCP3LB = Grade ≥3 thrombocytopenia AE based on laboratory data.

Table 22: Summary of model-predicted endpoint rates at 5.4 and 6.4 mg/kg in non-Asians

Endpoint	Population	Model-predicted Probability Estimate % (90% CI)		Difference between 6.4 and 5.4 mg/kg DS-8201a
		5.4 mg/kg DS-8201a	6.4 mg/kg DS-8201a	
ORR	All	62.9 (55.4, 69.5)	67.5 (58.4, 76.0)	4.6
DIAE	Non-Asian	26.7 (22.2, 31.5)	28.4 (23.5, 33.2)	1.7
DISCAE	Non-Asian	10.3 (7.7, 13.8)	12.7 (9.4, 17.3)	2.4
DRAE	Non-Asian	19.5 (16.8, 22.8)	23.5 (20.5, 27.2)	4.0
GR3	Non-Asian	49.9 (46.1, 54.1)	56.4 (52.5, 60.3)	6.5
SERAE	Non-Asian	19.2 (16.6, 22.1)	22.2 (19.4, 25.6)	3.0
ANMLB	Non-Asian	88.6 (85.4, 90.9)	90.6 (87.5, 92.4)	2.0
ANM3LB	Non-Asian	8.2 (6.1, 11.4)	10.2 (7.6, 14.2)	2.0
NTPLB	Non-Asian	55.6 (50.5, 60.4)	60.1 (54.9, 65.2)	4.5
NTP3LB	Non-Asian	9.6 (7.3, 12.8)	10.5 (7.8, 14.3)	0.9
TCPLB	Non-Asian	48.0 (43.1, 53.3)	52.8 (47.8, 58.2)	4.8
TCP3LB	Non-Asian	3.7 (2.3, 6.0)	4.8 (3.0, 8.0)	1.1
LVEF2CV	Non-Asian	14.2 (12.1, 16.9)	18.7 (15.7, 22.3)	4.5
ILD-180	Non-Asian	5.7 (3.5, 7.2)	7.1 (4.6, 8.9)	1.4
ILD-360	Non-Asian	11.5 (7.8, 14.6)	14.3 (10.2, 18.0)	2.8
ILD3-180	Non-Asian	2.2 (1.5, 2.9)	3.8 (2.2, 4.8)	1.6
ILD3-360	Non-Asian	2.8 (1.9, 3.6)	4.9 (2.9, 6.1)	2.1

AE = adverse event; ANMLB = any anemia based on laboratory data; ANM3LB = Grade ≥3 anemia based on laboratory data; CI = confidence interval; DIAE = dose interruption associated with AE; DISCAE = discontinuation associated with AE; DRAE = dose reduction associated with AE; GR3 = Grade ≥3 AE; ILD-180, ILD-360 = Any Grade ILD AE at 180 days or 360 days; ILD3-180, ILD3-360 = Grade ≥3 ILD AE at 180 days or 360 days;
LVEF2CV = left ventricular ejection fraction decrease Grade ≥2 determined by echocardiogram; NTPLB = Grade

≥1 neutropenia AE based on laboratory data; NTP3LB = Grade ≥3 neutropenia AE based on laboratory data; ORR = objective response rate; SERAE = serious adverse events; TCPLB = Grade ≥1 thrombocytopenia AE based on laboratory data; TCP3LB = Grade ≥3 thrombocytopenia AE based on laboratory data.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The Applicant presented popPK analysis which was composed of two models: intact DS-8201a model and released drug (MAAA-1181a) model. Data from 5 studies were included in the model development.

The PK of intact DS-8201a was described by a two-compartment model with linear elimination. The PK of the released drug is described by a time-varying one-compartment model, which presented discrepancies. The Applicant also provided results of the tested simultaneous 2-analyte model. The simultaneous 2-analyte model provided similar parameter estimates compared to current model, with a slightly lower OFV value. However, the differences between the current released drug model and the simultaneous 2 analyte model are considered minor, as a result, the current structural model is considered acceptable.

The popPK models are able to predict individual trastuzumab deruxtecan and MAAA-1181a exposures adequately and are fit for the purposes of PopPK and exposure-response analyses.

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan and topoisomerase I inhibitor, DXd, were estimated to be 2.77 L and 27.4 L, respectively.

In vitro, the mean human plasma protein binding of DXd was approximately 97%.

In vitro, the blood to plasma concentration ratio of DXd was approximately 0.6.

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

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer, the clearance of trastuzumab deruxtecan was estimated to be 0.42 L/day and the clearance of DXd was 19.2 L/h. In cycle 3, the apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan and released DXd was approximately 7 days. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.
Based on non-compartmental analysis Tmax of DS8201a was approximately 2 hours, whereas Tmax of the MAAA-1181a was approximately 6.8 hours.

In vitro interactions

Effects of Enhertu on the pharmacokinetics of other medicinal products

In vitro studies indicate DXd does not inhibit major CYP450 enzymes including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A. *In vitro* studies indicate that DXd does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

Effects of other medicinal products on the pharmacokinetics of Enhertu

In vitro, DXd was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.

No clinically meaningful interaction is expected with medicinal products that are inhibitors of MATE2-K, MRP1, P-gp, OATP1B1, or BCRP transporters (see section 4.5).

Linearity/non-linearity

The exposure of trastuzumab deruxtecan and released DXd when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate inter-subject variability. Based on population pharmacokinetic analysis, inter-subject variability in trastuzumab deruxtecan and DXd elimination clearances was approximately 25% and for central volume of distribution was approximately 16% and 42%, respectively. The intra-subject variability in trastuzumab deruxtecan and DXd AUC values (area under the serum concentration versus time curve) was approximately 8% and 14%, respectively.

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 DXd.

Elderly

The population PK analysis showed that age (range: 23-96 years) did not affect the PK of trastuzumab deruxtecan.

Renal impairment

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

Hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, the impact of changes on pharmacokinetics of trastuzumab deruxtecan in patients with total bilirubin ≤ 1.5 times ULN, irrespective of AST level, is not clinically meaningful. There are insufficient data for patients with total bilirubin > 1.5 to 3 times ULN, irrespective of AST level, to draw conclusions, and no data is available for patients with total bilirubin > 3 times ULN, irrespective of AST level (see sections 4.2 and 4.4).

The routes and patterns of excretion were not specifically investigated in humans. The Applicant was asked to discuss whether findings from animal studies, which suggest that majority of the MAAA-1181a is excreted unchanged in faeces, could be extrapolated to humans. Metabolism of MAAA-1181a by CYP3A4 into metabolite MAAA-1468a was suggested to be an important elimination pathway. This would suggest a different fate of MAAA-1181a in human compared to animal species and this would limit the use of PK/excretion and safety data obtained in animals to extrapolate to the human situation. It was argued that even if the CYP3A was identified to be the primary CYP enzyme metabolizing MAAA-1181a, it was not the primary elimination pathway for MAAA-1181a in humans, since the DDI study showed around 20% increase in MAAA-1181a AUC values and did not change the elimination half-life. During in vitro studies with human liver microsomes, one metabolite was identified (MA-1468a, product of CYP3A metabolism). However, the concentration of the metabolite accounted for <1,5% of the parent compound concentration. The MA-1468a was not identified in studies with cryopreserved

hepatocytes. The Applicant is recommended to conduct additional study using liver microsomes from other species in order to investigate the inconsistency observed in metabolism between the in vitro human liver microsomes versus cryopreserved hepatocyte studies and in vivo studies. The results of the study are expected to be available by June 2021.

After single dose ranging from 0.8 mg/kg to 8.0 kg/kg administration, Cmax increased dose-proportionally for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a. Tmax after single dose for trastuzumab deruxtecan varied from 1.95 to 4.12 hours, and was longer in 1.6 and 3.2 mg/kg doses. Tmax was more consistent for MAAA-1181a, approximately 6 hours. AUCinf increased in a dose proportionate manner with increasing dose for the trastuzumab deruxtecan and total anti-HER2 antibody, and for the MAAA-1181a, the AUCinf increased dose-proportionally up to 5.4 mg/kg dose, than at the 6.4 mg/kg dose decreased to 34.4 ng·d/mL, and with higher dose of 8.0 mg/kg increased to 44.5 ng·d/mL. Nevertheless, it is deemed that the dose-proportionality is maintained.

The exposure of trastuzumab deruxtecan and released DXd when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate inter-subject variability. Based on population pharmacokinetic analysis, inter-subject variability in trastuzumab deruxtecan and DXd elimination clearances was approximately 25% and for central volume of distribution was approximately 16% and 42%, respectively. The intra-subject variability in trastuzumab deruxtecan and DXd AUC values (area under the serum concentration versus time curve) was approximately 8% and 14%, respectively.

Data on Cl for total anti-HER2 antibody and MAAA-1181a are lacking. Clearance was decreasing with increasing doses of trastuzumab deruxtecan. However, no clearance data is suggested for the parts of the ADC: total anti-HER2 antibody and MAAA-1181a. The Applicant presented the clearance values for total anti-HER2 antibody, pooling the data from studies DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, and DS8201-A-U201. The clearance of anti-HER2 antibody (trastuzumab) is decreasing with increasing dose, but the limiting factor for comparison is small number of patients in the lower doses' groups. The clearance of MAAA-1181a based on popPK analysis was 19.2 L/h (460.8 L/day). The MAAA-1181a was not administered by itself in any clinical studies, and no mass balance study was performed in humans.
Steady state was achieved in approximately 42 days. Following administration of 6.4 mg/kg dose, the AUCtau of trastuzumab deruxtecan in the Cycle 3 was 35% higher than in Cycle 1.

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 DXd.

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

As a result, no dose adjustment is recommended for this patient population. Patients with severe renal impairment were not included, thus no dosing recommendation could be provided.

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, the impact of changes on pharmacokinetics of trastuzumab deruxtecan in patients with total bilirubin ≤ 1.5 times ULN, irrespective of AST level, is not clinically meaningful. There are insufficient data for patients with total bilirubin > 1.5 to 3 times ULN, irrespective of AST level, to draw conclusions, and no data is available for patients with total bilirubin > 3 times ULN, irrespective of AST level (see sections 4.2 and 4.4).

No dosing recommendations could be provided for subjects with moderate or severe hepatic impairment. The SmPC reflects that these patients should be monitored carefully (see SmPC section 4.4).

Elevated AST and total bilirubin were covariates of MAAA-1181a exposure and higher MAAA-1181a was associated with increased incidence of AEs (see discussion on clinical safety). The applicant plans to collect PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing clinical studies with trastuzumab deruxtecan and provide an overall assessment of these 10 subjects with moderate hepatic impairment (see RMP).

Subjects with body weight of 86kg (95th percentile) have higher exposure values of DS8201a (AUC) and MAAA-1181a (AUC and Cmax) compared to typical subject, as the exposure is increased with increasing weight. The exposure values obtained by the subjects in 95th percentile fall out of conventional bioequivalence limits. However, it was observed in the exposure-response safety analysis, that higher body weight (i.e. more than 60 kg) was associated with lower risk of anaemia, any grade 3 or more AE, and dose reduction associated with AEs, even though there was a clear relationship with higher exposures and more safety issues. The exponential factor of body-weight on clearance and volume was <0.5, which suggests that flat dosing rather than dosing based on body weight would result in lower intersubject variability. Further, the applicant was requested to discuss the therapeutic window of trastuzumab deruxtecan and if capping of the dose for subjects with high body weight is needed, since the patients in the 75th percentile of concentrations tend to have more SEAs, Grade 3 AEs and other safety issues. PK simulations for the recommended 5.4 mg/kg dose and a flat dose of 310 mg (calculated with 5.4 mg/kg multiplied by median body weight) in breast cancer patients indicated a similar intersubject variability and similar distributions of all exposure matrices for both intact and released drug. Exposures in subjects with body weight >86 kg (95th percentile of body weight) were 22% to 30% higher compared to a typical subject (57.8 kg). Rates of all AEs endpoints in subjects treated with 5.4 mg/kg trastuzumab deruxtecan weighing > 86 kg were generally similar with those in subjects with body weight ≤ 86 kg and ORR rate was slightly higher in subjects with body weight >86 kg. Based on these results capping of the dose for subjects with higher body-weight is considered not necessary (see SmPC section 4.2). In the exposure-response analyses for safety, the majority of subjects with the 75th percentile highest trastuzumab deruxtecan and MAAA-1181a concentrations were from the higher dose levels of 6.4 mg/kg to 8.0 mg/kg which is likely to explain the increased SEAs, Grade 3 AEs and other safety issues in the 75th percentile group.

DS-8201a dose does not need to be adjusted for albumin level, age, gender, race. Results from popPK analysis indicate that race does not influence PK of both DS-8201a or MAAA-1181a, although some effects on clearance and peripheral volume of distribution of DS-8201a were identified in Japanese patients.

Given the information from the nonclinical data, the MAAA-1181a exposure may have increased when OATP1B inhibitors are administered concomitantly. To further assess this possible interaction in vivo, the Applicant had performed the study DS8201-A-A104 with ritonavir as a double inhibitor of OATP1B and CYP3A. Since ritonavir is also a potent CYP3A inhibitor, to clarify the role of OATP1B inhibition, Cohort 2 was investigated using itraconazole as probe. Since the MAAA-1181a was not found to be UGT substrate, and in vitro or in the rat or monkey no conjugated metabolites of MAAA-1181a were detected, the DDI risk through the UGT enzyme is not evaluated. The exposure of MAAA-1181 increased by 22% in usage together with ritonavir and 18% in usage with itraconazole. This magnitude of increase of AUC is deemed clinically insignificant. However, as the results of the in vitro induction assay cannot be interpreted at this moment because too high concentrations of MAAA-1181a were used, the in vitro induction study should be repeated with lower, clinically relevant MAAA-1181a concentrations. The Applicant is recommended to repeat the in vitro induction assay with lower, clinically relevant MAAA-1181a concentrations.

Pharmacodynamics

Trastuzumab deruxtecan (DS-8201a) has been investigated in a two-part dose-escalation and dose-expansion Phase 1 study in Japan (DS8201-A-J101) and in an open-label two-part global Phase 2 study (DS- 8201-A-U201). Three other Phase 1 studies of DS-8201a (Studies DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104) also provide useful safety information for exposure-response analysis. Study DS8201-A-J102 was designed to assess DS-8201a potential for QTc prolongation and to explore the PK profile of DS-8201a after multiple dosing.

Trastuzumab deruxtecan at 6.4 mg/kg dose did not result in a positive tQT study. What is notable; however, is that there was a positive trend towards increase in the change of QTcF with increasing MAAA-1181a concentrations, and at the highest concentrations, the upper bound of the 90% CI exceeded 10 ms. Moreover, the study was conducted solely with Japanese subjects. Since the systemic exposures of trastuzumab deruxtecan and MAAA-1181a in the QT study (6.4 mg/kg Q3W) are higher than those in the intended EU population, including subjects with high body weight, at the recommended dosing regimen because of the dose difference (6.4 mg/kg Q3W in the QT study vs. the recommended 5.4 mg/kg Q3W in the EU population). Overall, the QTc interval in the intended EU population as the upper bound of the 90% CI for ΔQTcF (2.7 ms) at the recommended dose of 5.4 mg/kg is estimated to be below the 10 ms, the estimated MAAA-1181a exposures for subjects with high body weight at 5.4 mg/kg dose are also covered by the exposure values at the 6.4 mg/kg dose evaluated in the QT study.

Exposure-efficacy was evaluated in HER2-positive breast cancer subjects in Studies J101 and U201 for ORR, PFS, and DOR.

For the exposure-efficacy analysis, the Applicant tested the Cmax, Cmin, and AUC after cycle 1 and at steady state for both trastuzumab deruxtecan and MAAA-1181a, in addition to Cav up to the end of the cycle during which event occurred for both trastuzumab deruxtecan and MAAA-1181a, as described.

Slope estimates were either very shallow of statistically non-significant ($p>0.05$), thus revealing that candidate exposure markers are not informative for E-R-A associations. None of the tested covariates, including body weight, sex, race, tumor size, and others had statistically significant relationship with the efficacy endpoints.

To evaluate exposure-safety relationships in all subjects in Studies J101, J102, A103, A104, and U201 the following treatment-emergent AEs were selected: (1) discontinuation associated with AEs, (2) dose reduction associated with AEs, (3) dose interruption associated with AEs, (4) AEs of Grade ≥3, (5) serious AEs, (6) anemia, (7) neutropenia, (8) thrombocytopenia, and AEs of special interest (i.e., (9) ILD and decreased (10) LVEF). The Applicant has submitted the data on AEs and ORR for patients (n = 135) who received reduced doses of trastuzumab deruxtecan. The Applicant argues, that in the exposure-response analyses, average concentrations for both intact trastuzumab deruxtecan and MAAA-1181a until the dosing cycle of the event (for each safety and efficacy endpoint evaluated in the analyses) were evaluated, therefore, no additional exposure-response relationships were presented for subgroup with reduced doses. The overall rate of AEs and the efficacy metric (ORR) did not present any significant differences between the patients who received full and reduced doses. The Applicant will submit additional data from the Phase 3 study, once they are available (see discussion on clinical efficacy).

For the exposure-safety analysis, all safety endpoints, that were evaluated, did show a statistically significant ($p \leq 0.05$) E-R relationship with at least one of the exposure parameters of trastuzumab deruxtecan or MAAA-1181a. Trastuzumab deruxtecan steady-state exposure (AUCss) was a statistically significant predictor for (1) discontinuation associated with AEs and (7) ILD (any grade), trastuzumab deruxtecan Cmax,ss was a statistically significant predictor for ILD ≥Grade 3 and (6)

decreased LVEF, and MAAA-1181a Cav was a significant predictor for all other evaluated safety endpoints. For discontinuations due to AEs, the covariates that were evaluated as significant was race-country and number of prior therapies. However, it is not unexpected, that discontinuation was higher in patients with 6 or more lines of prior therapies (see discussion on clinical safety).

The probability of dose reduction was higher in the highest quartiles, and significant covariates were detected: lower probabilities of dose reduction due to AEs were in patients weighting more than 60 kg, having more than 6 lines of previous treatment, and having HER2 receptor status negative or unknown. The rate of dose interruption was up to 50.6% in the 4th quartile, and the modelling showed, that having more than 6 lines of previous treatment decreases the risk of dose interruption due to AEs. For the grade ≥3 AEs, rate of those in the 2nd quartile was 49.4% and increased with increasing Cavg. Even though the probability of grade ≥3 AE appeared to increase with increasing released drug exposure, the same was lower in subjects with body weight ≥60 kg compared with subjects weighing <60 kg. No other covariates were identified.

Higher ECOG PS score (i.e. 1 or more) was associated with higher probability for SAEs. Higher weight was a covariate, predicting lower probability of AE, and for grade 3 anaemia, this was also true for higher ECOG PS score (i.e. 1 or more). Low baseline haemoglobin was a clear predictor of anaemia,neutropenia, and thrombocytopenia.. No statistically significant covariates were identified for LVEF decrease; most accurate exposure metrics were Cmax,ss of the intact drug and the Cavg of the released drug. For the ILD, both intact drug AUCss and Cmax,ss were the most accurate exposure metrics. Only race (Asian-Japan vs Asian-Non-Japan) were identified as significant covariates. Higher weight (i.e. > 60 kg) predicted lower risk of dose reduction because of AEs, any grade ≥ 3 AEs, or anaemia, but this may well be a reflection of these patients being in a better health state.

Statistically significant relationships were found for all safety endpoints evaluated ($p<0.05$), with a greater rate of AEs for the 6.4 mg/kg dose group compared to the 5.4 mg/kg dose group.

Overall, dose-response projections suggested an increase in efficacy (4.6% increase in ORR), but also corresponding increases in most AEs, i.e. a dose increase from 5.4 to 6.4 mg/kg increases the incidence of Grade ≥3 AEs by 6.9%, the incidence of Grade ≥2 by ECHO LVEF reductions by 4.0%, and the incidence of Grade 3 or greater ILD events at 360-d by 1.6%.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK profile of the trastuzumab deruxtecan has been well characterised. Further, the Applicant is recommended to conduct additional study using liver microsomes from other species in order to investigate the inconsistency observed in metabolism between the in vitro human liver microsomes versus cryopreserved hepatocyte studies and in vivo studies. In addition, the Applicant is recommended to repeat the in vitro induction assay with lower, clinically relevant MAAA-1181a concentrations.

2.5. Clinical efficacy

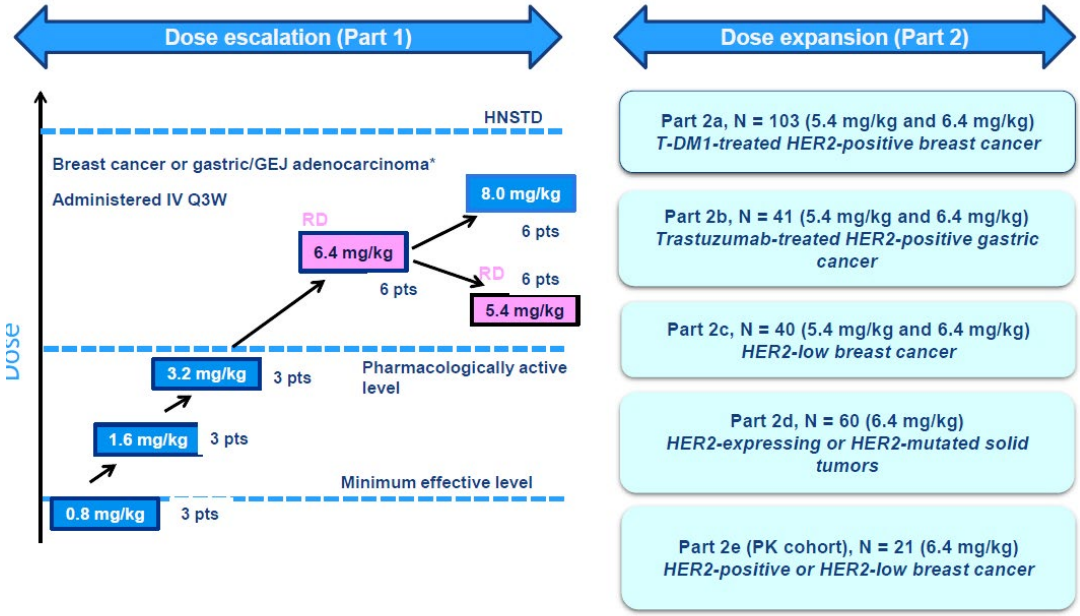
2.5.1. Dose response study

Study DS8201-A-J101 (J101): Phase 1, Two-part, Multicenter, Non-randomized, Open-label, Multiple-dose, First-in-human Study of DS-8201a, in Subjects with Advanced Solid Malignant Tumors.

Methods

Study J101 was a Phase 1, 2-part (Dose Escalation followed by Dose Expansion), multicenter, non-randomized, open-label, multiple-dose, first-in-human study of trastuzumab deruxtecan, with study sites in Japan and the US. The Dose Escalation (Part 1, n=27) was intended to identify the MTD or the RP2D of trastuzumab deruxtecan. Part 1 used modified continuous reassessment method with escalation with overdose control design with at least 3 subjects evaluable for assessment of dose-limiting toxicity (DLT) per dose level (0.8, 1.6, 3.2, 5.4, 6.4, and 8.0 mg/kg). The subsequent Dose Expansion (Part 2) was intended to further assess the safety, tolerability, and efficacy of trastuzumab deruxtecan at the MTD/RP2D. Part 2 enrolled patients with solid tumors and with human epidermal growth factor receptor 2 (HER2) expression including low HER2 levels and HER2 mutation.

Figure 22 Study J101 Design with Actual Enrollment



- HER2 status was assessed on archival tissue in both Parts 1 and 2

EWOC = escalation with overdose control; FL-DP1 = frozen liquid drug product 1; FL-DP2 = frozen liquid drug product 2; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = immunohisotchemistry; ISH = in situ hybridization (fluorescent [FISH] or dual color [DISH]); mCRM = modified continuous reassessment method; NGS = next generation sequencing; T DM1 = trastuzumab emtansine

Study Participants

The study included adult patients (≥20 years in Japan, ≥18 years in the USA) with multiple advanced/unresectable solid tumors and with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; left ventricular ejection fraction (LVEF) ≥50% within 28 days before registration; adequate organ function as defined in the protocol within 7 days before registration; adequate treatment washout period before registration, as defined in the protocol; able to provide written informed consent; willing to provide pre-existing diagnostic or resected tumor samples; and life expectancy of ≥3 months.

Part 1 (Dose Escalation) included patients with pathologically documented advanced/unresectable or metastatic breast cancer (BC) or gastric or gastroesophageal (GEJ) adenocarcinoma refractory to or

intolerable with standard treatment, or for which no standard treatment was available. There were no requirements regarding HER2-expression.

Part 2 (Dose Expansion) consisted of 5 cohorts with different tumor diagnosis criteria, including HER2-expression Of relevance for the current application is cohort 2a, which included patients with:

- pathologically documented advanced/unresectable or metastatic BC
- human epidermal growth factor receptor 2 (HER2) overexpression (immunohistochemistry [IHC]) 3+ or in situ hybridization [ISH]+ (fluorescence in situ hybridization [FISH] or dual in situ hybridization [DISH])
- refractory to or intolerable with standard treatment, or for which no standard treatment is available;
- treated with T-DM1;
- measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients were included based on local laboratory HER2 testing and confirmed by central laboratory testing.

Patients with clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms were excluded. Patients with treated brain metastases that were no longer symptomatic and who required no treatment with steroids may have been included in the study if they had recovered from the acute toxic effect of radiotherapy.

Main exclusion criteria included significant comorbidities (e.g. congestive heart failure, myocardial infarction/unstable angina within 6 months, uncontrolled infection). Patients with a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening were also excluded.

Treatments

Patients received trastuzumab deruxtecan intravenously on a day 1 of a 21-day cycle. Doses from 0.8 mg/kg up to 8.0 mg/kg were administered in the dose escalation phase. Dose escalation of DS-8201a to determine the MTD/RP2D was guided by the modified continuous reassessment method (mCRM) using a Bayesian logistic regression model following the escalation with overdose control (EWOC) principle (Neuenschwander et al. 2008[4]).

Two doses (5.4 mg/kg and 6.4 mg/kg) were chosen for continued evaluation in the Dose Expansion phase in Part 2. Assignment of individual subjects to each dose was performed in sequential blocks of months, with subjects assigned to a certain dose based on the time period of enrollment, and efforts were made to enroll to both doses equally.

Two types of drug product, FL-DP1 (part 1 and part 2a, 2b, 2c, 2d) and FL-DP2 (part 2e), were supplied in this study.

Treatment continued until there was no longer clinical benefit from therapy, withdrawal of consent, or until unacceptable toxicity occurred.

[4] Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008; 27(13):2420-39.

Concomitant treatment

Cytochrome P450 (CYP) 3A4 strong inhibitors and strong inducers were prohibited. If use of CYP3A4 inhibitors was unavoidable, treatment with trastuzumab deruxtecan should be delayed when possible or patients should be closely monitored for adverse reactions in case treatment could not be delayed.

Organic anion transporting polypeptide (OATP) inhibitors were also inhibited and in case concomitant use was unavoidable, the same approach as for CYP3A4 inhibitors was to be followed.

Outcomes/endpoints

Efficacy endpoints:

- Objective response rate (ORR), defined as the proportion of subjects who achieve either (confirmed) complete response [CR] or partial response [PR] per RECIST v1.1
- Disease control rate (DCR), defined as the sum of the proportion of subjects who achieve CR, PR, or stable disease (SD)
- Clinical benefit rate (CBR), defined as the sum of the proportion of subjects who achieve CR, PR, or >6 months of SD
- Duration of response (DoR)

Other efficacy endpoints include amongst others percent change in sum of diameters of target lesions from baseline to best post-baseline measurement, time to response (TTR) and the time-dependent endpoints PFS and OS.

Safety endpoints:

Safety endpoints will include DLTs, SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings. TEAEs will be graded according to the NCI-CTCAE. Dose escalation will be determined by the incidence of DLTs.

Sample size

For the Dose Expansion part (Part 2), approximately 260 subjects (100 subjects for Part 2a, 40 subjects for Part 2b, 20 to 40 subjects for Part 2c, 60 subjects for Part 2d and 20 subjects for Part 2e) will be enrolled.

Cohort 2a: If target ORR is more than 15% (null hypothesis: ORR ≤ 0.15, alternative hypothesis: ORR > 0.15), then the probability of less than 9 responders out of 100 subjects will be less than 5%. The probability that more than 21 responders out of 100 subjects (ORR > 21%) are observed will be less than 5% under the null hypothesis with ORR ≤ 0.15 but more than 90% under alternative hypothesis with ORR = 0.35.

Statistical methods

Efficacy analysis

Efficacy assessments were based on tumor assessments, using computerized tomography (CT) scan or magnetic resonance imaging (MRI) (spiral CT scan or MRI with ≤5 mm cuts) performed at screening and every 6 weeks in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks while the subject remained on study drug.

Efficacy analyses were to be performed on the Enrolled Analysis Set (intent-to-treat, ITT), with analyses of ORR, DCR, and CBR also performed on the Response Evaluable Set (at least one dose of trastuzumab deruxtecan and measurable tumors by ICR at baseline). Efficacy data from subjects dosed

at the RP2D in the Dose Escalation phase were pooled with the efficacy data from the corresponding tumor type cohorts in the Dose Expansion phase to calculate the overall efficacy estimates. Efficacy analyses were performed based on both ICR and investigator review, with ICR-based response rates in the Enrolled Analysis Set considered to be the main efficacy variables of interest.

The best overall response (BOR) of CR/PR was considered to be confirmed only if the criteria were met at a subsequent time point (at least 4 weeks from the time a response of CR/PR was first observed). Confirmed and unconfirmed BOR were to be summarized descriptively using the number and percentage of subjects along with exact 95% confidence intervals (CIs) based on Clopper and Peterson methods. For ORR, DCR, and CBR, point estimates and 95% exact binomial CIs were to be provided. Time-to-event variables including DoR, duration of SD, TTR, PFS, and OS were to be summarized descriptively using the Kaplan-Meier method. Kaplan-Meier estimates of median DoR, median duration of SD, median PFS, and median OS and the 95% CIs were to be provided. Kaplan-Meier curves for PFS and OS were to be presented.

Subgroup analyses were planned for selected efficacy endpoints by HER2 expression level, prior treatments, metastases (location of organ), other evaluable biomarkers, selected demographic and baseline characteristics, and tumor type, as appropriate, to assess the homogeneity of the estimate of treatment effect.

Safety analysis

The primary analysis is to assess the safety and tolerability of trastuzumab deruxtecan in subjects with advanced solid malignant tumors and to determine the MTD/RP2D or establish the safety and tolerability of the maximum administered dose of trastuzumab deruxtecan. The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or the last subject enrolled in Part 2 of the study has completed approximately 6 months of study drug treatment.

Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Potential events of interstitial lung disease (ILD) were adjudicated by an independent ILD Adjudication Committee. A DLT was defined as any TEAE not attributable to disease or disease-related processes that occurred during the DLT evaluation period (Day 1 to Day 21 in Cycle 1 of Part 1) and was Grade 3 or above according to NCI CTCAE v4.03, with some exceptions that were pre-defined in the protocol.

The Safety Analysis Set will include all subjects who received at least one dose of trastuzumab deruxtecan.

Results

Overall, 292 subjects were enrolled in the study at 8 study centers in the United States and 6 study centers in Japan.

Within the dose escalation part including 27 patients, the MTD was not reached up to 8.0 mg/kg as no DLTs were observed. Across all doses combined, 40.7% (95% CI: 22.4, 61.2) achieved a confirmed ORR by ICR, and 96.3% (95% CI: 81.0, 99.9) achieved disease control. A dose-response for activity was observed, with most of the responses PRs and the greatest response to treatment (best percent change from baseline in sum of diameters of target lesions) observed in patients treated with 5.4 mg/kg or higher. Doses of 5.4 mg/kg and 6.4 mg/kg were administered in the dose expansion part.

HER2-positive breast cancer cohort (escalation and expansion part)

Study disposition

A total of 118 HER2-positive BC subjects were enrolled and assigned to receive 5.4 mg/kg (n=51) or 6.4 mg/kg of trastuzumab deruxtecan (n=67) based on the dose escalation and dose expansion part. A total of 116 subjects received at least 1 dose of 5.4 (n=50) or 6.4 mg/kg (n=66). At DCO, median duration of exposure was 8.5 months (range: 0.7-31.0 months) and 9.0 months (range 1.4-35.0 months) for the 5.4 mg/kg and 6.4 mg/kg dose group, respectively (safety analysis set). Study duration was 9.8 months (range: 0.8-30.4 months) and 10.4 months (1.5-34.4 months) for the 5.4 mg/kg and 6.4 mg/kg dose group, respectively. For the 5.4 mg/kg dose group, 20% of patients were on study treatment at the time of DCO. Most common reasons for treatment discontinuation were progressive disease per RECIST (40.0%), AEs (18.0%) and clinical progression per investigator (10.0%). For the 6.4 mg/kg dose group, 18.2% of patients were still on study treatment. Most common reasons for treatment discontinuation were progressive disease per RECIST (30.3%), AEs (33.3%) and clinical progression per investigator (18.2%).

Baseline demographic and disease characteristics

Recommended dose 5.4 mg/kg: All but one patient were female, median age was 58.0 years (range 28-77; 66.7% <65 yrs), 37.3% were white and 52.9% Asian, 58.8% were from the US and most patients had an ECOG PS of 0 (64.7%). A total of 43.1% had mild renal impairment and 7.8% had moderate renal impairment at baseline. A total of 45.1% had mild hepatic impairment, no patients with moderate of severe hepatic impairment were included.

Median time from initial diagnosis was 73.5 months (range: 15.2-244.5 months). Most patients were hormone receptor status positive (HR+, 62.7%; ER+: 60.8% and PR+: 41.2). Lung metastases were observed in 37.3% patients, 23.5% had liver metastases, 11.8% had brain metastases and 39.2% had bone metastases. Most patients received ≥5 prior cancer regimens (82.4%, median 7; range 2-17) for locally advanced/metastatic BC; a total of 98.0% received prior trastuzumab, 84.3% received prior pertuzumab and all patients received prior T-DM1.

Baseline characteristics were in general comparable between dose groups, except for greater proportion of Asian subjects in the 6.4 mg/kg group (67.2% vs 52.9%), more patients with positive HR status (74.6% vs 62.7%) as well as a longer median time from initial diagnosis in patients (91.1 vs 73.5 months) with 6.4 mg/kg.

Patients were included based on local laboratory HER2 testing and confirmed by central laboratory testing. Based on local testing for the 5.4 mg/kg group, 78.4% of patients were IHC 3+ and 21.6% were ISH+. Based on central testing, 51.0% of patients were IHC 3+ and 11.8% were ISH+. Four patients had missing data for central testing.

Outcomes and estimations

Tumor response and duration of response

Efficacy results on tumor response are summarized below. Confirmed ORR by ICR was 51.0% (95% CI: 36.6, 65.2) for the 5.4 mg/kg; CR was observed in 3.9% of patients and PR in 47.1% of patients. Median duration of confirmed response by ICR was 12.7 months (95% CI: 6.7, -). A total of 53.8% of patients were censored. Median time to confirmed response by ICR was 2.7 months (95% CI: 1.5, 2.9).

Results for the 6.4 mg/kg were largely comparable to that of the 5.4 mg/kg group, except for a higher rate of CR by ICR (11.9% vs 3.9%).

Confirmed DCR was 88.2% and 95.5% in the 5.4 mg/kg and 6.4 mg/kg dose group, respectively.

Table 8.1: Efficacy Result in Dose Escalation (Enrolled Analysis Set)

Efficacy Variable	Cohort 1 (0.8 mg/kg) (N=3)	Cohort 2 (1.6 mg/kg) (N=3)	Cohort 3 (3.2 mg/kg) (N=3)	Cohort 4 (5.4 mg/kg) (N=6)	Cohort 5 (6.4 mg/kg) (N=6)	Cohort 6 (8.0 mg/kg) (N=6)	Total (N=27)
Confirmed Objective Response Rate (ORR), n (%) (95% CI[a])							
ORR by ICR	0 (0.0, 70.8)	1 (33.3) (0.8, 90.6)	0 (0.0, 70.8)	5 (83.3) (35.9, 99.6)	2 (33.3) (4.3, 77.7)	3 (50.0) (11.8, 88.2)	11 (40.7) (22.4, 61.2)
ORR by Investigator	0 (0.0, 70.8)	0 (0.0, 70.8)	0 (0.0, 70.8)	5 (83.3) (35.9, 99.6)	4 (66.7) (22.3, 95.7)	3 (50.0) (11.8, 88.2)	12 (44.4) (25.5, 64.7)
Confirmed Best Overall Response by ICR, n (%)							
Complete Response (CR)	0	0	0	1 (16.7)	1 (16.7)	0	2 (7.4)
Partial Response (PR)	0	1 (33.3)	0	4 (66.7)	1 (16.7)	3 (50.0)	9 (33.3)
Stable Disease (SD)	3 (100.0)	2 (66.7)	2 (66.7)	1 (16.7)	4 (66.7)	3 (50.0)	15 (55.6)
Progressive Disease (PD)	0	0	1 (33.3)	0	0	0	1 (3.7)
Non-evaluable (NE)	0	0	0	0	0	0	0
Confirmed Best Overall Response by Investigator (n, %)							
Complete Response (CR)	0	0	0	0	0	0	0
Partial Response (PR)	0	0	0	5 (83.3)	4 (66.7)	3 (50.0)	12 (44.4)
Stable Disease (SD)	3 (100.0)	3 (100.0)	1 (33.3)	1 (16.7)	2 (33.3)	3 (50.0)	13 (48.1)
Progressive Disease (PD)	0	0	2 (66.7)	0	0	0	2 (7.4)
Non-evaluable (NE)	0	0	0	0	0	0	0
Disease Control Rate[b] (DCR) n (%) (95% CI[a])							
DCR by ICR	3 (100.0) (29.2, 100.0)	3 (100.0) (29.2, 100.0)	2 (66.7) (9.4, 99.2)	6 (100.0) (54.1, 100.0)	6 (100.0) (54.1, 100.0)	6 (100.0) (54.1, 100.0)	26 (96.3) (81.0, 99.9)
DCR by Investigator	3 (100.0) (29.2, 100.0)	3 (100.0) (29.2, 100.0)	1 (33.3) (0.8, 90.6)	6 (100.0) (54.1, 100.0)	6 (100.0) (54.1, 100.0)	6 (100.0) (54.1, 100.0)	25 (92.6) (75.7, 99.1)

CI = confidence interval; ICR = independent central review; ORR = objective response rate
[a] 95% exact binomial confidence interval
[b] DCR was calculated as the proportion of subjects demonstrating CR, PR, or SD for a minimum of 6 weeks (±1week) from the first dosing date
Data cutoff date: 01 Feb 2019
Source: Table 14.2.1.1

Table 8.4: Efficacy Results in HER2-positive Breast Cancer (Enrolled Analysis Set)

Efficacy Variable	Subjects with HER2-positive Breast Cancer		
	5.4 mg/kg (N=51)	6.4 mg/kg (N=67)	Total (N=118)
Confirmed Objective Response Rate (ORR) n (%) (95% CI[a])			
ORR by ICR	26 (51.0) (36.6, 65.2)	36 (53.7) (41.1, 66.0)	62 (52.5) (43.1, 61.8)
ORR by Investigator	29 (56.9) (42.2, 70.7)	42 (62.7) (50.0, 74.2)	71 (60.2) (50.7, 69.1)
ORR by ICR in Response Evaluable Set, n/N	26/45(57.8) (42.2, 72.3)	34/57(59.6) (45.8, 72.4)	60/102(58.8) (48.6, 68.5)
Confirmed Best Overall Response by ICR (n, %)			
Complete Response (CR)	2 (3.9)	8 (11.9)	10 (8.5)
Partial Response (PR)	24 (47.1)	28 (41.8)	52 (44.1)
Stable Disease (SD)	19 (37.3)	28 (41.8)	47 (39.8)
Progressive Disease (PD)	4 (7.8)	1 (1.5)	5 (4.2)
Non-evaluable (NE)	2 (3.9)	2 (3.0)	4 (3.4)
Confirmed Best Overall Response by Investigator (n, %)			
CR	2 (3.9)	3 (4.5)	5 (4.2)
PR	27 (52.9)	39 (58.2)	66 (55.9)
SD	17 (33.3)	21 (31.3)	38 (32.2)
PD	3 (5.9)	3 (4.5)	6 (5.1)
NE	2 (3.9)	1 (1.5)	3 (2.5)
Duration of Confirmed Response (DoR), Median Months[c] (95% CI)			
DoR by ICR	12.7 (6.7, -)	13.6 (7.3, -)	13.3 (9.5, -)
DoR by Investigator	17.1 (6.9, 18.8)	13.6 (7.6, -)	17.1 (9.8, 20.0)
Confirmed Disease Control Rate,[b] (DCR) (n, %) (95% CI[a])			
DCR by ICR	45 (88.2) (76.1, 95.6)	64 (95.5) (87.5, 99.1)	109 (92.4) (86.0, 96.5)
DCR by Investigator	46 (90.2) (78.6, 96.7)	63 (94.0) (85.4, 98.3)	109 (92.4) (86.0, 96.5)
Time to Confirmed Response by ICR, Median Months[c] (95% CI)	2.7 (1.5, 2.9)	2.8 (1.4, 2.9)	2.8 (1.5, 2.8)
Duration of Confirmed Stable Disease by ICR, Median Months[c] (95% CI)	13.7 (5.5, -)	9.3 (5.6, -)	10.5 (8.2, -)

Table 8.4: Efficacy Results in HER2-positive Breast Cancer (Enrolled Analysis Set) (Continued)

Efficacy Variable	Subjects with HER2-positive Breast Cancer		
	5.4 mg/kg (N=51)	6.4 mg/kg (N=67)	Total (N=118)
Progression-free Survival (PFS)			
PFS by ICR			
Events (n, %)	22 (43.1)	28 (41.8)	50 (42.4)
Median Months[c] (95% CI)	13.7 (8.5, 19.6)	14.1 (8.5, -)	13.7 (9.4, 19.4)
PFS by Investigator			
Events (n, %)	24 (47.1)	24 (35.8)	48 (40.7)
Median Months[c] (95% CI)	18.2 (9.0, 22.1)	16.6 (10.5, -)	16.6 (11.3, 22.1)
Overall survival			
Events (n, %)	10 (19.6)	13 (19.4)	23 (19.5)
Median Months[c] (95% CI)	- (-, -)	- (26.4, -)	- (26.4, -)
Survival at 6 months, % (95% CI[d])	94.0 (82.5, 98.0)	95.3 (86.2, 98.5)	94.7 (88.7, 97.6)
Survival at 12 months, % (95% CI[d])	84.1 (69.3, 92.2)	84.7 (72.7, 91.8)	84.4 (75.7, 90.2)
Survival at 18 months, % (95% CI[d])	74.1 (56.4, 85.5)	80.4 (67.0, 88.7)	77.6 (67.3, 85.0)
Survival at 24 months, % (95% CI[d])	74.1 (56.4, 85.5)	74.2 (55.2, 86.0)	74.8 (63.1, 83.2)

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; ICR = independent central review

[a] 95% exact binomial confidence interval

[b] Disease Control Rate (DCR) was calculated as the proportion of subjects demonstrating CR, PR, or SD for a minimum of 6 weeks (±1week) from the first dosing date

[c] Median is from Kaplan-Meier Estimate. CI for median was computed using the Brookmeyer-Crowley method.

[d] CI for the rate at a fixed time point was computed by applying asymptotic normality to the log-log transformation of the rate

The range includes the censored observations where using "+" after value indicates censoring. Months were calculated as Days*12/365.25.

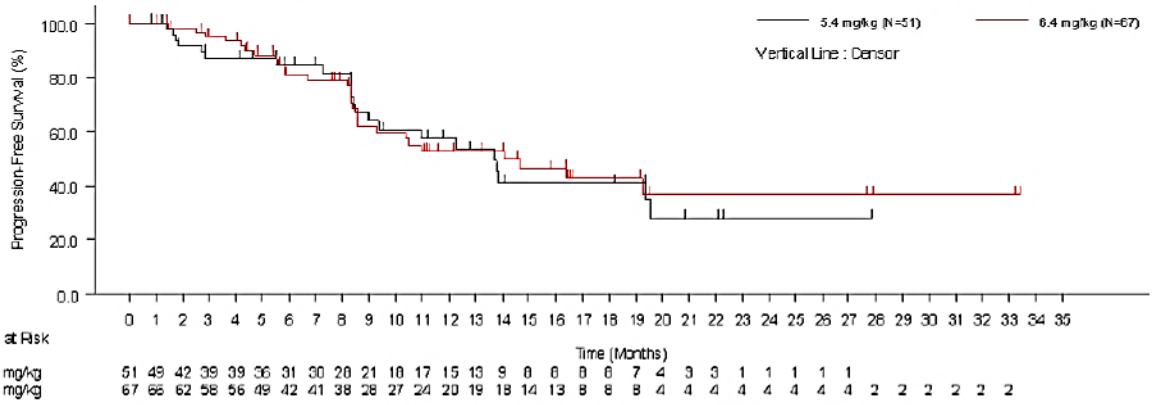
Part 1 (5.4 and 6.4 mg/kg) and Part 2 subjects are included.

Data cutoff date: 01 Feb 2019

Sources: Tables 14.2.2.2, 14.2.2.3, 14.2.3.2, 14.2.3.3, 14.2.2.10, 14.2.2.11, 14.2.2.14, and 14.2.2.15

Figure 23

Figure 8.5: Kaplan-Meier Plot of PFS Based on Independent Central Review for HER2-positive Breast Cancer Subjects at 5.4 mg/kg or 6.4 mg/kg (Months) (Enrolled Analysis Set)



HER2 = human epidermal growth factor receptor 2

Data cut-off date: 01 Feb 2019

Source: Figure 14.2.1.3.2.1

The phase 1 dose-finding J101 study first tested the dose range of 0.8 mg/kg to 8.0 mg/kg Q3W. Based on the balance between activity and safety, as demonstrated in the observed data and the ER analyses, doses of 5.4 mg/kg and 6.4 mg/kg were selected for further investigation in the dose expansion part (Part 2) of the study.

In this application, the efficacy in the patients included with HER2-positive MBC are of focus. For these patients, similar and clinically relevant efficacy was shown for both doses tested in Part 2. With a median follow-up of 11.6 months, confirmed ORR by ICR of 52.5% (95%CI: 43.1, 61.8) was observed among all 118 patients with HER2-positive BC (range 51-52.5%). The duration of response by ICR was 13.3 months (range: 12.7-13.6), which was similar across the dose groups and clinically relevant. It is agreed that there is no relevant dose-effect relationship between the two tested doses in HER2-positive MBC patients in Part 2 of the study, and both ORR and DOR by IRC were clinically meaningful.

Efficacy update

An efficacy update was performed based on a data cut-off (DCO) of 01 Aug 2019 for the 5.4 mg/kg dose group. As of the Update DCO, the median duration of study follow-up for subjects with metastatic HER2-positive breast cancer assigned to 5.4 mg/kg trastuzumab deruxtecan was 10.8 months (range: 0.8-36.4), median treatment duration was 8.54 months (range: 0.7, 37.1). Seven out of fifty (14.0%) patients were ongoing on study treatment at the time of the efficacy update DCO.

The confirmed ORR based on ICR was unchanged, at 51.0% (26/51 subjects) (95% CI: 36.6, 65.2). The median DoR in subjects with confirmed response based on ICR was 10.8 months (95% CI: 6.7, non-estimable). A total of 50.0% of patients were censored. There were 47% PFS events, and estimated median PFS by IRC remained unchanged (13.7 months; 95% CI: 8.5, 19.6). A total of 52.9% of patients were censored.

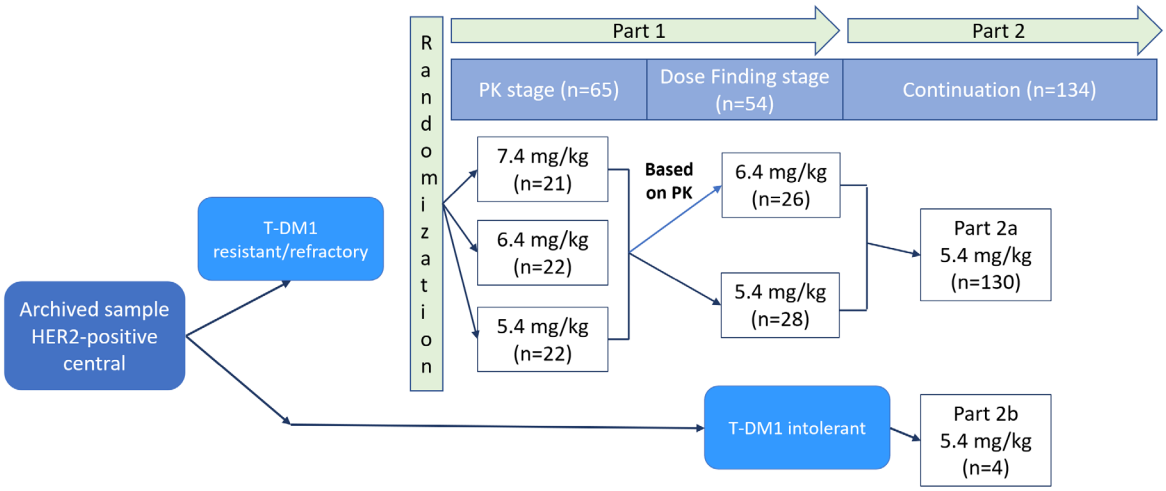
2.5.2. Main study

Study DS8201-A-U201 (Destiny-Breast 01): A Phase 2 Multicenter, Open-label Study of DS-8201a, an Anti-HER2-Antibody Drug Conjugate (ADC) for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1.

Methods

This was a Phase 2, open-label, multicenter, 2-part study designed to justify the recommended dose of trastuzumab deruxtecan and investigate further its safety and efficacy in subjects with unresectable and/or metastatic HER2-positive BC previously treated with T-DM1. The study design is shown in Figure below.

Figure 24 ***Study U201 Study Design Schema with Actual Enrollment***



HER2 = Human epidermal growth factor receptor 2; PK = pharmacokinetics; RP2D = recommended Phase 2 dose; T-DM1 = trastuzumab emtansine

Study Participants

Inclusion Criteria

Subjects had to satisfy all of the following criteria to be included in the study:

1. Men or women ≥20 years old in Japan and Korea, ≥18 years old in the US (for other countries, guidelines on the legal age to consent were to be followed).

2. Pathologically documented BC that:

- Was unresectable or metastatic.
- Had confirmed HER2-positive expression (estrogen receptor/progesterone receptor positive subjects could be enrolled if they were HER2 positive) according to American Society of Clinical Oncology - College of American Pathologists guidelines evaluated at a central laboratory.

3. Subjects had to have an adequate tumor sample available for confirmation of HER2 status by central laboratory (based on the most recent tumor tissue sample).

4. Subjects had to have BC that was resistant or refractory to TDM1, with documented clinical or radiographic progression of disease during or after treatment with TDM1.

- For Part 2b, subjects had to have discontinued treatment with TDM1 for reasons other than resistance or refractory disease.

5. Presence of at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

6. Left ventricular ejection fraction (LVEF) ≥50%.

7. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

8. Adequate bone marrow function, defined as:

- Absolute neutrophil count ≥1.5 × 109/L (granulocyte-colony stimulating factor [G-CSF] was not allowed within 1 week prior to screening assessment).

- Platelet count ≥100 × 109/L (platelet transfusion was not allowed within 1 week prior to screening assessment).
- Hemoglobin level ≥9.0 g/dL (red blood cell [RBC] transfusion was not allowed within 1 week prior to screening assessment).

9. Adequate renal function, defined as:

- Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation, multiplied by 0.85 if female.

10. Adequate hepatic function, including mild to moderate hepatic impairment, defined as the following:

- Normal hepatic function to mild hepatic dysfunction: total bilirubin (TBL) ≤1.5 ×upper limit of normal (ULN) or <3 × ULN in the presence of documented Gilbert's syndrome or liver metastases at baseline, and aspartate transaminase (AST)/alanine transaminase (ALT) ≤5 × ULN.
- Moderate hepatic dysfunction: TBL >1.5 × ULN and ≤3 × ULN, and AST/ALT ≤5 × ULN. After approximately 10 subjects with moderate hepatic dysfunction had been enrolled, subsequent subjects with moderate hepatic dysfunction were to be excluded.

11. Adequate blood clotting function, defined as:

- International normalized ratio (INR) and activated partial thromboplastin time ≤1.5 × ULN.

12. If less than 100 of the planned 150 subjects enrolled and dosed at the RP2D (20 from the Part 1 PK stage, 30 from the Part 1 Dose Finding stage, and 100 from Part 2a) had a history of pertuzumab treatment in the metastatic setting, enrollment could continue to achieve this number, and prior first- or second-line pertuzumab treatment in the advanced/metastatic BC setting was required for these additional subjects.

13. Subjects were to be able and willing to comply with protocol visits and procedures.

- Male and female subjects of reproductive/childbearing potential had to agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4.5 months after the last dose of study drug. For the purpose of this protocol, methods considered to be highly effective methods of contraception included:
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
  - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 4.5 months after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) was not an acceptable method of contraception.

- Nonchildbearing potential was defined as premenopausal females with a documented tubal ligation or hysterectomy; postmenopausal was defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >40 mIU/mL and estradiol <40 pg/mL [147 pmol/L] was confirmatory). Females on hormone replacement therapy (HRT) whose menopausal status was in doubt were required to use 1 of the contraception methods outlined for women of childbearing potential if they wished to continue their HRT during the study. Otherwise, they had to discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks elapsed between the cessation of therapy and the blood draw; this interval depended on the type and dosage of HRT. Following confirmation of their postmenopausal status, they could resume the use of HRT during the study without using a contraceptive method.

14. Men who were fertile and sexually active had to be willing to use highly effective methods of contraception if their partners were of reproductive potential.

15. Male subjects could not freeze or donate sperm starting at screening and throughout the study period, and at least 4.5 months after the final study drug administration. Preservation of sperm was to be considered prior to enrollment in the study.

16. Female subjects could not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 4.5 months after the final study drug administration.

17. Provided informed consent for study participation before performance of any studyspecific procedures or tests.

Exclusion Criteria

Subjects who met any of the following criteria were disqualified from entering the study:

1. Medical history of myocardial infarction within 6 months before randomization/registration; symptomatic congestive heart failure (New York Heart Association Class II to IV); troponin levels consistent with myocardial infarction as defined according to the manufacturer; unstable angina; or serious cardiac arrhythmia requiring treatment within 28 days before randomization/registration.

2. Had a corrected QT interval (QTc) prolongation >470 milliseconds (females) or >450 milliseconds (males) based on average of the screening triplicate 12-lead electrocardiogram (ECG).

3. Had a history of noninfectious ILD/pneumonitis that required steroids; had current ILD/pneumonitis; or had suspected ILD/pneumonitis that could not be ruled out by imaging at screening.

4. Brain metastases that were untreated, symptomatic, or required therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids or anticonvulsants, to control symptoms from brain metastases within 2 months (60 days) of randomization/registration. After approximately 30 subjects with inactive brain metastases had been enrolled at the RP2D (20% of the 150 planned to receive the RP2D), subsequent subjects with any current or past history of brain metastases were to be excluded.

5. Had clinically significant corneal disease in the opinion of the investigator.

6. History of severe hypersensitivity reactions to other mAbs.

7. Substance abuse or medical conditions such as clinically significant cardiac or pulmonary disease, or psychological conditions, that might, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.

8. Social, family, or geographical factors that would interfere with study participation or follow-up.

9. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

10. Known human immunodeficiency virus (HIV) infection or active hepatitis B surface antigen or hepatitis C infection. Subjects were to be tested for HIV prior to randomization if required by local regulations or IRB/IEC.

11. History of other malignancy(ies), except adequately treated nonmelanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated, with no evidence of disease for ≥3 years.

12. Prior treatment with an ADC that consisted of an exatecan derivative that was a topoisomerase inhibitor.

13. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities could have been eligible at the discretion of the investigator after consultation with the Sponsor Global Clinical Lead or designee (eg, Grade 2 chemotherapy-induced neuropathy).

14. Therapeutic radiation therapy or major surgery within 4 weeks before study drug treatment or palliative radiation therapy within 2 weeks before study drug treatment.

15. Systemic treatment with anticancer therapy, antibody-based therapy, retinoid therapy, or hormonal therapy within 3 weeks before study drug treatment; or treatment with nitrosoureas or mitomycin C within 6 weeks before study drug treatment; or treatment with small-molecule targeted agents within 2 weeks or 5 half-lives before study drug treatment, whichever was longer.

16. Current treatment with cytochrome P450 3A4 (CYP3A4) strong inhibitors and organic anion transporting polypeptide (OATP)1B inhibitors (washout of ≥3 elimination halflives was required).

17. Participation in a therapeutic clinical study within 3 weeks before study drug treatment (for small-molecule targeted agents [eg, inhibitors], this nonparticipation period was 2 weeks or 5 half-lives, whichever was longer); or current participation in other investigational procedures.

18. Pregnant or breastfeeding or planning to become pregnant.

19. Subject was not to be a family member of study site personnel or of Sponsor personnel.

20. Had a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.

Patients included had to have centrally confirmed HER2-positive expression according to the guidelines from the American Society of Clinical Oncology, which is standard for clinical trials and endorsed. It is acceptable that patients included in part 2b could have discontinued treatment with TDM1 for reasons other than resistance or refractory disease, since this is a moderately toxic treatment and discontinuations due to AEs is reflective of clinical practice.

Patients were excluded, if they had a history of non-infectious ILD/pneumonitis that required steroids; had current ILD/pneumonitis; or had suspected ILD/pneumonitis that could not be ruled out by imaging at screening. This is endorsed, since fatal cases of ILD/pneumonitis has been observed with trastuzumab deruxtecan. Moreover, this important information for prescribers have been included in the SmPC section 4.4, which is also endorsed.

Treatments

Trastuzumab deruxtecan (DS-8201a) was administered as an IV infusion once every 3 weeks, on Day 1 of each 21-day cycle.

- In the Part 1 PK stage, subjects were randomized to receive 1 of 3 doses: 5.4 mg/kg, 6.4 mg/kg, or 7.4 mg/kg.
- In the Part 1 Dose Finding stage, subjects were randomized to receive 1 of the 2 doses selected in the PK stage (identified as 5.4 mg/kg and 6.4 mg/kg).

Once assigned, subjects were to remain on study in their treatment group and not to change dose groups.

- In Part 2, all subjects received 5.4 mg/kg, which was determined to be the RP2D.

The first dose of trastuzumab deruxtecan was to be administered over 90 minutes ($\pm$10 minutes). If there was no infusion-related reaction (IRR) after the first dose, subsequent doses were to be administered over 30 minutes ($\pm$5 minutes).

Objectives

Primary Objectives

- To determine the objective response rate (ORR) of DS-8201a in HER2-positive, unresectable and/or metastatic BC subjects who were resistant or refractory to T-DM1.

Secondary Objectives

- To evaluate the duration of response (DoR), best percent change in the sum of diameters of measurable tumors, disease control rate (DCR), clinical benefit rate (CBR), PFS, and OS.
- To further evaluate the safety of DS-8201a.
- To determine the pharmacokinetics (PK) of DS-8201a.
- To determine the recommended Phase 2 dose (RP2D) of DS-8201a.

Exploratory Objectives

- To evaluate the duration of stable disease (SD) and time to response (TTR).
- To evaluate potential biomarkers of response, such as serum HER2 extracellular domain (HER2 ECD).
- To evaluate exposure-response (ER) relationships for efficacy and safety endpoints

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of the study was ORR assessed by an ICR based on tumor scans. Objective response rate was 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.

Secondary Efficacy Endpoints

• Investigator-assessed ORR, defined as the proportion of subjects who achieved a BOR of CR or PR based on local radiologists/investigators' tumor assessments using RECIST 1.1.

• DCR, defined as the proportion of subjects who achieved a BOR of CR, PR or SD.

• CBR, defined as the proportion of subjects who achieved a BOR of CR or PR or more than 6 months of SD.

• DoR, defined as the time interval between the date of first documentation of objective response (CR or PR) and the date of the first objective documentation of disease progression or death due to any cause.

• PFS, defined as the time interval between the date of randomization/registration and the first documentation of disease progression or death due to any cause. Disease progression was determined through an ICR of tumor scans using RECIST 1.1. Clinical progression without objective documentation of disease progression per RECIST 1.1 was not considered to be progression while deriving the PFS endpoint.

• OS, defined as the time interval between the date of randomization/registration and the date of death due to any cause. If the analysis subject was not known to have died prior to the data cut-off (DCO) date, OS was censored at the last contact date at which the subject was known to be alive.

• Best percent change in sum of diameters of measurable tumors, based on RECIST 1.1. The best percent change was defined as the percent change in the smallest sum of diameters from all post-baseline tumor assessments, taking as reference the baseline sum of diameters.

The assessment of DCR, CBR, DoR, PFS, and best percent change in measurable tumor sum of diameters was based on ICR.

Exploratory Objectives

• To evaluate the duration of stable disease (SD) and time to response (TTR).

• To evaluate potential biomarkers of response, such as serum HER2 extracellulardomain (HER2 ECD).

• To evaluate exposure-response (ER) relationships for efficacy and safety endpoints.

Safety endpoints

Safety is monitored based on reporting of adverse events (AEs), clinical laboratory tests (hematology and blood chemistry tests), vital signs, ECGs, and physical examinations. AEs are recorded and categorized using the medical dictionary for regulatory activities (MedDRA) version 20.1. AEs and abnormal laboratory test results, if applicable, were to be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. AEs of special interest (AESIs) were ILD, LVEF decrease, QT prolongation and infusion related reactions (IRRs). An independent ILD adjudication committee (AC) was established for the trastuzumab deruxtecan program that was responsible for reviewing all cases of potential ILD on an ongoing basis.

Sample size

The sample size of approximately 230 subjects was chosen to further confirm the safety profile and secure adequate accuracy to determine ORR of trastuzumab deruxtecan. A sample size of 50 subjects (30 subjects from dose finding and 20 subjects from PK stage) provides ORR with 90% CI within plus or minus about 10% under the expected ORR=35%. The probabilities of observing the lower bound of

the 90% CI > 15% and ORR ≥ 30% are 93.4% (72.0% for the lower bound of the 90% CI > 20%) and 81.2% under the expected ORR=35%, respectively. A sample size of 150 subjects (50 subjects from Part 1 who receive the optimal dose level and 100 subjects from Part 2a) provides ORR with 95% CI within plus or minus 10% of the ORR. The probabilities of observing the lower bound of the 95% CI > 20% and ORR ≥ 30% are 98.2% and 91.6% under the expected ORR=35%, respectively.

Randomisation

Part 1 of the study was randomized and consisted of 2 stages: a PK stage and a Dose Finding stage. Part 1 was designed to bridge Phase 1 experience to the to-be marketed product (new process, new formulation) and adequately support dose and regimen recommendations:

In the PK stage of Part 1, approximately 60 subjects were to be randomized in a 1:1:1 ratio to 1 of 3 doses of DS-8201a (5.4 mg/kg, 6.4 mg/kg, and 7.4 mg/kg; approximately 20 subjects per dose level). After review of the PK findings, 2 dose levels were to be selected for further evaluation.

In the Dose Finding stage of Part 1, approximately 60 subjects were to be randomized in a 1:1 ratio to 1 of the 2 doses selected (approximately 30 subjects per dose level), and a dose-justification ER (exposure-efficacy and exposure-safety) analysis was to be conducted in order to determine the optimal dose of DS-8201a.

Randomization in Part 1 was stratified by region (Asia, rest of the world). Part 2 was not randomized, and all subjects were to receive DS-8201a at the recommended dose determined in Part 1.

The study was divided into two parts. Part 1 aimed to determine the optimal dose, and it was further divided into Part 1a (3 test doses) and Part 1b (2 of the best performing doses from Part 1a). Part 2 included subjects, who received the optimal dose selected in Part 1b. Part 1 was randomized 1:1 equally among the included doses and stratified by region (Asia, Rest of the World (RoW)). Part 2 was a single arm trial, and thus randomization was not applicable.

Blinding (masking)

This was a single arm study and thus all patients received the active treatment. No blinding for the different dose levels was applied in Part 1.

Statistical methods

Analysis Sets

Analysis Set	Definition
Enrolled Analysis Set (EAS) (Intent-to-Treat Analysis Set)	All subjects who signed an ICF and were randomized in Part 1 or registered in Part 2.
Safety Analysis Set	All subjects enrolled in Part 1 or Part 2 who received at least 1 dose of study drug. The Safety Analysis Set is identical to the Full Analysis Set introduced in the protocol.
Response Evaluable Set (RES)	All subjects enrolled in Part 1 or Part 2 who received at least 1 dose of study drug and had measurable tumors assessed by ICR at baseline.
Pharmacokinetic (PK) Analysis Set	All subjects enrolled in Part 1 or Part 2 who received at least 1 dose of study drug and had measurable serum concentrations of DS-8201a.

Efficacy analyses were to be performed on the Enrolled Analysis Set (EAS, which was the same as the Intent-to-Treat [ITT] Analysis Set) and the Response Evaluable Set (RES).

The primary analysis population is the EAS, which includes all subjects with signed ICF who were randomized or registered. The response evaluable set was used as supplementary analysis for the primary efficacy endpoint. This is agreed.

Tumor assessment was performed at Screening and every 6 weeks thereafter using computerized tomography (CT) scan or magnetic resonance imaging (MRI) (spiral CT scan or MRI with ≤5 mm cuts). Imaging data obtained every 6 weeks per protocol were provided by the investigators to the ICR. Confirmation was performed no earlier than 4 weeks (28 days) from the time a response of CR/PR is first suspected.

Dose selection analysis

The following criteria were to be included as part of the information used for dose selection. Additional factors such as depth of response (ie, best change from baseline in sum of diameters of measurable tumors), DoR, and chronic toxicity were also to be included.

Assuming binomial distribution for the ORR, and a beta conjugate prior, the high dose level was to be considered efficacious relative to the low dose level if the posterior probability of the difference in ORR given the observed data showed that:

Probability (ORRhigh - ORRlow >5% | data) >80%.

Assuming normal-normal conjugate prior mode, the high dose level was to be considered toxic relative to the low dose level if the posterior probability of the differences in the percent change from baseline in neutrophil count (PCNC) given the observed data showed that: Probability (PCNChigh - PCNClow <-10% | data) >80%.

Primary Efficacy Endpoint: IRC-ORR

The estimate of ORR and its 2-sided 95% exact (Clopper-Pearson) confidence interval (CI) were to be provided in each Part/dose group and overall. In addition, ORR based on BOR within a fixed duration (eg, 3, 6, 9, 12 months) along with their 2-sided 95% exact CIs were to be provided in each Part/dose group and overall. DCR, CBR, and investigator-assessed ORR without confirmation of CR/PR were to be performed using the same methods as for the ORR analysis.

Secondary efficacy endpoints

Distribution of time to event endpoints such as duration of response, PFS, and OS will be estimated using Kaplan-Meier method and results presented graphically. Additionally, quartile event times and their 2-sided 95%CI using Brookmeyer and Crowley methods will be presented for each part/dose group and overall. In addition, Kaplan-Meier estimates of duration of response, PFS, and OS rates at fixed time points (e.g. 3, 6, 9, 12 months) along with their 2-sided 95%CIs will be provided for each part/dose group and overall provided enough events are recorded. The CIs for the rates at fixed time points will be calculated by applying asymptotic normality to the log-log transformation of the rates.

Duration of response (DoR)

The rules for censored cases are defined as follows:

- Subjects who are not known to have progressed or died at the data cut-off date will be censored at the date of last evaluable tumor assessment. An evaluable tumor assessment is defined as an assessment where the overall tumor response is not "Inevaluable (NE)".

- Subjects who start other anti-cancer therapy prior to disease progression or death will be censored at the date of the last tumor evaluable assessment prior to starting new anticancer therapy.
- Subjects who progress or die after missing ≥ 2 consecutive scheduled tumor assessments will be censored at the date of the last evaluable tumor evaluation prior to progression or death. In this study, tumor assessment is performed at every 6 weeks (±7 days), therefore, progression or death after missing ≥ 2 consecutive scheduled tumor assessments are defined as progression or death that occurs after more than 14 weeks (two tumor assessment visits plus 2 weeks visit window).

Progression free survival (PFS)

The rules for censored cases are defined as follows:

- Subjects known to not have progressed or died at the data cut-off date will be censored at the date of last evaluable tumor assessment.
- Subjects who discontinue from the study prior to first post-baseline evaluable tumor assessment for a reason other than death will be censored at the date of randomization (the date of registration for not randomized subjects).
- Subjects who start other anti-cancer therapy prior to disease progression or death will be censored at the date of last tumor evaluable assessment prior to starting new anti-cancer therapy.
- Subjects who have progressive disease or die after missing ≥ 2 consecutive scheduled tumor assessments (i.e., more than 14 weeks, allowing for 2 weeks visit window) will be censored at the date of last evaluable tumor assessment prior to progression.
- Subjects without baseline evaluable tumor assessment will be censored at the date of randomization or registration, except death within first 2 scheduled tumor assessments (i.e., 14 weeks) will be considered as a PFS event.

Overall survival (OS)

After discontinuation from study treatment, follow-up information for survival and subsequent anticancer therapy will be obtained every 3 months (±14 days) from the date of the Follow-up visit until death, withdrawal of consent, loss to follow up, or study closure, whichever occurs first.

The rules for censored cases are defined as follows:

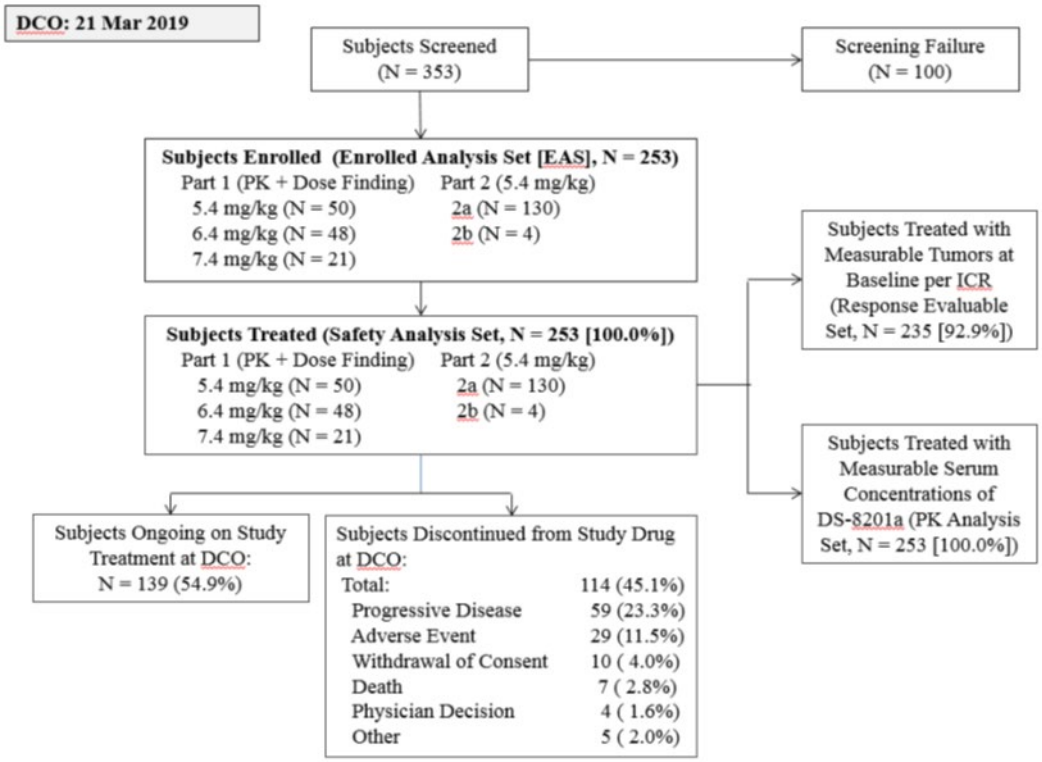
- If analysis patient is not known to have died prior to the data cut-off date, OS will be censored at the last contact date at which the subject is known to be alive. The last contact date is defined as the last date the subject was known to be alive up-to the data cut-off date.

The primary endpoint is ORR (CR + PR). The proportion of responders were presented together with the 95%CI (Clopper-Pearson). Patients with no postbaseline data or non-evaluable were included as non-responders. Secondary endpoints included in the statistical section are DoR, PFS and OS, which were described using the Kaplan-Meier method. The following patients were censored in the DoR analysis: patients who did not experience an event while being observed, patients who switched to another anti-cancer therapy before PD or death, patients who only had clinical progression, and patients who died or experienced PD after two or more missed assessments. For PFS, the DoR censoring rules were used. In addition, subjects without a baseline assessment or who discontinue from the study prior to first post-baseline evaluable tumor assessment for a reason other than death

were also censored. For OS, patients not known to have died will be censored at the date of last contact. The main analysis was repeated using the INV-assessments and the RES set.

Results

Participant flow



Recruitment

A total of 253 subjects were enrolled and treated at 1 of 72 study sites in the following countries: US (24 study sites), Japan (10), France (9), Spain (8), South Korea (7), Belgium (5), UK (5), and Italy (4); an additional 5 study sites screened, but did not enroll, subjects. The first subject was dosed at 03 Oct 2017 and the last enrolled patient was first dosed on 21 Sep 2018. DCO was 21 Mar 2019.

Enrollment was proportional across geographic regions with each region treating over 30% of subjects: Asia, 56 (22.1%) subjects in Japan and 40 (15.8%) subjects in South Korea; US, 77 (30.4%) subjects; and Europe: 80 (31.6%) subjects.

Conduct of the study

The initial protocol (version 1.0) was dated 15 May 2017. There were 3 global and 4 country-specific amendments to the initial protocol. Amendments mainly included clarification to certain efficacy analyses, safety monitoring, additional exclusion criteria and updates of dose modification guidance. There were no changes from the analyses planned in the statistical analysis plan (SAP) version 2.0.

A total of 117 (46.2%) subjects met criteria for any major protocol deviations, predominantly in the category study procedures criteria (18.2%) and laboratory assessment criteria (13.8%). Major protocol deviations with regard to efficacy and eligibility criteria were reported at frequencies of 4.0% and 6.3%, respectively.

Protocol amendments

Key changes (excluding minor editorial changes) in each of the global amendments were as follows:

Amendment 1 (global protocol version 2.0, dated 19 Oct 2017):

- Change in study title from "A Phase 2, Multicenter, Open-Label Study of DS-8201a, an Anti HER2-Antibody Drug Conjugate (ADC) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Who are Resistant or Refractory to T-DM1"to "A Phase 2, Multicenter, Open-Label Study of DS-8201a, an Anti HER2-Antibody Drug Conjugate (ADC) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1" to more accurately address the subject population of this study.
- Addition of the following endpoints: determination of the RP2D; TEAEs leading to discontinuation, AESIs, and elevated troponin levels. Clarification that other biomarkers of response such as HER2 ECD could be evaluated.
- Clarification that subjects in Part 1 were to be randomized while subjects in Part 2 were to be registered (no randomization in Part 2).
- Clarification about the forms of drug product to be used in each part of the study.
- Clarification that the primary efficacy analysis was to be performed for all subjects who received the RP2D of DS-8201a and had measurable tumors assessed by ICR at baseline (RES).
- Clarification that analyses of ORR, DCR and CBR were to be performed on the RES.
- Addition of information on the metabolite profile of DS-8201a. An exclusion criterion for current treatment with OATP1B inhibitors was added, with a washout period of ≥3 elimination half-lives.
- Removal of phototoxicity warnings following review of data from a new nonclinical safety study.
- Addition of a restriction on administration of G-CSF, platelet transfusion, and RBC transfusion within 1 week before the start of screening.
- Addition of a cap of approximately 30 subjects with inactive brain metastases.
- Addition of the following tests: urinalysis, troponin, magnesium, and coagulation.
- Clarification of the definitions of mild and moderate hepatic dysfunction, and addition of a cap of approximately 10 subjects with moderate hepatic impairment.
- Clarification of guidance on dose modifications for troponin elevation and hepatic abnormalities.
- Clarification of the frequency of ophthalmologic and ECHO/MUGA assessments.
- Addition of guidance on AESIs (ILD/pneumonitis; QT prolongation; LVEF decrease; and IRR).
- Clarification of guidance on pregnancy reporting during the study.
- Update of the information on Study DS8201-A-J101.

Amendment 2 (global protocol version 3.0, dated 22 Jan 2018):

- Updated the phototoxicity study data, the summary of clinical PK, and the risk and benefits for study subjects.
- Clarified the number of subjects to be enrolled in Part 2b and study timing, and the timing from randomization to first dose; and increased the number of study sites.
- Updated the inclusion criteria to: (1) include information on legal age of consent in different countries; (2) clarify the inclusion criterion for subjects with Gilbert's syndrome or liver metastases at baseline; (3) clarify the definition of complete sexual abstinence; (4) include the possibility of freezing sperm before treatment; and (5) extend to 4.5 months for female subjects the period during which they could not donate or retrieve ova for their own use.
- Updated the exclusion criteria to add: (1) history of noninfectious ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that could not be ruled out; and (2) history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
- Updated the dose modification guidance for ILD/pneumonitis/pulmonary toxicity, troponin elevation, and hepatic toxicity.
- Added respiratory rate to vital signs.
- Updated the management guidance and reporting procedures for AESIs.
- Updated the reporting requirements in case of pregnancy.

Amendment 3 (global protocol version 4.0, dated 27 Jul 2018)

- Updated the starting dose of DS-8201a for Part 2 to 5.4 mg/kg, which was determined to be the RP2D.
- Removed the statement that subjects were to remain on the same drug product form throughout the study.
- Clarified the wording regarding the action to be taken if toxicity continued after 2 dose reductions.
- Included dose modifications required for WBC count decreased and deleted specificity regarding CTCAE Grade 3 and 4 neutrophil count decreased.
- Revised dose modification criteria for CTCAE Grade 1 troponin increased. Updated specifications for troponin testing.

Major protocol deviations are listed in the following table

Table 23 Major Protocol Deviations (Enrolled Analysis Set)

Protocol Deviation Category	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b	Overall
	6.4 mg/kg N = 48 n (%)	7.4 mg/kg N = 21 n (%)	5.4 mg/kg N = 180 n (%)	5.4 mg/kg N = 184 n (%)	All Doses N = 253 n (%)
Subjects with any major protocol deviations	21 (43.8)	9 (42.9)	85 (47.2)	87 (47.3)	117 (46.2)
Concomitant or prohibited medications or non-drug therapy	0	0	2 (1.1)	2 (1.1)	2 (0.8)
Efficacy criteria	1 (2.1)	2 (9.5)	7 (3.9)	7 (3.8)	10 (4.0)
Eligibility and entry criteria	5 (10.4)	0	11 (6.1)	11 (6.0)	16 (6.3)
IP compliance	1 (2.1)	2 (9.5)	13 (7.2)	15 (8.2)	18 (7.1)
Informed consent	4 (8.3)	4 (19.0)	16 (8.9)	16 (8.7)	24 (9.5)
Laboratory assessment criteria	7 (14.6)	3 (14.3)	23 (12.8)	25 (13.6)	35 (13.8)
SAE criteria	0	1 (4.8)	1 (0.6)	1 (0.5)	2 (0.8)
Study procedures criteria	11 (22.9)	0	34 (18.9)	35 (19.0)	46 (18.2)

PK = pharmacokinetics; SAE = serious adverse event; IP = investigational product
Subjects may have had protocol deviations in multiple categories.
DCO = 21 Mar 2019
Source: DS8201-A-U201 CSR Table 14.1.1.2.

Baseline data

Demographic characteristics of the patients are summarised in Table 24. For patients receiving the recommended dose of 5.4 mg/kg (N=184), median age at baseline was 55.0 years and all subjects were female. Most patients were either white (54.9%) or Asian (38.0%).

Table 24 Key demographic characteristics (Enrolled analysis set, U201)

Demographic Characteristics	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b	Overall
	6.4 mg/kg N = 48	7.4 mg/kg N = 21	5.4 mg/kg N = 180	5.4 mg/kg N = 184	All Doses N = 253
Age at informed consent,[a] years					
Mean (Std Dev)	55.8 (12.98)	54.4 (10.47)	56.1 (11.75)	56.0 (11.72)	55.8 (11.83)
Median	57.0	54.0	55.5	55.0	56.0
Range	29-79	32-69	28-96	28-96	28-96
Age group, n (%)					
<65 years	33 (68.8)	16 (76.2)	136 (75.6)	140 (76.1)	189 (74.7)
≥65 years	15 (31.3)	5 (23.8)	44 (24.4)	44 (23.9)	64 (25.3)
<75 years	45 (93.8)	21 (100.0)	171 (95.0)	175 (95.1)	241 (95.3)
≥75 years	3 (6.3)	0	9 (5.0)	9 (4.9)	12 (4.7)
Sex, n (%)					
Female	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)
Race, n (%)					
Asian	22 (45.8)	12 (57.1)	69 (38.3)	70 (38.0)	104 (41.1)
White	23 (47.9)	8 (38.1)	100 (55.6)	101 (54.9)	132 (52.2)
Black or African American	0	1 (4.8)	3 (1.7)	4 (2.2)	5 (2.0)
American Indian or Alaskan Native	1 (2.1)	0	0	1 (0.5)	2 (0.8)
Native Hawaiian or Pacific Islander	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Other	1 (2.1)	0	3 (1.7)	3 (1.6)	4 (1.6)
Missing	1 (2.1)	0	4 (2.2)	4 (2.2)	5 (2.0)

PK = pharmacokinetics; Std Dev = standard deviation
[a] Age in years was calculated using the informed consent date and the birth date.
DCO = 21 Mar 2019
Source: DS8201-A-U201 CSR Table 14.1.2.1

Baseline disease characteristics are summarised in Table 25. For patients receiving 5.4 mg/kg (N=184), all but 1 of the patients enrolled in the study had confirmation that their tumors were HER2-positive based on central laboratory testing of submitted archival tissue. Most patients had metastatic disease (93.5%), with 30.4% having liver metastases and 13.0% having brain metastases. Half of the patients were hormone-receptor positive (52.7%) and 50.5% estrogen-receptor positive. Patients had either ECOG performance status 0 (55.4%) or 1 (44.0%), and normal renal function (48.9%) or mild renal impairment (37.5%). Further, patients had either normal hepatic function (57.1%) or mild hepatic impairment (41.3%).

Table 25 Baseline disease characteristics (Enrolled analysis set, U201)

Baseline Disease Characteristics	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b	Overall
	6.4 mg/kg N = 48	7.4 mg/kg N = 21	5.4 mg/kg N = 180	5.4 mg/kg N = 184	All Doses N = 253
ECOG performance status, n (%)[a]					
0	30 (62.5)	14 (66.7)	101 (56.1)	102 (55.4)	146 (57.7)
1	18 (37.5)	7 (33.3)	78 (43.3)	81 (44.0)	106 (41.9)
2	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Weight, kg					
Mean (Std Dev)	59.75 (13.324)	54.58 (10.686)	62.49 (13.998)	62.47 (14.040)	61.30 (13.803)
Median	57.05	54.90	61.10	60.55	59.40
Range	37.9-90.7	38.5-77.8	35.6-121.0	35.6-121.0	35.6-121.0
Body mass index, kg/m²					
n	48	21	177	181	250
Mean (Std Dev)	23.82 (5.028)	21.76 (3.957)	24.33 (4.951)	24.31 (4.961)	24.01 (4.932)
Median	22.95	20.20	23.20	23.20	23.05
Range	14.6-37.9	16.7-31.2	15.2-44.4	15.2-44.4	14.6-44.4
Estrogen receptor status, n (%)					
Positive	21 (43.8)	8 (38.1)	91 (50.6)	93 (50.5)	122 (48.2)
Negative	27 (56.3)	13 (61.9)	87 (48.3)	88 (47.8)	128 (50.6)
Not available, not done or unknown	0	0	2 (1.1)	3 (1.6)	3 (1.2)
Progesterone receptor status, n (%)					
Positive	13 (27.1)	4 (19.0)	50 (27.8)	51 (27.7)	68 (26.9)
Negative	35 (72.9)	17 (81.0)	123 (68.3)	125 (67.9)	177 (70.0)
Not available, not done or unknown	0	0	7 (3.9)	8 (4.3)	8 (3.2)
Hormone receptor status, n (%)					
Positive	22 (45.8)	8 (38.1)	94 (52.2)	97 (52.7)	127 (50.2)
Negative	26 (54.2)	13 (61.9)	83 (46.1)	83 (45.1)	122 (48.2)
Unknown	0	0	3 (1.7)	4 (2.2)	4 (1.6)
HER2 expression (IHC) by central laboratory, n (%)					
1+	0	0	2 (1.1)	2 (1.1)	2 (0.8)
ISH positive	0	0	2 (1.1)	2 (1.1)	2 (0.8)
2+	7 (14.6)	3 (14.3)	28 (15.6)	28 (15.2)	38 (15.0)
ISH positive	7 (14.6)	3 (14.3)	26 (14.4)	26 (14.1)	36 (14.2)
ISH equivocal	0	0	1 (0.6)	1 (0.5)	1 (0.4)
ISH examined but not evaluable	0	0	1 (0.6)	1 (0.5)	1 (0.4)
3+	41 (85.4)	18 (85.7)	150 (83.3)	154 (83.7)	213 (84.2)
Presence of metastases, n (%)[b]					
Yes	46 (95.8)	19 (90.5)	168 (93.3)	172 (93.5)	237 (93.7)
Brain metastases	12 (25.0)	2 (9.5)	24 (13.3)	24 (13.0)	38 (15.0)
Bone metastases	19 (39.6)	4 (19.0)	51 (28.3)	53 (28.8)	76 (30.0)
Lung metastases	24 (50.0)	8 (38.1)	103 (57.2)	105 (57.1)	137 (54.2)
Liver metastases	13 (27.1)	5 (23.8)	55 (30.6)	56 (30.4)	74 (29.2)
Visceral disease[c]	44 (91.7)	17 (81.0)	165 (91.7)	169 (91.8)	230 (90.9)
Sum of diameters of target lesions, cm					
n	44	21	167	170	235
Mean (Std Dev)	7.10 (4.097)	6.37 (5.627)	6.68 (4.530)	6.67 (4.524)	6.72 (4.540)
Median	6.15	4.50	5.40	5.40	5.40
Range	1.5-17.4	1.1-23.8	1.2-24.5	1.2-24.5	1.1-24.5
Renal function at baseline,[d] n (%)					
Normal	23 (47.9)	9 (42.9)	90 (50.0)	90 (48.9)	122 (48.2)
Mild impairment	15 (31.3)	11 (52.4)	66 (36.7)	69 (37.5)	95 (37.5)
Moderate impairment	9 (18.8)	1 (4.8)	24 (13.3)	25 (13.6)	35 (13.8)
Missing	1 (2.1)	0	0	0	1 (0.4)
Hepatic function at baseline,[e] n (%)					
Normal	25 (52.1)	14 (66.7)	102 (56.7)	105 (57.1)	144 (56.9)
Mild impairment	22 (45.8)	7 (33.3)	75 (41.7)	76 (41.3)	105 (41.5)
Moderate impairment	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Missing	1 (2.1)	0	2 (1.1)	2 (1.1)	3 (1.2)

Baseline disease characteristics (Enrolled analysis set, U201) (Continued)

Baseline Disease Characteristics	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b	Overall
	6.4 mg/kg N = 48	7.4 mg/kg N = 21	5.4 mg/kg N = 180	5.4 mg/kg N = 184	All Doses N = 253
Time from initial diagnosis to study treatment, months					
n	48	21	180	184	253
Mean (Std Dev)	93.87 (61.864)	80.21 (82.046)	88.89 (66.479)	88.70 (65.900)	88.97 (66.429)
Median	75.68	49.87	74.17	74.17	73.79
Range	17.2-279.3	10.3-288.5	1.6-431.4	1.6-431.4	1.6-431.4

[a] ECOG performance status based on last value prior to first infusion; [b] Lung, liver and bone metastases were derived from baseline target of non-target lesions; brain metastases were form the eCRF collection; [c] visceral disease included target or non-target lesions except ones in skin, breast, lymph nodes, and bone; [d] renal function based on laboratory results; [e] hepatic function based on laboratory results.

Prior cancer therapy is summarized in Table 26. For patients receiving 5.4 mg/kg (N=184), the median number of prior cancer systemic therapy excluding hormone therapy was 6 (range: 2-24) and 53.8% received >5 prior cancer systemic therapies. All received prior trastuzumab and T-DM1 in line with the inclusion criteria, and abou two-third received prior pertuzumab (65.8%).

Table 26 Prior Cancer Therapy (Enrolled analysis set, study U201)

Prior Cancer Therapy	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b	Overall
	6.4 mg/kg N = 48	7.4 mg/kg N = 21	5.4 mg/kg N = 180	5.4 mg/kg N = 184	All Doses N = 253
Lines of prior systemic therapy not including hormone therapy, n (%)					
<3	1 (2.1)	4 (19.0)	17 (9.4)	17 (9.2)	22 (8.7)
≥3	47 (97.9)	17 (81.0)	163 (90.6)	167 (90.8)	231 (91.3)
Prior pertuzumab, n (%)					
Yes	34 (70.8)	20 (95.2)	118 (65.6)	121 (65.8)	175 (69.2)
No	14 (29.2)	1 (4.8)	62 (34.4)	63 (34.2)	78 (30.8)
Prior pertuzumab in first or second line in advanced/metastatic BC, n (%)					
Yes	15 (31.3)	9 (42.9)	50 (27.8)	51 (27.7)	75 (29.6)
No	33 (68.8)	12 (57.1)	130 (72.2)	133 (72.3)	178 (70.4)
Prior cancer systemic therapy, n (%)					
Yes	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)
Trastuzumab	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)
T-DM1	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)
Pertuzumab	34 (70.8)	20 (95.2)	118 (65.6)	121 (65.8)	175 (69.2)
Other anti-HER2	26 (54.2)	3 (14.3)	97 (53.9)	100 (54.3)	129 (51.0)
Hormone therapy	22 (45.8)	7 (33.3)	87 (48.3)	90 (48.9)	119 (47.0)
Other systemic therapy	48 (100.0)	21 (100.0)	179 (99.4)	183 (99.5)	252 (99.6)
Best response to T-DM1 therapy,[a] n (%)					
CR/PR	15 (31.3)	2 (9.5)	39 (21.7)	40 (21.7)	57 (22.5)
SD	9 (18.8)	5 (23.8)	38 (21.1)	39 (21.2)	53 (20.9)
Not evaluable	3 (6.3)	2 (9.5)	38 (21.1)	39 (21.2)	44 (17.4)
PD	21 (43.8)	12 (57.1)	65 (36.1)	66 (35.9)	99 (39.1)
Number of regimens of prior cancer systemic therapy including hormone therapy, n (%)					
1	0	0	0	0	0
2	0	3 (14.3)	15 (8.3)	15 (8.2)	18 (7.1)
3	8 (16.7)	1 (4.8)	16 (8.9)	16 (8.7)	25 (9.9)
4	6 (12.5)	4 (19.0)	21 (11.7)	22 (12.0)	32 (12.6)
5	6 (12.5)	4 (19.0)	16 (8.9)	16 (8.7)	26 (10.3)
>5	28 (58.3)	9 (42.9)	112 (62.2)	115 (62.5)	152 (60.1)
Mean (Std Dev)	6.8 (3.23)	6.5 (4.24)	6.6 (3.49)	6.6 (3.46)	6.7 (3.48)
Median	6.0	5.0	6.0	6.0	6.0
Range	3-16	2-19	2-27	2-27	2-27
Number of regimens of prior cancer systemic therapy excluding hormone therapy, n (%)					
2	1 (2.1)	4 (19.0)	17 (9.4)	17 (9.2)	22 (8.7)
3	8 (16.7)	1 (4.8)	17 (9.4)	17 (9.2)	26 (10.3)
4	6 (12.5)	3 (14.3)	27 (15.0)	28 (15.2)	37 (14.6)
5	8 (16.7)	4 (19.0)	23 (12.8)	23 (12.5)	35 (13.8)
>5	25 (52.1)	9 (42.9)	96 (53.3)	99 (53.8)	133 (52.6)
Mean (Std Dev)	6.1 (2.65)	6.0 (3.96)	6.1 (3.16)	6.1 (3.14)	6.1 (3.11)
Median	6.0	5.0	6.0	6.0	6.0
Range	2-13	2-19	2-24	2-24	2-24

BC=breast cancer; CR=complete response; HER2=epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH: in situ hybridization; PD=progressive disease; PK=pharmacokinetics; PR=partial response; SD=stabdel disease, Std Dev=standard deviation.
[a] The eCRF entry did not specify whether the response to T-DM1 was confirmed or not.

Numbers analysed

The Applicant presents data from 184 HER2-positive breast cancer patients from the pivotal study U201 and 51 patients from the phase 1 Study J101, who were treated with the proposed dose of 5.4 mg/kg. Moreover, a pooled analysis of all 235 patients treated with the proposed dose of 5.4 mg/kg were presented.

Table 27: Data sets analysed

Analysis Sets	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b	Overall
	6.4 mg/kg N = 48 n (%)	7.4 mg/kg N = 21 n (%)	5.4 mg/kg N = 180 n (%)	5.4 mg/kg N = 184 n (%)	All Doses N = 253 n (%)
Enrolled Analysis Set (EAS)	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)
Safety Analysis Set	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)
Response Evaluable Set (RES)	44 (91.7)	21 (100.0)	167 (92.8)	170 (92.4)	235 (92.9)
Pharmacokinetic (PK) Analysis Set	48 (100.0)	21 (100.0)	180 (100.0)	184 (100.0)	253 (100.0)

Outcomes and estimation

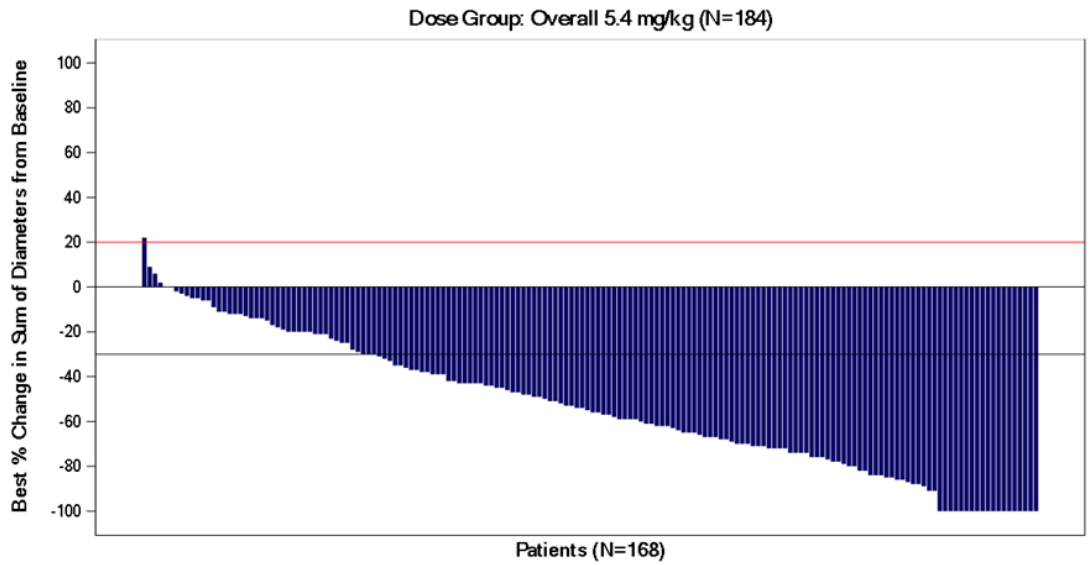
Primary endpoint – confirmed ORR by ICR

Table 28: Confirmed Objective Response Rate and Best Objective Response by Independent Central Review (Intent-to-Treat Population)

	Pooled Analysis 5.4 mg/kg (N = 235)	Study J101 (5.4 mg/kg) Parts 1 + 2a (N = 51)		Study U201 (5.4 mg/kg) Parts 1 +2a +2b (N = 184)	
	CSR DCO	CSR DCO	Update DCO	CSR DCO	Update DCO
Subjects with measurable tumors at baseline					
n (%)	215 (91.5)	45 (88.2)	46 (90.2)	170 (92.4)	169 (91.8)
Best overall response, confirmed					
Complete response	10 (4.3)	2 (3.9)	2 (3.9)	8 (4.3)	11 (6.0)
Partial response	127 (54.0)	24 (47.1)	24 (47.1)	103 (56.0)	101 (54.9)
Stable disease	87 (37.0)	19 (37.3)	19 (37.3)	68 (37.0)	67 (36.4)
Progressive disease	7 (3.0)	4 (7.8)	4 (7.8)	3 (1.6)	3 (1.6)
Non-evaluable	4 (1.7)	2 (3.9)	2 (3.9)	2 (1.1)	2 (1.1)
Objective response rate, confirmed					
n (%)	137 (58.3)	26 (51.0)	26 (51.0)	111 (60.3)	112 (60.9)
95% CI[a]	51.7, 64.7	36.6, 65.2	36.6, 65.2	52.9, 67.4	53.4, 68.0

CI = confidence interval; CSR = clinical study report; ITT = intent-to-treat;
Notes: Percentages were calculated using the number of subjects in the ITT Analysis Set as the denominator.
Overall response was determined by independent central review based on RECIST v1.1 criteria.
[a]The 2-sided 95% CIs are based on the exact (Clopper-Pearson) binomial distribution.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Update DCO = 01 Aug 2019
Source: ISE Tables 1.1.1 and 1.2.1.1, and Efficacy Update Tables 14.2.2.3 and 14.2.3.3 (DS8201-A-J101) and 14.2.1.1 and 14.2.1.3 (DS8201-A-U201)

Figure 25: Waterfall Plot of Best (Minimum) Percent Change from Baseline in Sum of Diameters of Target Lesions Based on Independent Central Review at the Update Data Cut-off in Study U201 (Intent-to-Treat Population)



Baseline was defined as the last measurement taken before randomization/registration.
Note: For each subject, the minimum (best) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical line.
Update DCO = 01 Aug 2019
Source: Efficacy Update Figure 14.2.1.2 (DS8201-A-U201)

Table 29 Sensitivity Analyses of Objective Response Rate (Response Evaluable Set)

Efficacy Parameters	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b
	6.4 mg/kg N = 44	7.4 mg/kg N = 21	5.4 mg/kg N = 167	5.4 mg/kg N = 170
Confirmed ORR by ICR				
n (%)	33 (75.0)	17 (81.0)	107 (64.1)	109 (64.1)
95% CI	59.7, 86.8	58.1, 94.6	56.3, 71.3	56.4, 71.3
Confirmed ORR by investigator				
n (%)	34 (77.3)	18 (85.7)	108 (64.7)	109 (64.1)
95% CI	62.2, 88.5	63.7, 97.0	56.9, 71.9	56.4, 71.3

CI = confidence interval; ICR = independent central review; ORR = objective response rate; PK = pharmacokinetics
The 2-sided 95% CI were based on the exact (Clopper-Pearson) binomial distribution.
Percentages were based on the number of subjects in the Enrolled Analysis Set.
DCO = 21 Mar 2019
Source: DS8201-A-U201 CSR Table 14.2.1.3

The primary endpoint of the pivotal study U201 of ORR by independent review in the ITT population was 60.3% at the initial data cut and this result was maintained at the updated DCO and 12.2 months of follow-up time i.e. 60.9% (95%CI: 53.4; 68). Update DCO show that 6% of the patients had a CR and 54.9% had a PR, while 36.4% had SD as best overall response.

Updated efficacy data DCO 8 June 2020

Updated data are provided based on a data cut-off (DCO) of 08 Jun 2020, referred to as the European Medicines Agency (EMA) DCO, with a median duration of follow-up of 20.5 months. At that time, 37 patients (20.1%) were still on treatment (**Table 30**).

Table 30 Subject Disposition and Duration of Expose in Study U201 by DCO (Enrolled Analysis Set)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Treatment status		
Ongoing	79 (42.9)	37 (20.1)
Discontinued	105 (57.1)	147 (79.9)
Duration of treatment (months)		
Median	9.97	10.10
Min-max	0.7, 20.5	0.7, 29.5
Duration of follow-up (months)		
Median	11.1	20.5
Min-max	0.7, 19.9	0.7, 31.4

DCO = data cut-off; EMA = European Medicines Agency
The median and 95% CI for treatment duration or study duration were estimated based on the Kaplan-Meier method.
Source: 90-day Update Table 14.1.1.1, 90-day Safety Update Table 1.1.3.1; EMA Tables 14.1.1.1, 14.1.5.1

The updated results based on the EMA DCO are presented in **Table 31**

Table 31 Overall Response Rate, Duration of Response , Progression-free Survival, and Overall Survival in Study U201 by DCO (Enrolled Analysis Set)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Confirmed BOR by Investigator		
CR	8 (4.3)	9 (4.9)
PR	115 (62.5)	114 (62.0)
SD	56 (30.4)	56 (30.4)
PD	4 (2.2)	4 (2.2)
NE	1 (0.5)	1 (0.5)
ORR by Investigator		
Subjects with confirmed CR/PR, n (%)	123 (66.8)	123 (66.8)
95% CI	59.5, 73.6	59.5, 73.6
Confirmed BOR by ICR		
CR	11 (6.0)	12 (6.5)
PR	101 (54.9)	101 (54.9)
SD	67 (36.4)	66 (35.9)
PD	3 (1.6)	3 (1.6)
NE	2 (1.1)	2 (1.1)
ORR by ICR		
Subjects with confirmed CR/PR, n (%)	112 (60.9)	113 (61.4)
95% CI	53.4, 68.0	54.0, 68.5
DoR by ICR		
Subjects with confirmed CR/PR, n	112	112[a]
Subjects with events of PD or death, n (%)	29 (25.9)	39 (34.8)
Subjects censored, n (%)	83 (74.1)	73 (65.2)
Ongoing without PD, n (%)	53 (47.3)	27 (24.1)
Other, n (%)	30 (26.8)	46 (41.1)
DoR (months)		
Median	14.8	20.8
95% CI	13.8, 16.9	15.0, NE

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
PFS by ICR		
Subjects with PFS events, n (%)	58 (31.5)	70 (38.0)
Subjects with PD	48 (26.1)	58 (31.5)
Death	10 (5.4)	12 (6.5)
Subjects censored, n (%)	126 (68.5)	114 (62.0)
New anti-cancer therapy	7 (3.8)	26 (14.1)
Missed 2 consecutive tumor assessments	0	2 (1.1)
No post-baseline tumor assessments	1 (0.5)	1 (0.5)
No PD/death	118 (64.1)	85 (46.2)
PFS (months)		
Median	16.4	19.4
95% CI	12.7, NE	14.1, NE
OS		
Subjects with OS events, n (%)	25 (13.6)	65 (35.3)
Subjects censored, n (%)	159 (86.4)	119 (64.7)
OS (months)		
Median	NE	24.6
95% CI	NE, NE	23.1, NE
Landmark OS rate		
Point estimate at 12 months	0.86	0.85
95% CI	0.80, 0.91	0.79, 0.90
Point estimate at 18 months	NE	0.74
95% CI	NE	0.67, 0.80

BOR = best overall response; CI = confidence interval; CR = complete response; CSR = clinical study report; DCO = data cut-off; DoR = duration of response; EMA = European Medicines Agency; ICR = independent central review; NE = not evaluated or not estimable; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

[a] One subject had a PR prior to the 08 Jun 2020 cut-off date that was confirmed after the cut-off date. The subject had a confirmed BOR of PR on the first PR date in the central data but was not included in the analysis of DoR.

Source: 90-day Update Tables 14.2.1.1, 14.2.1.2, 14.2.2.1, 14.2.2.2, 14.2.2.3; EMA Tables 14.2.1.1, 14.2.1.2, 14.2.2.1, 14.2.2.2, 14.2.2.3

The further updated confirmed overall response rate (ORR) by independent central review (ICR) was 61.4% (95%CI: 54.0, 68.5) with a median duration of response (DoR) of 20.8 (15.0, NE).

Secondary endpoints

Duration of response by ICR

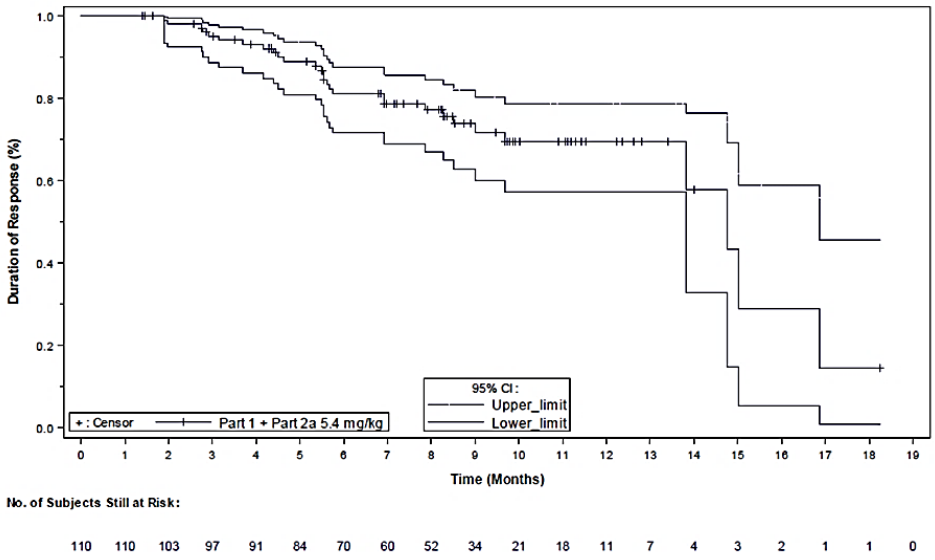
Table 32 Duration of Confirmed Response by Independent Central Review (Intent-to-Treat Population)

	Pooled Analysis 5.4 mg/kg (N = 235)	Study J101 5.4 mg/kg Parts 1 + 2a (N = 51)		Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	CSR DCO	**CSR DCO**	**Update DCO**	**CSR DCO**	**Update DCO**
Subjects with confirmed CR/PR, n	137	26	26	111	112
Subjects with progressive disease or death, n (%)	26 (19.0)	12 (46.2)	13 (50.0)	14 (12.6)	29 (25.9)
Subjects censored, n (%)	111 (81.0)	14 (53.8)	13 (50.0)	97 (87.4)	83 (74.1)

	Pooled Analysis 5.4 mg/kg (N = 235)	Study J101 5.4 mg/kg Parts 1 + 2a (N = 51)		Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	CSR DCO	CSR DCO	Update DCO	CSR DCO	Update DCO
Duration of response (months)					
Median	16.9	12.7	10.8	NE	14.8
95% CI[a]	(9.5, NE)	(6.7, NE)	6.7, NE	(NE, NE)	13.8, 16.9

CI = confidence interval; CR = complete response; CSR = clinical study report; DCO = data cut-off; ICR = independent central review; NE = nonestimable; PR = partial response;
Note: Percentages were calculated using the number of subjects with CR/PR as the denominator.
[a]The 2-sided 95% CIs for quartile survival times were computed using the Brookmeyer-Crowley method.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Update DCO = 01 Aug 2019
Source: ISE Table 1.2.2.1 and Efficacy Update Tables 14.2.2.11 (DS8201-A-J101) and 14.2.2.1 (DS8201-A-U201)

Figure 26 Kaplan-Meier Plot of Duration of Confirmed Response Based on Independent Central Review in Study U201 at Update Data Cut-off (Intent-to-Treat Population)



Update DCO = 01 Aug 2019
Source: Efficacy Update Figure 14.2.4.3 (DS8201-A-U201)

The duration of response by IRC at update DCO show a median of 14.8 months (95%CI: 13.8, 16.9), with a median follow-up time of 12.2 months. Further updated data showed a median duration of response of 20.8 months (95%CI: 15.0, NE) with a median follow-up time of 20.5 months and 34.8% events of PD or death.

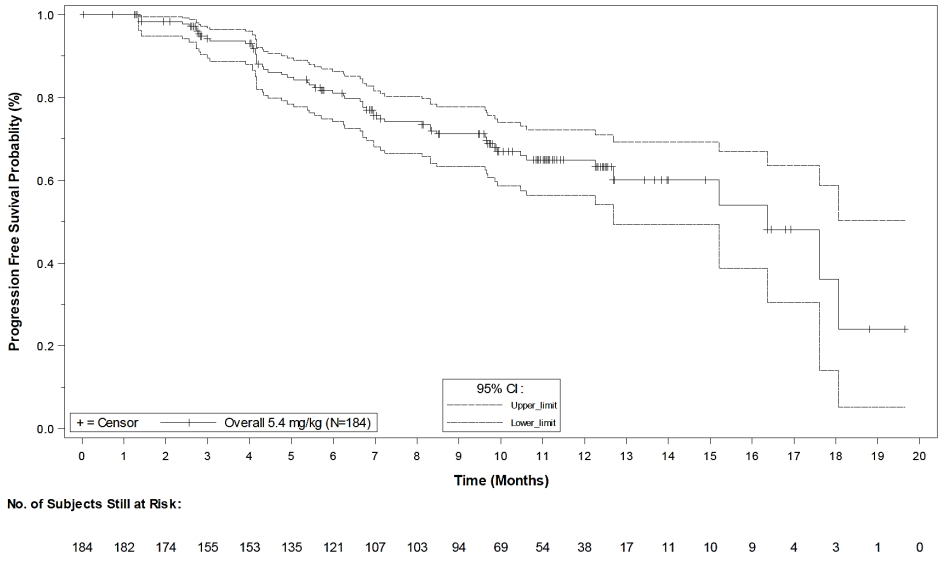
Progression-free survival by IRC

Table 33 Progression-free Survival Based on Independent Central Review (Intent-to-Treat Population)

	Pooled Analysis 5.4 mg/kg (N = 235)	Study J101 5.4 mg/kg Parts 1 + 2a (N = 51)		Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	CSR DCO	CSR DCO	Update DCO	CSR DCO	Update DCO
Subjects with PFS events, n (%)	62 (26.4)	22 (43.1)	24 (47.1)	40 (21.7)	58 (31.5)
Subjects censored, n (%)	173 (73.6)	29 (56.9)	27 (52.9)	144 (78.3)	126 (68.5)
Progression-free survival (months)					
Median	13.9	13.7	13.7	NE	16.4
95% CI[a]	(10.9, NE)	8.5, 19.6	8.5, 19.6	10.6, NE	12.7, NE

CI = confidence interval; CSR = clinical study report; DCO = data cut-off; PFS = progression-free survival; NE = nonestimable;
Percentages were calculated using the number of subjects in the Intent-to-Treat population as the denominator.
Median is based on a Kaplan-Meier estimate.
[a] The 2-sided 95% CIs for quartile survival times are computed using the Brookmeyer-Crowley method.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Update DCO = 01 Aug 2019
Source: ISE Table 1.2.4.1 and Efficacy Update Tables 14.2.2.15 (DS8201-A-J101) and 14.2.2.2 (DS8201-A-U201)

Table 34 Kaplan-Meier Plot of Progression-free Survival Based on Independent Central Review in Study U201 at Update Data Cut-off (Intent-to-Treat Population)

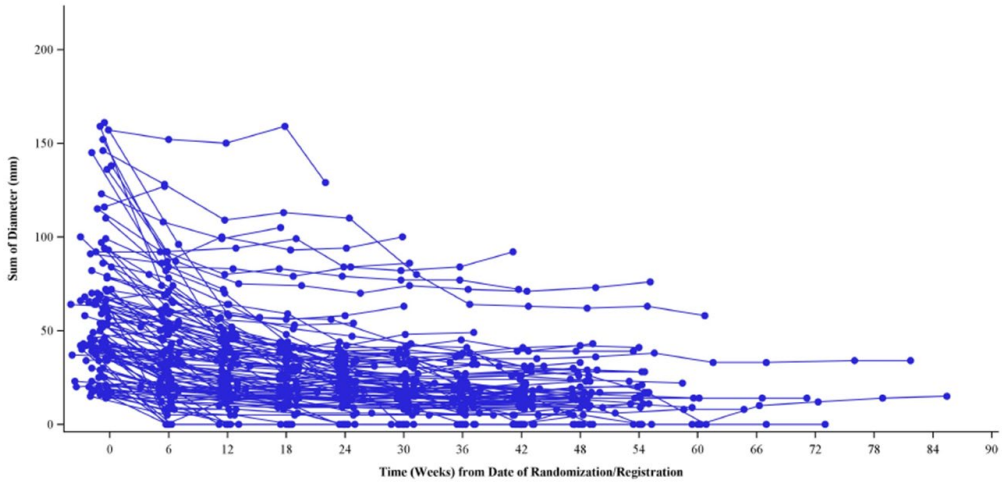


CI = confidence interval
Update DCO = 01 Aug 2019
Source: Efficacy Update Figure 14.2.4.1

Spaghetti plots of the repeated tumour measurements (sum of diameters at each tumour assessment) for each patient, who was censored from the PFS and DoR analyses for reasons apart from data cut off are presented below for PFS and for DoR (below figures) at the time of the updated DCO 08Jun20.

Figure 27 Spaghetti Plot of Sum of Diameters of Target Lesions by ICR for Subjects Censored from the Progression-free Survival Analysis in Study U201 (Enrolled Analysis Set, EMA DCO)

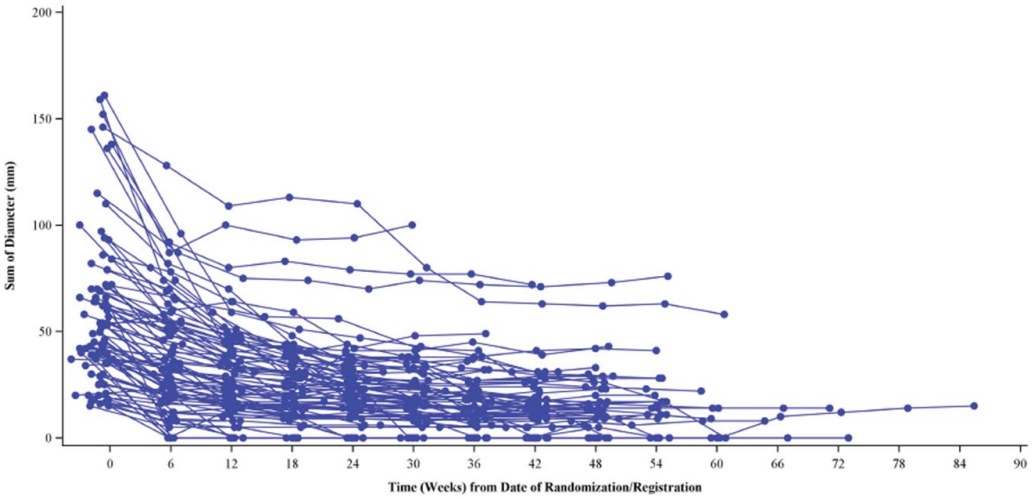
Dose Group: Overall 5.4 mg/kg (N=184)



PFS = progression-free survival
Only includes subjects who were censored from the PFS analyses for reasons apart from data cut-off
Source: EMA Figure 1.1

Figure 28: Spaghetti Plot of Sum of Diameters of Target Lesions by ICR for Subjects Censored from the Duration of Response Analysis in Study U201 (Enrolled Analysis Set, EMA DCO)

Dose Group: Overall 5.4 mg/kg (N=184)

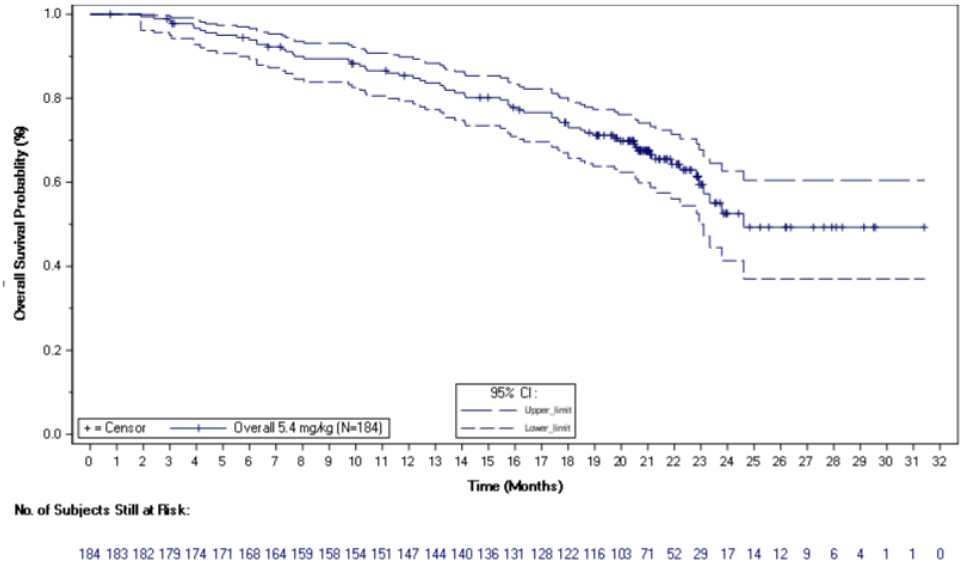


DoR = duration of response
Only includes subjects who were censored from the DoR analyses for reasons apart from data cut-off
Source: EMA Figure 1.3

Additional spaghetti plots of the sum of diameters at each tumour assessment in relation to baseline tumour size for all patients in the EAS with separate figures by best overall response, show that complete responses were mainly recorded in smaller tumours, whereas partial responses were recorded for the full range of tumour sizes (*figures not shown*).

Overall survival

Figure 29 Kaplan-Meier Plot of Overall Survival for the 5.4 mg/kg Dose Cohort (Enrolled Analysis Set)



CI = confidence interval; DCO = data cut-off; EMA = European Medicines Agency; No = number
Source: EMA DCO: Figure 14.2.4.2

The Applicant provided updated OS data based on a DCO of 08 Jun 2020 (EMA DCO), with a median duration of follow-up of 20.5 months. At that time, 37 patients (20.1%) were still on treatment and a total of 65 deaths (35.3% OS events) had occurred among the 184 subjects treated at 5.4 mg/kg. The updated median OS is 24.6 months (95%CI: 23.1, NE) and a further data cut-off for Study U201 is planned for the second quarter of 2021.

Table 35 Updated Overall survival in Study U201 (Enrolled analysis Set) and Published Data

	Median Duration of Follow-up (months)	Overall Survival (months) Median (95% CI)
Study U201 EMA DCO (N = 184)	**20.5**	
Trastuzumab deruxtecan 5.4 mg/kg		24.6 (23.1, NE)
NALA study (N = 621) [1]	**29.9**	
Neratinib + capecitabine (n = 307)		21.0 (17.7, 23.8)
Lapatinib + capecitabine (n = 314)		18.7 (15.5, 21.2)
SOPHIA study (N = 536) [2,3]	**NA (first interim analysis)**	
Margetuximab + chemotherapy (n = 266)		18.9 (16.16, 25.07)
Trastuzumab + chemotherapy (n = 270)		17.2 (15.80, 33.31)
HER2CLIMB (N = 612) [4]	**14.0**	
Tucatinib + trastuzumab + capecitabine (n = 410)		21.9 (18.3, 31.0)
Placebo + trastuzumab + capecitabine (n = 202)		17.4 (13.6, 19.9)

CI = confidence interval; DCO = data cut-off; EMA = European Medicines Agency; NA = not available; NE = not estimable
Source: EMA Tables 14.1.1.1, 14.2.2.3

Exploratory endpoints

Disease control rate (DCR), Clinical benefit rate (CBR), and Time to response (TTR)

Table 36 Confirmed Disease Control Rate and Clinical Benefit rate (Enrolled Analysis Set)

	Part 1 (PK + Dose Finding Stages)		Part 1 + Part 2a	Part 1 + Parts 2a and 2b
	6.4 mg/kg N = 48	7.4 mg/kg N = 21	5.4 mg/kg N = 180	5.4 mg/kg N = 184
Confirmed DCR by ICR				
n (%)	47 (97.9)	21 (100.0)	175 (97.2)	179 (97.3)
95% CI	88.9, 99.9	83.9, 100.0	93.6, 99.1	93.8, 99.1
Confirmed CBR by ICR				
n (%)	41 (85.4)	20 (95.2)	127 (70.6)	130 (70.7)
95% CI	72.2, 93.9	76.2, 99.9	63.3, 77.1	63.5, 77.1
Confirmed DCR by investigator				
n (%)	47 (97.9)	21 (100.0)	175 (97.2)	179 (97.3)
95% CI	88.9, 99.9	83.9, 100.0	93.6, 99.1	93.8, 99.1
Confirmed CBR by investigator				
n (%)	40 (83.3)	20 (95.2)	129 (71.7)	132 (71.7)
95% CI	69.8, 92.5	76.2, 99.9	64.5, 78.1	64.6, 78.1

CBR = clinical benefit rate; CI = confidence interval; DCR = disease control rate; ICR = independent central review; PK = pharmacokinetics
DCR = CR + PR + SD; CBR = CR + PR + SD >6 months
The 2-sided 95% CI were based on the exact (Clopper-Pearson) binomial distribution.
Percentages were based on the number of subjects in the Enrolled Analysis Set.
DCO = 21 Mar 2019
Source: DS8201-A-U201 CSR Table 14.2.4.1

As of the Update DCO, the median TTR by ICR for subjects with confirmed responses by ICR was 1.6 months (95%CI: 1.4, 2.6) for the 184 subjects in Study U201. The median follow-up time is 7.8 months.

Ancillary analyses

Sensitivity analysis (censoring)

The Applicant provided the reasons for censoring patients due to "other reasons" and performed a supplementary analysis, where patients censored due to discontinuation before PD, PD after missing two or more assessments, and initiation of new anti-cancer therapy before PD are imputed as events. Censoring reasons for DoR per the Update DCO (01 Aug 2019) due to "other reasons" were all due to discontinuation before PD/death.

Table 37 Sensitivity Analyses of DoR (Enrolled Analysis Set)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Prespecified Original Analysis of DoR by ICR		
Subjects with confirmed CR/PR, n	112	112[a]
Censored, n (%)	83 (74.1)	73 (65.2)
Ongoing without PD	53 (47.3)	27 (24.1)
Other	30 (26.8)	46 (41.1)
Median	14.8	20.8
95% CI	13.8, 16.9	15.0, NE
Sensitivity Analysis of DoR by ICR		
Events	59 (52.7)	85 (75.9)
Subjects with PD, n (%)	24 (21.4)	32 (28.6)
Imputed events for initiation of new anti-cancer therapy before PD/death, n (%)	0	14 (12.5)
Imputed events for missing 2 or more assessments before PD/death, n (%)	0	1 (0.9)
Imputed events for discontinuation of treatment before PD/death, n (%)	30 (26.8)	31 (27.7)
Death, n (%)	5 (4.5)	7 (6.3)
Subjects censored, n (%)	53 (47.3)	27 (24.1)
Ongoing without PD, n (%)	53 (47.3)	27 (24.1)
Other, n (%)	0	0
DoR (months)		
Median	9.8	10.0
95% CI	7.9, 14.0	7.9, 12.7

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Sensitivity Analysis of DoR by Investigator		
Subjects with confirmed CR/PR, n	123	123
Events	59 (48.0)	92 (74.8)
Subjects with PD, n (%)	28 (22.8)	50 (40.7)
Imputed events for initiation of new anti-cancer therapy before PD/death, n (%)	0	10 (8.1)
Imputed events for missing 2 or more assessments before PD/death, n (%)	0	1 (0.8)
Imputed events for discontinuation of treatment before PD/death, n (%)	29 (23.6)	28 (22.8)
Death, n (%)	2 (1.6)	3 (2.4)
Subjects censored, n (%)	64 (52.0)	31 (25.2)
Ongoing without PD, n (%)	64 (52.0)	31 (25.2)
Other, n (%)	0	0
DoR (months)		
Median	11.1	11.1
95% CI	9.0, 15.2	9.1, 14.5

BOR = best overall response; CI = confidence interval; CR = complete response; DCO = data cut-off; DoR = duration of response; EMA = European Medicines Agency; ICR = independent central review; PD = progressive disease; PR = partial response

[a] One subject had a PR prior to the 08 Jun 2020 cutoff date which was confirmed after the cut-off date. The subject had a confirmed BOR of PR on the first PR date in the central data, but was not included in the analysis of DoR

Subjects censored due to discontinuation before PD, PD after missing 2 or more assessments, and initiation of new anti-cancer therapy before PD are imputed as events

95% CI is computed using the Brookmeyer-Crowley method

Source: 90-day Update Table 14.2.2.1; EMA Tables 14.2.2.1, 1.1, 1.2, 1.3, 1.4

Table 38 Sensitivity Analyses of DoR (Enrolled Analysis Set)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Prespecified Original Analysis of DoR by ICR		
Subjects with confirmed CR/PR, n	112	112[a]
Censored, n (%)	83 (74.1)	73 (65.2)
Ongoing without PD	53 (47.3)	27 (24.1)
Other	30 (26.8)	46 (41.1)
DoR (months)		
Median	14.8	20.8
95% CI	13.8, 16.9	15.0, NE
Sensitivity Analysis of DoR # 1 by ICR with Imputed Events for Subjects Without a PFS Event per ICR, but Who Had PD per Investigator or Treatment Discontinuation for Clinical Progression		
Events, n (%)	39 (34.8)	58 (51.8)
Subjects with PD per ICR	24 (21.4)	32 (28.6)
Subjects with PD per investigator	6 (5.4)	13 (11.6)
Clinical progression	4 (3.6)	6 (5.4)
Death	5 (4.5)	7 (6.3)
Subjects censored, n (%)	73 (65.2)	54 (48.2)
Ongoing without PD	53 (47.3)	27 (24.1)
Other	20 (17.9)	27 (24.1)
DoR (months)		
Median	13.8	14.6
95% CI	9.7, 15.0	10.3, 18.2

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Sensitivity Analyses of DoR #2 by ICR with Imputed Events for Subjects Without a PFS Event per ICR, but Who Had PD per Investigator or Treatment Discontinuation for Clinical Progression, or Started New Cancer Therapy		
Events, n (%)	50 (44.6)	74 (66.1)
Subjects with PD per ICR	24 (21.4)	32 (28.6)
Subjects with PD per investigator	6 (5.4)	13 (11.6)
Clinical progression	4 (3.6)	6 (5.4)
Started new cancer therapy	11 (9.8)	16 (14.3)
Death	5 (4.5)	7 (6.3)
Subjects censored, n (%)	62 (55.4)	38 (33.9)
Ongoing without PD	53 (47.3)	27 (24.1)
Other	9 (8.0)	11 (9.8)
DoR (months)		
Median	13.8	11.4
95% CI	8.5, 14.8	8.5, 14.8

BoR = best overall response; CI = confidence interval; CR = complete response; DCO = data cut-off; DoR = duration of response; EMA = European Medicines Agency; ICR = independent central review; NE = not evaluated or not estimable; PD = progressive disease; PFS = progression-free survival; PR = partial response

[a] One subject had a PR prior to the 08 Jun 2020 DCO which was confirmed after the cut-off date. The subject had a confirmed BOR of PR on the first PR date in the central data, but was not included in the analysis of DoR

95% CI was computed using the Brookmeyer-Crowley method

Median, 25th Percentile, 75th Percentile, Point Estimate and 95% CI at 3, 6, 9, 12, 18 and 24 months are based on Kaplan-Meier Estimate

For PD per investigator, event date = first PD date per investigator; for clinical progression, event date = date of treatment discontinuation; for starting new cancer therapy, event date = censoring date per prespecified original analysis (date of last tumor scan prior to start of new cancer therapy).

Source: 90-day Update Table 14.2.2.1; EMA Tables 14.2.2.1, Tables 4.1, 4.2, 5.1, 5.2

The sensitivity analyses presented in table 1 above show that the median DOR is changed from 14.8 months per the original (prespecified) analysis to 9.8 months or from 20.8 months per the original (prespecified) analysis to 10.0 months. It is noted that more patients were censored for DOR at EMA DCO (n=46) vs update DCO (n=30) and this may have impacted the analyses.

Table 2 show performed the requested additional sensitivity analyses, with clinical progression and investigator determined PD counted as events rather than censored, and the median DoR for the EMA DCO is estimated to be 14.6 months (95%CI 10.3, 18.2).

Table 39 Sensitivity Analyses of PFS (Enrolled Analysis Set)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Original Prespecified Analysis of PFS by ICR		
Subjects with events, n (%)	58 (31.5)	70 (38.0)
Subjects censored, n (%)	126 (68.5)	114 (62.0)
No PD or death, n (%)	118 (64.1)	85 (46.2)
No post-baseline tumor assessment, n (%)	1 (0.5)	1 (0.5)
New anticancer therapy, n (%)	7 (3.8)	26 (14.1)
Missed 2 consecutive tumor assessments	0	2 (1.1)
Median	16.4	19.4
95% CI	12.7, NE	14.1, NE
Sensitivity Analysis of PFS by ICR		
Subjects with events, n (%)	116 (63.0)	148 (80.4)
Subjects with PD, n (%)	48 (26.1)	58 (31.5)
Imputed events for initiation of new anti-cancer therapy without prior PD, n (%)	7 (3.8)	26 (14.1)
Imputed events for missing 2 or more assessments before PD/death, n (%)	0	2 (1.1)
Imputed events for discontinuation of treatment before PD/death, n (%)	51 (27.7)	50 (27.2)
Death	10 (5.4)	12 (6.5)
Subjects censored, n (%)	68 (37.0)	36 (19.6)
No baseline tumor assessments	0	0
No post-baseline tumor assessment	1 (0.5)	1 (0.5)
Ongoing without PD or death	67 (36.4)	35 (19.0)
PFS (months)		
Median	9.6	9.5
95% CI	7.1, 11.1	7.0, 11.3
Sensitivity Analysis of PFS by Investigator		
Subjects with events, n (%)	105 (57.1)	146 (79.3)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	EMA DCO 08 Jun 2020
Subjects with PD, n (%)	51 (27.7)	74 (40.2)
Imputed events for initiation of new anti-cancer therapy without prior PD, n (%)	2 (1.1)	15 (8.2)
Imputed events for missing 2 or more assessments before PD/death, n (%)	1 (0.5)	2 (1.1)
Imputed events for discontinuation of treatment before PD/death, n (%)	43 (23.4)	46 (25.0)
Death	8 (4.3)	9 (4.9)
Subjects censored, n (%)	79 (42.9)	38 (20.7)
No baseline tumor assessments	0	0
No post-baseline tumor assessment	1 (0.5)	1 (0.5)
Ongoing without PD or death	78 (42.4)	37 (20.1)
PFS (months)		
Median	10.5	10.6
95% CI[a]	8.2, 12.7	8.2, 12.5

CI = confidence interval; DCO = data cut-off; EMA = European Medicines Agency; ICR = independent central review; NE = not evaluated or not estimable; PD = progressive disease; PFS = progression free survival
Subjects censored due to discontinuation before PD, PD after missing 2 or more assessments, and initiation of new anti-cancer therapy before PD are imputed as events.
[a] 95% CI is computed using the Brookmeyer-Crowley method.
Source: 90-day Update Table 14.2.2.2; EMA Tables 14.2.2.2, 2.1, 2.2, 2.3, 2.4

Table 40 Sensitivity Analyses of PFS with Imputed Events for Discontinuation due to an Investigator-assessed Progressive Disease (Enrolled Analysis Set)

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	EMA DCO 08 Jun 2020
Original Prespecified Analysis of PFS by ICR		
Subjects with events, n (%)	58 (31.5)	70 (38.0)
Subjects censored, n (%)	126 (68.5)	114 (62.0)
No PD or death	118 (64.1)	85 (46.2)
No post-baseline tumor assessment	1 (0.5)	1 (0.5)
New anticancer therapy	7 (3.8)	26 (14.1)
Missed 2 consecutive tumor assessments	0	2 (1.1)
PFS (months)		
Median	16.4	19.4
95% CI	12.7, NE	14.1, NE
Sensitivity Analysis of PFS # 1 by ICR with Imputed Events for Subjects Without a PFS Event per ICR, but Who Had PD per Investigator or Treatment Discontinuation for Clinical Progression		
Subjects with events, n (%)	82 (44.6)	103 (56.0)
Subjects with PD per ICR	48 (26.1)	58 (31.5)
Subjects with PD per investigator	19 (10.3)	26 (14.1)

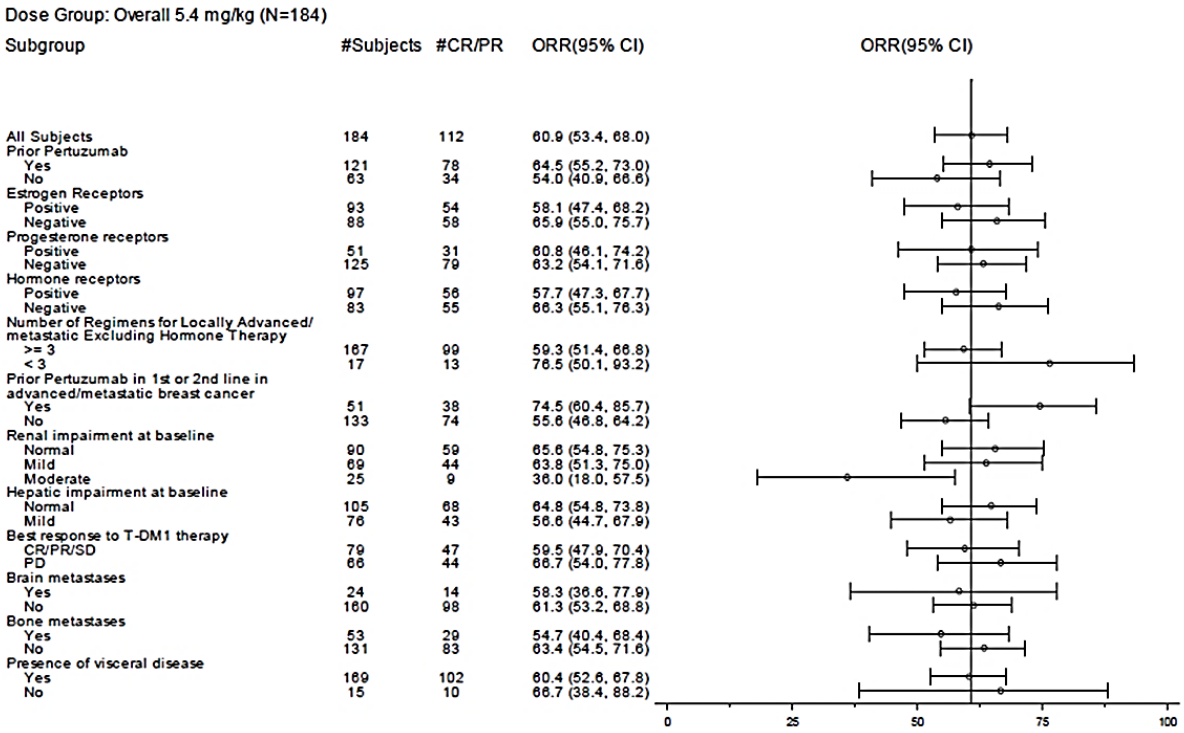
	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Clinical progression	5 (2.7)	7 (3.8)
Death	10 (5.4)	12 (6.5)
Subjects censored, n (%)	102 (55.4)	81 (44.0)
No baseline tumor assessments	0	0
No post-baseline tumor assessment	1 (0.5)	1 (0.5)
Start new cancer therapy	2 (1.1)	12 (6.5)
Missed 2 or more tumor assessments before PD/death per ICR	0	1 (0.5)
Ongoing without PD or death	99 (53.8)	67 (36.4)
PFS (months)		
Median	12.7	12.7
95% CI	9.9, 16.4	(10.5, 15.8

	Study U201 5.4 mg/kg Parts 1 + 2a + 2b (N = 184)	
	Update DCO 01 Aug 2019	**EMA DCO 08 Jun 2020**
Sensitivity Analyses of DoR #2 by ICR with Imputed Events for Subjects Without a PFS Event per ICR, but Who had PD per Investigator or Treatment Discontinuation for Clinical Progression, or Started New Cancer Therapy		
Subjects with events, n (%)	103 (56.0)	133 (72.3)
Subjects with PD per ICR	48 (26.1)	58 (31.5)
Subjects with PD per investigator	19 (10.3)	26 (14.1)
Clinical progression	5 (2.7)	7 (3.8)
Start new cancer therapy	21 (11.4)	30 (16.3)
Death	10 (5.4)	12 (6.5)
Subjects censored, n (%)	81 (44.0)	51 (27.7)
No baseline tumor assessments	0	0
No post-baseline tumor assessment	1 (0.5)	1 (0.5)
Missed 2 or more tumor assessments before PD/death per ICR	0	1 (0.5)
Ongoing without PD or death	80 (43.5)	49 (26.6)
PFS (months)		
Median	9.9	9.7
95% CI	8.1, 12.7	8.1, 12.4

CI = confidence interval; DCO = data cut-off; EMA = European Medicines Agency; ICR = independent central review; NE = not evaluated or not estimable; PD = progressive disease; PFS = progression free survival
95% CI was computed using the Brookmeyer-Crowley method.
Median, 25th Percentile, 75th Percentile, Point Estimate and 95% CI at 3, 6, 9, 12, 18 and 24 months are based on Kaplan-Meier Estimate
For PD per investigator, event date = first PD date per investigator; for clinical progression, event date = date of treatment discontinuation; for starting new cancer therapy, event date = censoring date per prespecified original analysis (date of last tumor scan prior to start of new cancer therapy). Source: 90-day Update Table 14.2.2.2; EMA Tables 14.2.2.2, 2.1, 2.2, 3.1, 3.2

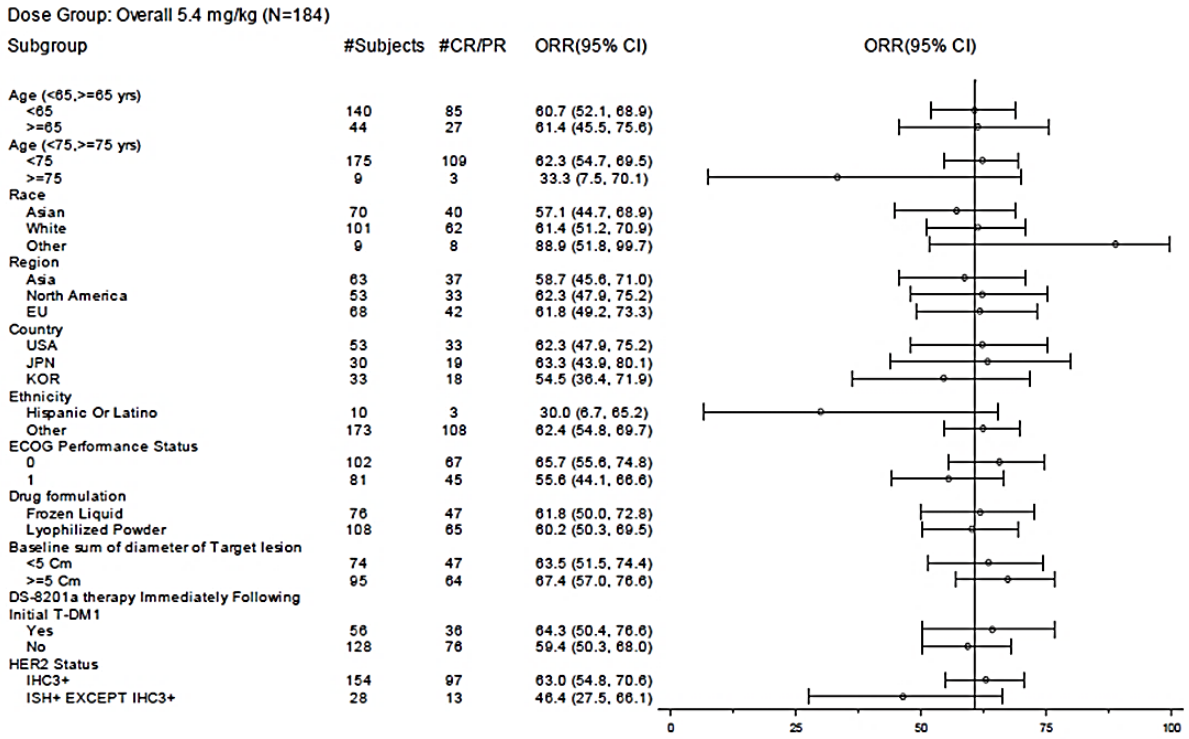
Subgroup Analysis of Duration of Confirmed Response Study 201

Figure 30 Forest Plot of Objective Response Rate by Independent Central Review by Subgroup in Study U201 at Update Data Cut-off (Intent-to-Treat Population) (Please note: 15 subjects had no measurable target lesions at baseline by ICR)



CI = confidence interval; CR = complete response; PR = partial response; ORR = objective response rate (% of subjects with best overall response of complete response and partial response with confirmation by independent central review, based on RECIST version 1.1); PD = progressive disease; SD = stable disease
The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) distribution.
Update DCO = 01 Aug 2019
Source: Efficacy Update Figure 14.2.5.1

Figure 31 Forest Plot of Objective Response Rate by Independent Central Review by Subgroup in Study U201 at Update Data Cut-off (Intent-to-Treat Population) (Please note: 15 subjects had no measurable target lesions at baseline by ICR) (Continued)



CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EU = Europe; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; JPN = Japan; KOR = South Korea; PR = partial response; ORR = objective response rate (% of subjects with best overall response of complete response and partial response with confirmation by independent central review, based on RECIST version 1.1); T-DM1 = trastuzumab emtansine; USA = United States of America;

The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) distribution.

Update DCO = 01 Aug 2019

Source: Efficacy Update Figure 14.2.5.1

Subgroup analyses of DoR for confirmed responses by ICR as of the Update DCO for subgroups based on HR status (positive/negative) and prior pertuzumab use (yes/no) in Study U201 showed the following:

- The median DoR was 13.8 months (95%CI: 9.7, 15.0) for patients, who were HR-positive (54/184 patients) and 14.8 months (95%CI: 14.8, NE) for those who were HR-negative (55/184 patients).
- The median DoR was 15.0 months (95%CI: 14.8, NE) for patients, who had received prior pertuzumab (76/184 patients) and 13.8 months (95%CI: 9.0, 13.8) for those who had not received prior pertuzumab (34/184 patients).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 41. Summary of efficacy for trial DS8201-A-U201

Title: Phase 2 Multicenter, Open-label Study of DS-8201a [Trastuzumab Deruxtecan], an Anti-HER2-Antibody Drug Conjugate (ADC) for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1

Study identifier	DS8201-A-U201; Eudra CT: 2016-004986-18 / IND Number: 127553		
Design	Phase 2, 2-part open-label, multicentre study to justify the recommended dose of trastuzumab deruxtecan and investigate further the safety and efficacy in subjects with unresectable and/or metastatic human epidermal growth factor receptor (HER)2-positive breast cancer (BC) previously treated with trastuzumab emtansine (TDM1). Eligible subjects were administered trastuzumab deruxtecan intravenously (IV) every 3 weeks (Q3W). Part 1 was randomized (stratified by region: Asia, rest of the world) and designed to bridge Phase 1 experience to the to-be marketed product (new process, new formulation) and adequately support dose and regimen recommendations. • In the PK stage of Part 1, subjects were randomized (1:1:1) to either 5.4, 6.4, or 7.4 mg/kg trastuzumab deruxtecan. After review of the PK, 2 dose levels were to be selected for further evaluation. • In the Dose Finding stage of Part 1, subjects were randomized in a 1:1 ratio to 1 of the 2 doses selected, and a dose-justification exposure response (ER) (exposure-efficacy and exposure-safety) analysis was to be conducted to determine the optimal dose of trastuzumab deruxtecan. Part 2 was not randomized, all subjects received trastuzumab deruxtecan at the recommended dose determined in Part 1. Part 2 was subdivided into 2 cohorts: • Part 2a included approximately 100 subjects. • Part 2b, was an exploratory cohort to explore the efficacy of trastuzumab deruxtecan in subjects who discontinued T-DM1 for reasons other than disease progression (PD). Enrollment in Part 2b would be completed when approximately 100 subjects had been enrolled in Part 2a. The expected enrolment in Part 2b was approximately 10 to 15 subjects.		
	Duration of main phase:		Treatment continued until there was no longer clinical benefit from therapy, withdrawal of consent, or until unacceptable toxicity occurred.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Exploratory: trastuzumab deruxtecan will confer a significant benefit in Overall response rate (ORR) in subjects with HER2-positive BC who are resistant or refractory to T-DM1		
Treatment groups	5.4 mg/kg		Part 1+ Parts 2a and 2b receiving trastuzumab deruxtecan IV Q3W 5.4 mg/kg 184 subjects treated
	6.4 mg/kg		Part 1 receiving trastuzumab deruxtecan IV Q3W 6.4 mg/kg 48 subjects treated
	7.4 mg/kg		Part 1 receiving trastuzumab deruxtecan IV Q3W 7.4 mg/kg 21 subjects treated
Endpoints and definitions	Overall response rate	ORR	Proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by ICR.
	Duration of response	DoR	Time interval between the date of the first documentation of objective response (CR or PR) and the date of the first objective documentation of PD or death due to any
	Disease control rate	DCR	Proportion of subjects with a BOR of CR, PR, or stable disease (SD).

	Progression-free survival	PFS	Time from the date of registration/ randomization to the earlier of the dates of the first documentation of disease progression or death due to any cause.
	Overall survival	OS	Time interval from the date of registration/ randomization to the date of death from any cause.
Database lock	The data cut-off (DCO) date for the primary analysis (clinical study report [CSR] DCO) was set to occur after approximately 6 months of follow-up from the date of first dosing of the last subject enrolled. The DCO for the clinical study report was 21 Mar 2019. The database lock date was 18 Apr 2019. In addition, an efficacy update has been provided using a DCO of 01 Aug 2019.		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Enrolled analysis set Median duration of follow-up up (last visit date – randomization/registration date +1]/365.25*12) in subjects who received 5.4 mg/kg for the CSR DCO (21 Mar 2019) was 7.2 months (range: 0.7-17.2) and median duration of treatment was 6.90 (0.7-16.1). Subjects assigned to 6.4 mg/kg trastuzumab deruxtecan, had a median treatment duration of 9.70 months (range: 0.7-16.2). Subjects assigned to 7.4 mg/kg trastuzumab deruxtecan, had a median treatment duration of 7.60 months (range: 2.7-15.6). At the Efficacy Update DCO (01 Aug 2019), the median treatment duration for subjects receiving 5.4 mg/kg was 9.97 months (range: 0.7, 20.5) and the median duration of follow-up was 11.1 months (range: 0.7-19.9).

Descriptive statistics and estimate variability	Treatment group	5.4 mg/kg	6.4 mg/kg	7.4 mg/kg
	CSR DCO (21 Mar 2019)			
	Number of subjects	184	48	21
	ORR[a], n (%) [95% CI]	111 (60.30) [52.9, 67.5]	33 (68.8) [53.8, 81.3]	17 (81.0) [58.1, 94.6]
	DoR Median[b] [95% CI] months	NE [NE, NE]	NE [8.3, NE]	6.0 [4.8, 8.3]
	DCR[c], n (%) [95% CI]	179 (97.3) [93.8, 99.1]	47 (97.9) [88.9, 99.9]	21 (100.0) [83.9, 100.0]
	PFS, n (%) Median[b] [95% CI] months	40 (21.7) NE [10.6, NE]	12 (25.0) NE [NE, NE]	11 (52.4) 9.5 [7.4, 13.2]
	OS, n (%) Median[b] [95% CI] months	19 (10.3) NE [NE, NE]	7 (14.6) NE [NE, NE]	8 (38.1) NE [NE, NE]
	Efficacy update (DCO 01 Aug 2019)			
	ORR, n (%) [95% CI]	112 (60.9) [53.4, 68.0]		
	DoR Median[b] [95% CI] months	14.8 [13.8, 16.9]		
	PFS, n (%) Median[b] [95% CI] months	58 (31.5) 16.4 [12.7, NE]		
	Efficacy update (DCO 08 June 2020)			

	ORR, n (%) [95% CI]	111 (61.4) [54.0, 68.5]	
	DoR Median[b] [95% CI] months	20.8 [15, NE]	
	PFS, n (%) Median[b] [95% CI] months	70 (38) 19.4 [14.1, NE]	
	OS, n (%) Median[b] [95% CI] months	65 (35.3%) 24.6 23.1; NE	
Notes	NE represents not estimable Results, apart from OS, are based on the ICR assessment [a] 95% exact binomial confidence interval (CI) [b] Median is from a Kaplan-Meier estimate. The CI for the median was computed using the Brookmeyer-Crowley method. [c] Disease Control Rate (DCR) was calculated as the proportion of subjects demonstrating CR, PR, or SD.		

Analysis performed across trials (pooled analyses and meta-analysis)

A pooled efficacy analysis was performed based on DS8201-A-J101 and DS8201-A-U201 at time of DCO for patients with HER2-positive breast cancer and assigned to the 5.4 mg/kg dose of trastuzumab deruxtecan. The pooled analysis set included a total of 235 randomized patients (n=51 from J101 and n=184 from U201) of which 234 were treated. The median duration of follow-up was 7.40 months (range: 0.7, 30.4) and 120 (51.3%) patients were ongoing on study treatment. For the pooled analysis set, ORR was 58.3% (95%CI: 51.7%, 64.7%), median DoR was 16.9 months (95%CI: 9.5, NE), and median PFS was 13.9 months (95%CI: 10.9, NE).

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Comparison with available therapies in the context of CMA

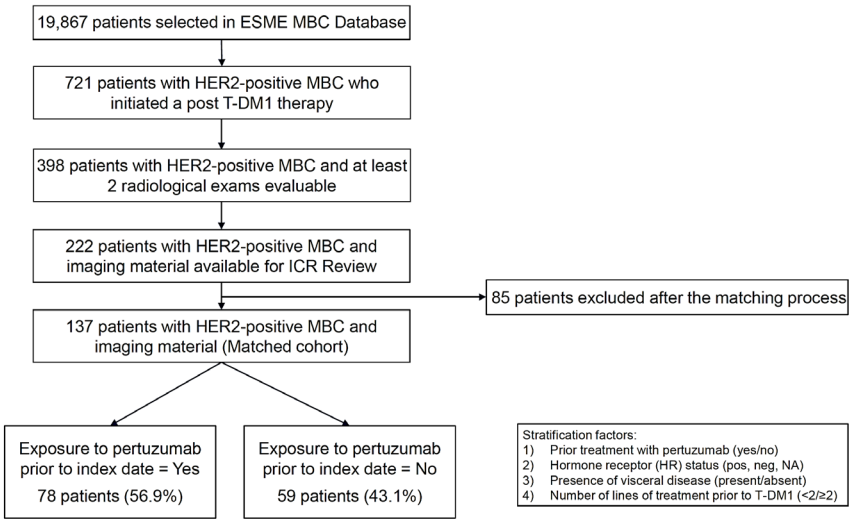
The Applicant submitted results from two additional studies (historical controls) to contextualize the results of the pivotal study, the Unicancer study and a literature-based study (DS8201-PMx004).

Real World Evidence – the Unicancer Study

To supplement the clinical data package with real-world evidence and to estimate the expected clinical benefit (PFS, ORR) of other therapies with a comparable patient population, individual patient data were collected and analysed by Unicancer, a French network of 18 FCCCs. Beginning in 2008, Unicancer ESME research program has centralized existing real-world patient data in oncology to provide independent aggregated data for analysis. From the Unicancer ESME database of approximately 60,000 patients, a total of 19,867 patients were treated for metastatic breast cancer at any of the 18 FCCCs. From this database, 2 datasets were generated by Unicancer: The Reference Cohort and the Matched Cohort.

The Reference Cohort dataset (N=721) consisted of data from patients with metastatic HER2-positive breast cancer who had initiated treatment in the metastatic setting between 01 Jan 2008 and 31 Dec 2016 and received at least 1 therapy post treatment with TDM1 as of 17 Sep 2018. Of these 721 patients, 398 patients had at least 2 evaluable radiological exams and imaging data from 222 patients could be made available for ICR assessment. These 222 patients in the Reference Cohort went through a matching process to identify patients with comparable baseline characteristics to those of the 180 subjects treated at the 5.4 mg/kg dose in Study U201 Part 1 and Part 2a (at a DCO of 10 Dec 2018). Using the propensity score caliper matching method, 1 patient from the Reference Cohort was matched to 1 subject from Study U201 without replacement, provided that the absolute difference in the logit of propensity score of the matched pair was less than a prespecified threshold (the caliper). Prespecified demographics and baseline characteristics considered for matching were: 1) Prior treatment with pertuzumab (yes/no); 2) HR status at T DM1 therapy (positive/negative/not determined); 3) Presence of visceral disease at index date (present/absent); 4) Number of lines of treatment prior to T DM1 (<2/≥2). The matching algorithm continued until either each Study U201 subject was matched with a patient from the Reference Cohort or no matching pairs could be found using the caliper. A 1:1 match within the prespecified threshold of the caliper was not possible for all Study U201 subjects as the Reference Cohort did not include enough patients within the caliper: 137/222 patients from the Reference Cohort were matched with 137 subjects from Study U201; 85/222 patients were excluded after the matching process.

Figure 32 Generating the Matched Cohort in the Unicancer Study



Source: adapted from Module 5.3.5.3 UARP MBC2018-10 v2.1 Table 1

In the Matched Cohort, 136 patients were female and 1 was male, whereas all 137 Study U201 subjects were female. A total of 40.9% of Matched Cohort patients and 48.2% of Study U201 subjects were <55 years of age. There were 59.9% of Matched Cohort patients and 56.9% of Study U201 subjects who were HR-positive at the time that TDM1 treatment was initiated. A difference in ECOG PS between Matched Cohort patients and Study U201 subjects was observed: 35.8% of Matched Cohort patients had an ECOG PS of 0 and 64.2% had an ECOG PS ≥1, while 54.7% of Study U201 subjects had an ECOG PS of 0 and 45.3% had an ECOG ≥1. However, patients in the Matched Cohort were relatively healthy as evidenced by the 91.7% 6-month survival rate from the date of the first subsequent treatment following the TDM1 based regimen.

The primary objective of both the Reference Cohort and Matched Cohort was to describe patient characteristics and clinical features, and a secondary objective was to describe the treatment strategies for these patients. A comparison of the baseline characteristics indicates that patients in the Reference Cohort had a lower rate of exposure to pertuzumab prior to TDM1 therapy than patients in the Matched Cohort (38.7% vs. 56.9%, respectively). The difference between the Reference Cohort and Matched Cohort in pertuzumab exposure prior to TDM1 therapy is likely due to the difference in enrolment timeframes.

The Reference Cohort included patients treated between 01 Jan 2008 and 31 Dec 2016. Pertuzumab became available for commercial use in France beginning Mar 2013. The first subject was enrolled in Study U201 in Sep 2017. The Matched Cohort, therefore, included a higher proportion of patients with prior pertuzumab to correspond to the more recent treatment patterns included in Study U201.

Matched patients received a median of 7.0 lines of treatment for their metastatic breast cancer with a median of 3.0 lines of treatment, including TDM1, prior to the index date. Prior to the index date, 94.9% of matched patients received trastuzumab. A total of 89.8% received a taxane, 48.9% received an anthracycline, 32.8% received an anti-estrogen, and 32.8% received an aromatase inhibitor.

In the line of therapy immediately after TDM1, a total of 73.7% of patients in the Matched Cohort received an anti-HER2 therapy: 48.9% of patients received trastuzumab, 29.9% received lapatinib, 2.2% received TDM1, and 2.2% received another anti-HER2 treatment. A total of 35.0% of patients received oral chemotherapy, 37.2% received IV chemotherapy, and 12.4% received endocrine therapy. Disease progression was the most common reason for termination.

Table 42: Baseline characteristics of patients before and after matching

		Before Matching			After Matching		
		U201 (N=180)	Unicancer (N=222)	Standardized Difference of the Mean	U201 (N=137)	Unicancer (N=137)	Standardized Difference of the Mean
Exposure to pertuzumab prior the index date		118 (65.6%)	106 (47.7%)	0.3653	81 (59.1%)	78 (56.9%)	-0.0444
HR Status at T-DM1	Positive	92 (51.1%)	142 (64.0%)	0.2857	78 (56.9%)	82 (59.9%)	0.0599
	Negative	81 (45.0%)	77 (34.7%)		57 (41.6%)	53 (38.7%)	
	ND	7 (3.9%)	3 (1.4%)		2 (1.5%)	2 (1.5%)	
Metastases type at index date: Visceral		121 (67.2%)	193 (86.9%)	-0.4825	115 (83.9%)	111 (81.0%)	-0.0769
Treatment lines before TDM-1 (excluded)	<2	34 (18.9%)	50 (22.5%)	-0.0898	29 (21.2%)	30 (21.9%)	0.0178
	≥2	146 (81.1%)	172 (77.5%)		108 (78.8%)	107 (78.1%)	
ECOG at index date in classes	0	100 (55.6%)	42 (33.1%)	0.4647	75 (54.7%)	29 (35.8%)	0.3876
	≥1	80 (44.4%)	85 (66.9%)		62 (45.3%)	52 (64.2%)	
	Not Available	0	95		0	56	
Age at index date in classes	<55	87 (48.3%)	101 (45.5%)	0.0569	66 (48.2%)	56 (40.9%)	0.1473
	≥55	93 (51.7%)	121 (54.5%)		71 (51.8%)	81 (59.1%)	
Sex	Male	0	4 (1.8%)	-0.1916	0	1 (0.7%)	-0.1213
	Female	180 (100.0%)	218 (98.2%)		137 (100.0%)	136 (99.3%)	

ECOG = Eastern Cooperative Oncology Group; HR = hormone receptor; ND = not determined; T-DM1 = trastuzumab emtansine; U201 = Study DS8201-A-U201

Objective response rates in first-line treatment post-TDM1 for patients in the Matched Cohort were evaluated by an ICR. Of the 137 patients in the Matched Cohort, 22 patients were excluded during central review because the image quality of the submitted scans was such that the radiologist reviewer was not able to assess the response. These subjects are listed as "unknown". The remaining 115 matched subjects were used for analysis of response. The ORR for the Matched Cohort was equal to

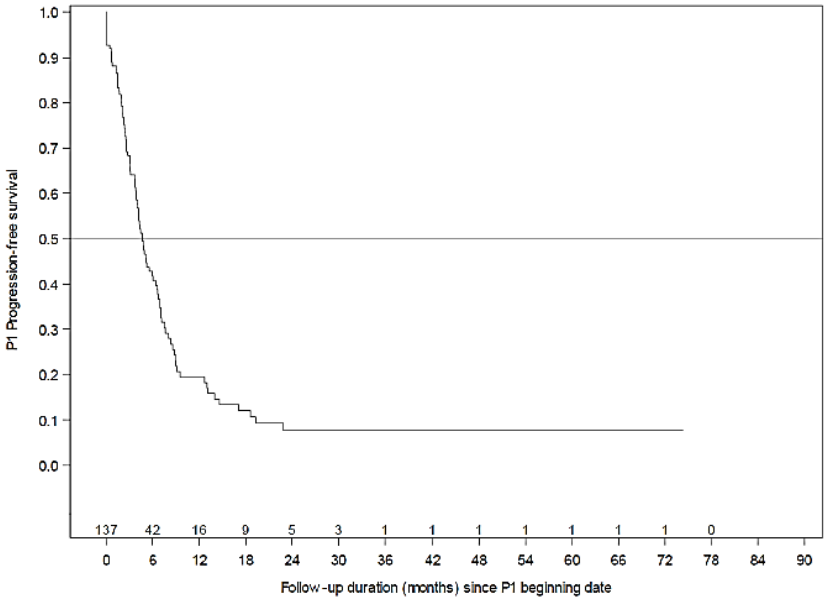
the PR rate (12.2%; 95%CI: 6.2, 18.2) (Table 2.2). The DCR, which included both subjects with target lesions and those with non-target lesions only (as per RECIST v1.1) at baseline, was 73.9% (95%CI: 65.9, 81.9) (Table below).

Table 43: Objective Response Rate and Disease Control Rate for the Matched Cohort and According to Exposure to Pertuzumab Prior to the Index Date (Unicancer Study)

		Matched Cohort (N=115)	Pertuzumab Exposure Prior Index Date	
			Yes (N=66)	No (N=49)
BOR	CR	0	0	0
	PR	14 (12.2%)	11 (16.7%)	3 (6.1%)
	SD	42 (36.5%)	27 (40.9%)	15 (30.6%)
	PD	30 (26.1%)	16 (24.2%)	14 (28.6%)
	Non-CR/Non-PD	29 (25.2%)	12 (18.2%)	17 (34.7%)
ORR (CR + PR)		14 (12.2%)	11 (16.7%)	3 (6.1%)
95% CI		6.2 - 18.2*	7.7 - 25.7*	1.3 - 16.9**
DCR (CR + PR + SD + non-CR/non-PD)		85 (73.9%)	50 (75.8%)	35 (71.4%)
95% CI		65.9 - 81.9*	65.4 - 86.1*	58.8 - 84.1*

BOR = best overall response; CI = confidence interval; CR = complete response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease
*95% normal CI
**95% exact binomial CI
Source: Module 5.3.5.3 UARP MBC2018-10 Table 21

***Figure 33** PFS curve during the first subsequent treatment post TDM-1 – matched cohort*



The median PFS for patients in the Matched Cohort was 4.7 months (95%CI: 3.8, 6.0). The median OS evaluated using the start date of the line of therapy after T-DM1 as the reference date was 24.1 months (95%CI: 18.5, 26.4). A sensitivity analysis was performed to determine the robustness of the results from the Matched Cohort analysis, but is not shown here.

Literature Based Analysis (DS8201-PMx004): Comparator Analysis in Metastatic Breast Cancer using Model-Based Meta-Analysis

To understand the historical context of expected response rates of trastuzumab deruxtecan in the post-trastuzumab setting, a literature-based analysis was conducted. The objectives of this analysis were twofold:

• Review literature for prospective or retrospective trials in second line or later advanced or metastatic breast cancer who previously received prior trastuzumab and chemotherapy.

• Perform a model-based meta-analysis to quantify ORR, median PFS time, and median OS time in this population for comparison with ongoing trials of trastuzumab deruxtecan.

An initial review was performed for trials conducted in populations after prior trastuzumab and a taxane. The search criteria were subsequently broadened to include trials in second line or later advanced or metastatic breast cancer in subjects who received prior trastuzumab and any chemotherapy. Specifically, the following study inclusion and exclusion criteria were applied:

Inclusion criteria:

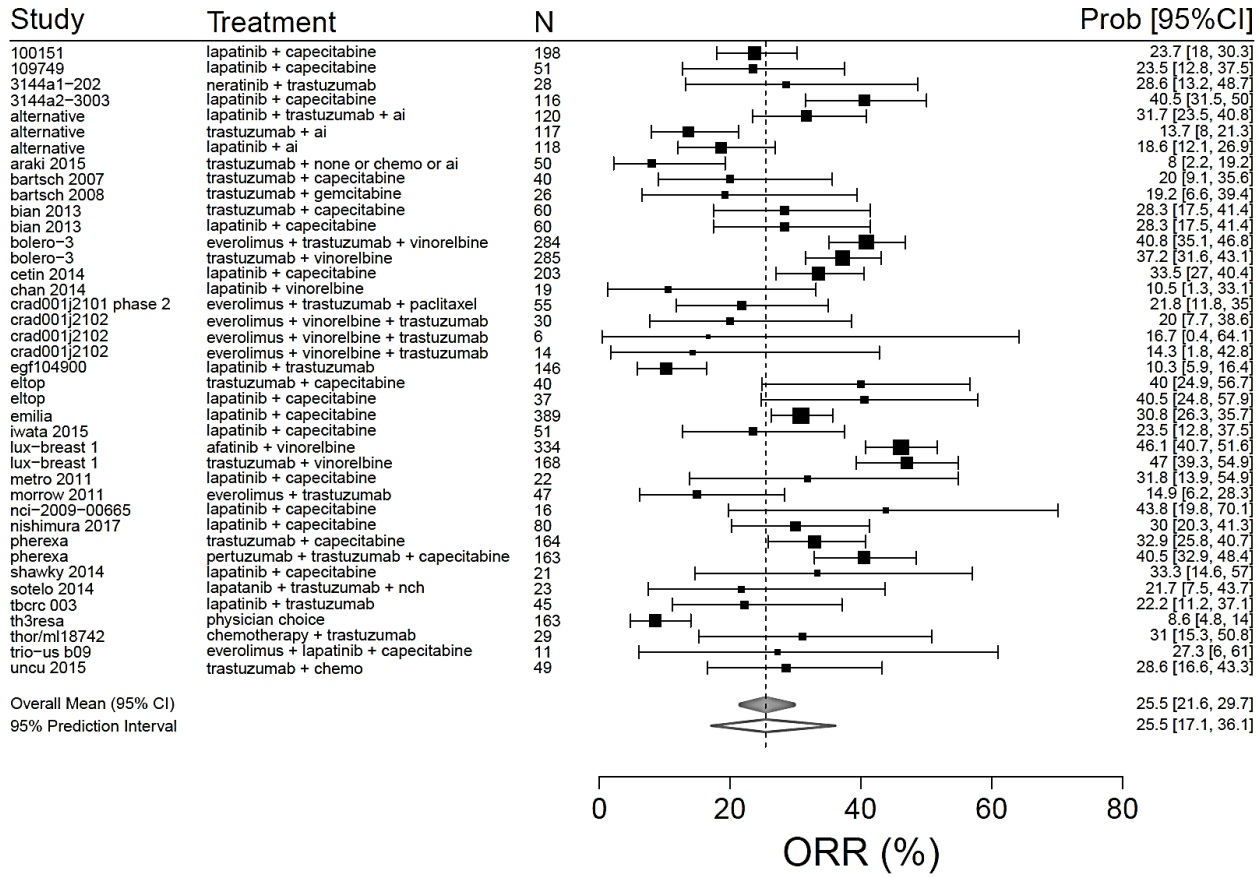
- Reports (full papers and abstracts) of prospective and retrospective studies on treatment of subjects with advanced or metastatic breast cancer who were HER2-positive and had previously received trastuzumab and taxanes or other chemotherapies.
    - The study included an anti-HER2 therapy, which is required by NCCN and ESMO guidelines. The study had to include at least 1 of the clinical outcomes, response to treatment (i.e., ORR) or survival (i.e., median PFS, median OS) (English language)

Exclusion criteria:

- Indication: The purpose of the study was not second-line or later treatment for advanced or metastatic breast cancer.
- Publication: The study did not add new data (e.g., reviews, meta-analysis, preclinical research, letter, case report, etc.) or the report duplicated prior published results.
- Treatment: The regimens in the study did not include an anti-HER2 therapy; or the study or arm reported unapproved therapies, surgery, radiotherapy, dietary supplements, or observation; or the study or arm reported TDM1 treatment results.
- Population: Prior therapy was not trastuzumab plus taxanes or other chemotherapies.
- Endpoints: no outcome of interest.

In total, 258 references were selected for review and 64 references from 58 studies were selected for data extraction. Another 21 studies were excluded, as either reporting results for TDM1 or for investigational agents that have not received marketing authorization. In total, 8827 subjects from 48 treatment arms and 37 studies were included in the analysis of ORR, median PFS, and median OS.

***Figure 34**: Forest Plot of Objective Response Rates (Literature Based Analysis)*

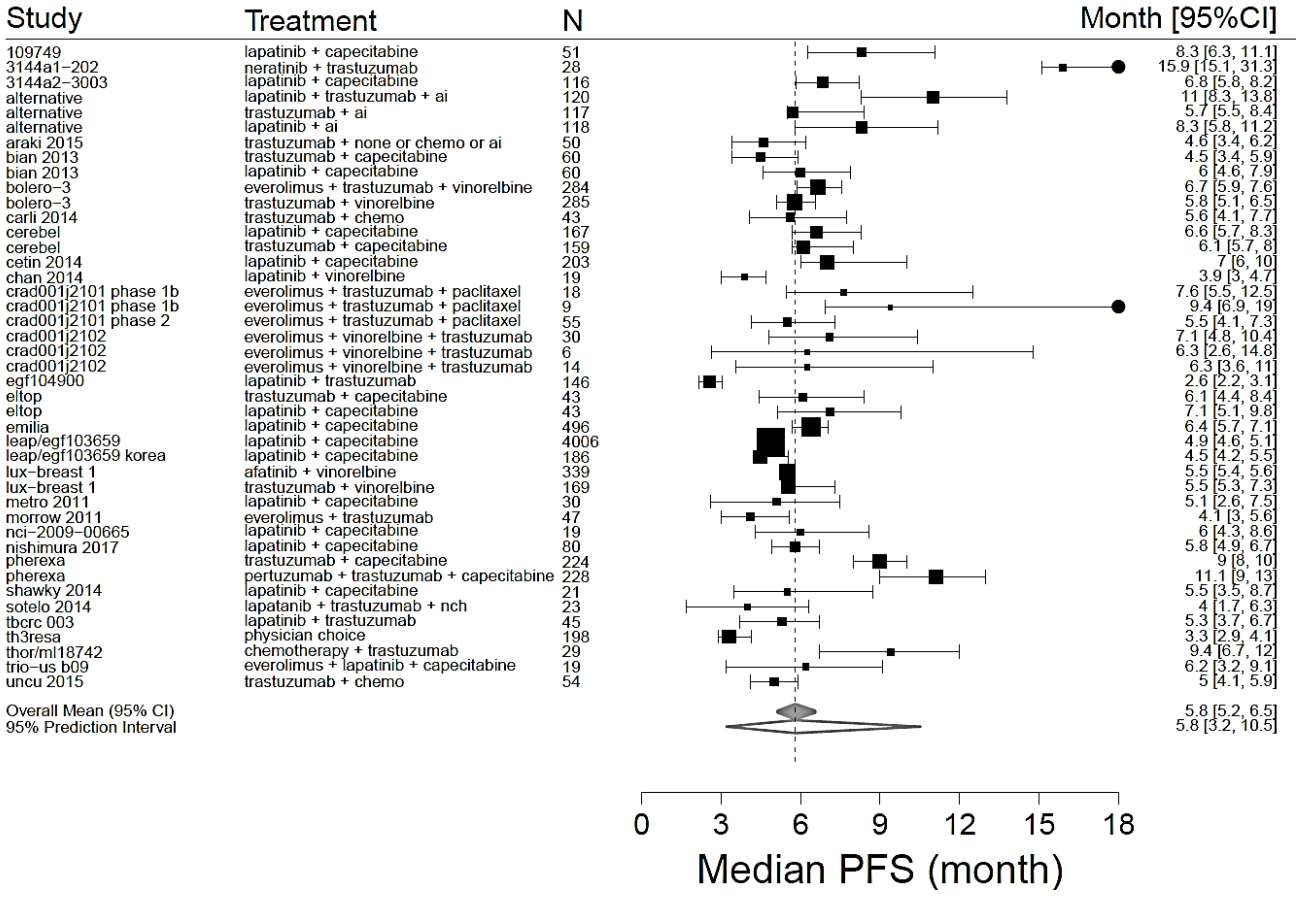


CI = confidence interval; ORR = objective response rate; prob = probability

Note: Points indicate the objective response rate (ORR, %), and horizontal lines indicate the corresponding 95% CI. Symbol sizes indicates relative sample size. Dashed vertical line is the weighted mean. The shaded diamond represents 95% CIs for the mean value using a mixed-effects model. The nonshaded diamond represents 95% prediction intervals incorporating trial-to-trial variability. Some controlled trials, eg, THE3RESA, are only represented by one arm, because the treatment for the other arm, eg, T-DM1, was excluded from this analysis.

Source: Module 5.3.5.3 Literature Based Analysis Figure 4-2

Figure 35 ***Forest Plot of Median Progression-free Survival (Literature Based Analysis)***



CI = confidence interval; PFS = progression-free survival; prob = probability
Note: Points indicate the median PFS value. Horizontal lines indicate the 95% CI. The solid circle at 18 months indicates the upper confidence band goes past 18 months. Symbol sizes indicates relative sample size. Dashed vertical line is the weighted mean. The shaded diamond represents 95% CIs for the mean value using a mixed-effects model. The nonshaded diamond represents 95% prediction intervals incorporating trial-to-trial variability. Some controlled trials, eg, THE3RESA, are only represented by one arm, because the treatment for the other arm, eg, T-DM1, was excluded from this analysis.
Source: Module 5.3.5.3 Literature Based Analysis Figure 4-4

Table 44: Summary of Studies in Published Literature with a Median of at Least 2 Prior Anti-HER2-Based Regimens

Study	Arm	Treatment	Prior Regimens of Anti- HER2	N	ORR (%)	PFS (months)	OS (months)
Araki 2015	1	trastuzumab + none or chemotherapy or aromatase inhibitor	3	50	8	4.6	33.7
Bartsch 2008	1	trastuzumab + gemcitabine	2-5	29	19	--	17
Carli 2014	1	trastuzumab + chemotherapy	2+	43	--	5.6	28
Chan 2014	1	lapatinib + vinorelbine	2	19	11	3.9	9.1
Egf104900	2	lapatinib + trastuzumab	3	146	10	2.6	14
Nishimura 2017	1	lapatinib + capecitabine	2+	80	30	5.8	30
Th3resa	2	physician choice	2+	198	9	3.3	15.8
Uncu 2015	1	trastuzumab + chemotherapy	2+	54	29	5	10
Median (95% CI)					15 (9-30)	4.8 (3.3-5.45)	15.8 (11-28)
Range					8-32	2.6-5.8	9.1-33.7

CI = confidence interval; N = number of subjects in arm; ORR = objective response rate; OS = median overall survival; PFS = median progression-free survival;
Study = trial names which are referenced in Module 5.3.5.3 Literature Based Analysis Table 4-1.
95% CI calculated using a one-sample Wilxocon statistic.
Source: Module 5.3.5.3 Literature Based Analysis Table 4.14.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the new active substance trastuzumab deruxtecan is primarily based on the pivotal Study 201, which is a phase 2, two-part, open-label, single-arm, cohort study. Patients were recruited from 72 study sites and a third of the patients were enrolled in the geographic regions of either Asia, US or Europe, respectively. A total of 184 HER2-positive breast cancer patients were treated with the proposed dose of 5.4 mg/kg. Supportive clinical trial evidence was submitted from 51 patients treated in the phase 1 study J101.

Primarily, patients being progressive during or after T-DM1 treatment (resistant/refractory) were included which allows assessment of efficacy of treatment with trastuzumab deruxtecan. All patients had at least 2 prior anti-HER2 based regimens, about half in the neo(adjuvant setting) and almost all patients in the metastatic setting. The criterion for prior pertuzumab in the advanced/metastatic setting (at least 100/150) ensures that the patient population reflects current EU treatment practice (ESMO guideline).

Patients had to have measurable disease at baseline as the primary endpoint was ORR. It is noted that patients with stable brain metastases were to be included, and recruitment was restricted to 30 patients with inactive brain metastases due to a similar approach in other studies of anti-HER2 therapy (the NALA and TH3RESA study), and since 24 patients with brain metastases were enrolled in the study, none were excluded based on the limitation on brain metastases enrolment. This is acceptable as an adequate update of the SmPC has been done. There seems to be no clinically relevant difference in ORR in patients with stable brain metastases (n=24) compared with the subgroup without brain metastases; however, no firm conclusions can be drawn due to small numbers.

The RP2D of 5.4 mg/kg is adequately justified based on the phase 1 study J101 and the dose-finding part 1 of study U201. Higher doses did not lead to a significant increase in efficacy whereas tolerability was considerably worse. There is limited support for the efficacy of reduced doses in case of toxicity. The overall number of patients treated with 3.2 mg/kg was 12/253 in study U201. Further information is expected post-authorisation from the ongoing phase 3 studies.

The single-arm, open-label design of the pivotal study U201 is acceptable in the context of a CMA, since the targeted indication is for the last-line setting and there is no SOC. Confirmatory randomised data is requested from one of the two ongoing phase 3 randomised trials as a specific obligation (SOB) to the CMA, ie, Study U301, since the study population from this study is more similar to the currently evaluated study population from the pivotal Study U201.

The statistical methods (calculation of proportions and Kaplan-Meier method) are overall agreed. The Applicant has conducted sensitivity analyses following a conservative approach and provided the reasons for censoring patients due to "other reasons" and performed a supplementary analysis, where patients censored due to discontinuation before PD, PD after missing two or more assessments, and initiation of new anti-cancer therapy before PD are imputed as events. The Applicant has clarified that

the censoring reasons for DoR per the Update DCO (01 Aug 2019) due to other reasons were all due to discontinuation before PD/death.

In Study U201, baseline characteristics showed that the median age was 55 years, with 76% of the patients being less than 65 years of age, and 24% of the patients were ≥65 years, which is reflective of the patient population. No male patients were included, which is acceptable since breast cancer is rare in men. However, the results from the pivotal trial is considered extrapolatable to men with HER2-positive metastatic breast cancer, in line with previous EMA decisions for HER2-targeted treatments (e.g. trastuzumab). Most patients were white (54.9%) or Asian (38%), of ECOG PS 0 (55.4%) or 1 (44%), and the mean weight and BMI were within the normal range although the range was wide. The level of HR/PR positive or negative disease and HER2 expression by central lab were acceptable and reflects the target population. The vast majority of patients had visceral metastases located at the lungs (57%), liver (30%), and/or brain (13%), while 28% had bone metastases, which is also reflective of the targeted disease. 90% of the patients had more than 3 prior systemic therapy regimens, not counting endocrine (HR) therapy, so the study population was heavily pre-treated. A total of 65.8% had prior pertuzumab, but only 27.7% as first or second line in the metastatic setting, which is consistent with the inclusion criteria and the proposed indication and appears to reflect clinical practice at the time of the study. It is noted that ~36% of the patients had PD as best response to TDM1, and considering the high response rate in the pivotal study U201, this does not seem to affect later response to trastuzumab deruxtecan. Subgroup analyses on ORR for patients with/without prior pertuzumab in the 1st or 2nd line setting in advanced/metastatic breast cancer showed at least comparable ORR for patients with prior treatment, providing reassurance on the efficacy of trastuzumab deruxtecan in this patient population.

The primary objective is to assess the ORR by independent blinded review and the secondary objectives are to assess the duration of the responses (DOR), DCR, CBR, PFS and OS. The independent assessment of the primary efficacy endpoint is endorsed for this single-arm, open-label, non-comparative pivotal study, which could otherwise be subject to investigator bias. The clinical benefit rate (CBR) is clinically relevant to measure for the targeted disease, as patients with SD for 6 months or longer is deemed to have clinical benefit from the given treatment.

Study U201 was conducted in accordance with the ICH for GCP and the Declaration of Helsinki. Though a high number of major protocol deviations were reported, these do not raise particular concerns. This is supported by data from national GCP inspections and monitoring reports.

The Applicant provided supportive data in the form of RWE from the Unicancer study and a literature-based analysis. The Unicancer study matched cohorts from a) real-world evidence describing the use of regimens including anti-HER2 agents, chemotherapies, and endocrine therapy post-TDM1 from a patient population and b) matched these to the patients enrolled in Study U201, using 1) Prior treatment with pertuzumab (yes/no); 2) HR status at T DM1 therapy (positive/negative/not determined); 3) Presence of visceral disease at index date (present/absent); 4) Number of lines of treatment prior to T DM1 (<2/≥2), but not age, no CVD, no other diseases, and the time frame is also different. Hence, the matching is not optimally done.

Efficacy data and additional analyses

This assessment focuses on the 184 HER2-positive breast cancer patients treated with the proposed dose of 5.4 mg/kg, included in Part 1 and Parts 2a and 2b of the pivotal study U201, as they reflect the targeted patient population. The median age was 55 years (range 28-96), 76% of the patients were less than 65 years of age, and 24% of the patients were ≥65 years. No male patients were included. Most patients were white (54.9%) or Asian (38%). The majority of patients were of ECOG PS 0

(55.4%) or 1 (44%), and the mean weight and BMI were within the normal range. Approximately half of the patients had tumors, which were either Estrogen receptor positive or negative, while a third of the tumors were Progesterone receptor positive. 83.7% of the tumors had HER2-ekspression on ICH of 3+ by central lab. The vast majority of patients had visceral metastases, which were located at the lungs (57%), liver (30%), and/or brain (13%). It is also noted that 28% of the patients had bone metastases, which is unmeasurable per RECIST 1.1. 90% of the patients had more than 3 prior systemic therapy regimens not counting endocrine (HR) therapy. ~66% of the patients had prior pertuzumab, ~54% other anti-HER2 treatment, while all of the patients had prior TDM1 and trastuzumab. Efficacy after TDM1 was presented under Ancillary analyses. The sample size is considered sufficient for the evaluation of clinically meaningful benefit for a CMA.

The primary endpoint of **ORR** by ICR was 60.3% at the initial data cut and this result was maintained at the updated DCO with 12.2 months of follow-up time i.e. 60.9% (95%CI: 53.4; 68). Update DCO show that 6% of the patients had a CR and 54.9% had a PR, while 36.4% had SD as best overall response. Further updated ORR was 61.4% (95%CI: 54.0; 68.5). This response rate is considered promising and much higher than expected beforehand (~35%) based on literature data. Sensitivity analyses support the reported ORR. The magnitude of response is considered highly clinically relevant for this heavily pre-treated study population, who have no standard of care. It is noted that very few had a non-evaluable best overall response, which is reassuring. The waterfall plot clearly reflects these data, which are considered highly clinically relevant for this heavily pre-treated study population, who have no standard of care. Hence, the ORR data show clinically significant activity of trastuzumab deruxtecan even though no comparative data is available. The sensitivity analyses of ORR are overall consistent with the results of the primary endpoint.

The secondary endpoint of **duration of response** by IRC at update DCO show a median of 14.8 months (95%CI: 13.8, 16.9), which is a clinically relevant result with a median follow-up time of 12.2 months. Further updated data showed a median duration of response of 20.8 months (95%CI: 15.0, NE) with a median follow-up time of 20.5 months and 34.8% events of PD or death. Approximately 65% of the patients were censored for DOR and 24.1% of the patients are ongoing without an event, so this is considered a highly clinically relevant DOR for this heavily treated study population.

The updated **PFS** at EMA DCO was 19.4 months (95%CI: 14.1, NE), and this data is partly immature as well as difficult to assess without a comparator arm. The low event rate of 38% is showing a low incidence of either progression or death in the follow-up period and the estimate is in line with the DOR.

Spaghetti plots of the repeated tumour measurements (sum of diameters at each tumour assessment) for each patient, who was censored from the PFS and DoR analyses for reasons apart from data cut off were presented for PFS and for DoR at the time of the updated DCO 08Jun20. These plots indicate that the initial decreases in tumour size after starting treatment with trastuzumab deruxtecan were maintained for subjects who were censored for any reason other than DCO.

OS data were initially immature with only 10% deaths, but the Applicant has also provided updated OS data based on a DCO of 08 Jun 2020 with a median duration of follow-up of 20.5 months showing a median OS of 24.6 months (95% CI: 23.1, NE). At that time, 37 subjects (20.1%) were still on treatment and a total of 65 deaths had occurred among the 184 subjects treated at 5.4 mg/kg. This is clinically meaningful and compares favorably to other reported OS outcomes from similar studies in patients with HER2-positive breast cancer, who had been previously treated with 2 lines of prior anti-HER2-based regimens (targeted treatment setting), where median OS in the range of 17.2-21.9 months has been reported in literature. Moreover, the Applicant was recommended to provide the final OS data after the Study U201 closes.

The ORR of and apparent durable responses observed are considered to be clinically meaningful in the target population; however, data were immature with a high rate of censored patients. Updated data based on an update at DCO 8 June 2020 showed that the median DoR increased from 14.8 months to 20.8 months and these results provide further support for the conclusion that the high response rate of about 60% is accompanied by a highly durable response. However, the censoring rate remained above 60%, with a high percentage of patients now censored for other reasons (n=46/112 for DoR). For some of these patients, no reason for discontinuation of treatment was provided (n=31/112 for DoR). This might be due to adverse events, but it could also be that patients were censored after an investigator-determined progression without central confirmation, which along with receiving new anticancer therapy, could be considered to be an example of informative censoring. A conservative sensitivity analysis was performed, with the censored times in the updated DoR analysis imputed as event times for all patients censored for other reasons than ongoing without PD. This approach substantially lowered the median DoR to 10.0 months (95%CI: 7.9, 12.7). Moreover, additional sensitivity analyses of DoR with clinical progression and investigator determined PD counted as events rather than censored, and the median DoR for the EMA DCO is estimated to be 14.6 months (95%CI 10.3, 18.2). Given that it is reasonable to presume that these patients may have showed signs of progression, an event based on investigator or ICR progression could be a better measure of efficacy, so this may be a more realistic estimate than the 20 months that was first estimated in the EMA DCO. However, a median DoR of 14 months in combination with an ORR of around 60% is just as well considered a major therapeutic advantage (MTA) over existing therapies in the target population.

Subgroup analyses for the 184 HER2-positive breast cancer patients treated with the proposed dose overall show consistent results for ORR by ICR across important subgroups, with a point estimate of more than 50% for all except for the subgroups of very small sample size, e.g. the 9 patients who have moderate renal impairment. It is noted that even for the ER/HR negative; for patients with prior pertuzumab treatment in the metastatic setting, and for patients with PD as best response to TDM1, the point estimate for ORR was more than 60%. The subgroup analyses for ORR by ICR were also consistent regardless of age, race, region, country, ECOG PS 0 vs 1, disease burden (sum of diameter target lesions), following immediately TDM1 treatment, and HER2 status (ICH3+ vs ISH+). It is highly encouraging that efficacy seems established across important subgroups regardless of presence of negative prognostic factors such as old age, ECOG PS 1, visceral disease, HR negative status. It is also reassuring that trastuzumab deruxtecan showed similar and clinically relevant response in patients (n=56), who had treatment with TDM1 just before entering the study. Subgroup analyses of DOR were also consistent in patients regardless of HR status (positive vs negative) and prior pertuzumab use (yes vs no), which is supportive of the primary endpoint.

Evaluating the updated efficacy results summarized above, it is agreed that trastuzumab deruxtecan was associated with longer median DoR and median PFS than the data currently reported for available therapies in the proposed setting. Hence, these updated efficacy data establish that the ORR, PFS, and OS observed with trastuzumab deruxtecan 5.4 mg/kg show a major therapeutic benefit over existing treatments in the proposed patient population, which has no clearly preferential treatment options and where there remains an unmet medical need.

Of main relevance for the targeted patient population with HER2+ MBC is the clinical benefit rate (CBR), and the confirmed CBR (i.e. CR+PR+ SD >6 months) was 70.7% (95%CI: 63.5; 77.1) for the relevant study population at the proposed dose (N=184). This is considered clinically relevant that two-thirds of the patients derive clinical benefit from the study treatment, as both response to treatment (ORR) and stabilisation of the disease for more than 6 months is considered beneficial for these heavily treated patients. The DCR is not considered of great relevance in this patient population, where the ORR and DOR results are considered to better reflect benefit in this single arm pivotal trial.

The median time to response was 1.6 months, which is in line with other chemotherapies and clinically relevant for patients with metastatic HER2-positive breast cancer.

To contextualize the results in the absence of a comparator arm, the Applicant submitted data from a matched cohort using the Unicancer database and results from a literature-based analysis to provide an understanding of the range of ORR and PFS reported in published clinical studies. However, since patients in the control and experimental could differ in important prognostic factors despite matching, this is considered data of an exploratory nature. Moreover, even though the assessment of ORR was done by IRC, of the 137 patients in the Matched Cohort, 22 patients had to be excluded because of poor image quality precluding an assessment of response, so only 115 matched subjects were used for analysis of response.

In nearly all cases, the lower limit of the 95%CI for ORR and median PFS with trastuzumab deruxtecan exceeds the upper limit of the 95%CI reported in a variety of literature studies, including those studied in patients with two prior anti-HER2 regimens. For the Unicancer study, selection was based on a post-baseline variable (tumour scan) which may introduce selection bias. The impact is unknown as no further information was available. About 74% of patients received anti-HER2 therapy as their first treatment post-T-DM1. The ORR in the matched cohort (N=115) was 12.2% (95%CI: 6.2, 18.2), which is considerably lower (five times) than that reported for the overall population in U201. Further, median PFS was 4.7 months (95% CI: 3.8, 6.0) which is about three times lower than observed after trastuzumab deruxtecan. These data might support compelling efficacy of trastuzumab deruxtecan. However, comparisons to historical controls carry inherent biases with regards to different factors and the following points are especially raising uncertainties on/questioning the current historical comparison: 1. The timing and measurement of ORR and PFS may differ between the matched cohort and study U201; 2. Data on ORR and PFS for those patients in study U201 who were matched with the external cohort have not been provided; 3. Uncertainties remain on the comparability of patient populations for other factors than those included for matching. It was clarified that in the matched cohort, ORR was based on unconfirmed CR and PR. The ORR for 137 patients in study U201 used for the 115 Unicancer matched cohort was 59.1% based on ICR, slightly lower than for the overall study. Information on timing and follow-up scans with information on tumour status at each assessment was not available. Further, a full comparison of baseline characteristics between patients in U201 and the Unicancer matched cohort could not be provided. Information on definition of and censoring of PFS, suggest a broader definition. A further major limitation is the lack of DoR data. So, given the identified limitations and remaining uncertainties related to the use of the Unicancer cohort, the results from this cohort cannot be considered supportive .

A literature study was performed and searched for patients on second line or later therapy for advanced or metastatic breast cancer, who previously had received prior trastuzumab and a chemotherapy, and the search yielded 37 studies and 8827 patients with ORR, PFS, or OS data. The results showed that the overall mean ORR was estimated to be 25.5% (95% prediction range: 17.1-36.1), while the median PFS was estimated to be 5.8 months (95% prediction range: 3.2-10.5). In the subgroup of studies that had a median of at least 2 prior chemotherapies or at least 2 prior anti-HER2-based regimens, the median ORR was estimated to be 15% (95%CI: 9, 30) and the median PFS was estimated to be 4.8 months (95%CI: 3.3, 5.5).

Overall, the analyses of RWE and historical data from the literature seem to reflect lower efficacy than observed in the pivotal study U201; however, the data is considered of an exploratory nature, since there are too many uncertainties such as non-optimal matching and missing assessment of response in 16% of the matched subjects, which cannot be properly estimated or adjusted for.Despite the uncertainties described above, the comparison with literature data from currently anti-HER2 regimens used in the same setting/target population support a major therapeutic advantage based on efficacy for trastuzumab deruxtecan; the median DoR of 20.8 months is about 3 times higher than the reported

median DoR (6.0 -8.5 months) or median PFS (4.9 – 7.8 months) and the differences is as such that it is considered to overcome the uncertainties related to the lack of an active comparator arm and thus indirect comparisons, in the context of the requested CMA.

The data translate in clinical benefit with trastuzumab deruxtecan where currently there is an unmet medical need.

Additional efficacy data needed in the context of a conditional MA

The Applicant's proposal to provide comprehensive data relevant to the target population comes from two global phase 3 randomised controlled studies of trastuzumab deruxtecan in advanced HER2-positive breast cancer which are currently ongoing, DS8201-A-U301 (Study U301) and DS8201-A-U302 (Study U302). The proposal to provide comprehensive data in reasonable timelines is overall considered acceptable and the Study U301 is considered the most informative for efficacy in terms of time-dependent endpoints PFS and OS, which is the main uncertainty in this dossier hence submission of interim data from that study is proposed as a SOB to the CMA.

2.5.4. Conclusions on the clinical efficacy

The updated results from the pivotal Study U201 show clinically relevant efficacy of trastuzumab deruxtecan regarding a high response rate, and durations of response, which appear durable in a heavily pre-treated population with unresectable or metastatic HER2-positive breast cancer. The updated efficacy data have justified the clinical relevance of the results and the major therapeutic advantage of trastuzumab deruxtecan compared to existing therapies. The Applicant is recommended to provide final efficacy and safety data from the study U201.

The CHMP considers the following measure (SOB) necessary to address the missing efficacy data in the context of a conditional MA:

Submission of interim efficacy and safety data from the ongoing randomised phase 3 study DS-8201-A-U301, a Phase 3 multicentre, randomised open-label, active-controlled study of trastuzumab deruxtecan versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pre-treated with prior standard of care HER2 therapies, including T-DM1. Due date: March 2022.

2.6. Clinical safety

The primary data on clinical safety of trastuzumab deruxtecan are based on a DCO of 01 Aug 2019 for pooled data from the 2 clinical studies J101 and U201 (i.e., the Safety Update DCO). The primary safety database includes 542 subjects, who have received at least 1 dose of trastuzumab deruxtecan in Study J101 or Study U201, of whom 234 subjects with HER2-positive unresectable or metastatic BC were treated with 5.4 mg/kg. For comparison purposes, data from the primary analyses for each of the 2 studies were combined using the individual CSR DCOs (01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201); hereafter this pool is referred to as "CSR DCO." Update safety DCO was 01 Aug 2019.

To allow for evaluation of the safety of the proposed dose, data from Study J101 and Study U201 were combined to create the HER2-positive BC 5.4 mg/kg Pool (N=234). The following 3 additional pooled groups of data from Study J101 and Study U201 were designed to allow evaluation of possible dose response effects and safety in other tumor types:

- HER2-positive BC treated with ≥6.4 mg/kg (6.4, 7.4 or 8.0 mg/kg) (N=137)

- All tumor types treated with 5.4 mg/kg (N=275)
- All tumor types treated with ≥6.4 mg/kg (6.4, 7.4, or 8.0 mg/kg) (N=258)

The overall safety population consisted of 542 patients, who have received at least 1 dose of trastuzumab deruxtecan in Study J101 or Study U201, and of these 234 patients with HER2-positive unresectable or metastatic BC were treated with 5.4 mg/kg the study treatment at the proposed dose (5.4 mg/kg). The size of the safety data available on patients, who have received the study treatment at the proposed dose is considered acceptable for a CMA.

Patient exposure

Table 45: Summary of Exposure (Safety Analysis Set)

Parameter	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Treatment Duration (months) [a]								
Mean (Std Dev)	7.83 (4.709)	9.69 (5.844)	7.64 (4.973)	9.41 (6.102)	10.95 (7.555)	11.91 (8.847)	6.98 (3.093)	9.09 (4.562)
Median	6.96	9.82	6.90	9.43	8.54	8.54	6.90	9.97
Range	0.7, 31.0	0.7, 37.1	0.7, 32.0	0.7, 37.9	0.7, 31.0	0.7, 37.1	0.7, 16.1	0.7, 20.5
Treatment Duration (categories) [a] n (%)								
0 to ≤3 months	35 (15.0)	35 (15.0)	48 (17.5)	48 (17.5)	8 (16.0)	8 (16.0)	27 (14.7)	27 (14.7)
>3 to ≤6 months	35 (15.0)	35 (15.0)	46 (16.7)	46 (16.7)	6 (12.0)	6 (12.0)	29 (15.8)	29 (15.8)
>6 to ≤9 months	104 (44.4)	37 (15.8)	115 (41.8)	40 (14.5)	12 (24.0)	12 (24.0)	92 (50.0)	25 (13.6)
>9 to ≤12 months	30 (12.8)	58 (24.8)	32 (11.6)	64 (23.3)	7 (14.0)	5 (10.0)	23 (12.5)	53 (28.8)
>12 to ≤24 months	28 (12.0)	64 (27.4)	30 (10.9)	70 (25.5)	15 (30.0)	14 (28.0)	13 (7.1)	50 (27.2)
>24 months	2 (0.9)	5 (2.1)	4 (1.5)	7 (2.5)	2 (4.0)	5 (10.0)	0	0
Patient-years of Exposure [b]	152.6	188.9	175.1	215.6	45.6	49.6	107.0	139.3
Cumulative Dose Level [c] (mg/kg)								
Mean (Std Dev)	55.90 (31.481)	68.55 (39.788)	54.44 (33.213)	66.45 (41.471)	75.31 (49.195)	81.53 (57.807)	50.63 (21.975)	65.02 (32.593)
Median	54.00	65.50	53.40	64.42	64.44	64.44	53.45	68.05
Range	5.3, 179.7	5.3, 222.7	5.3, 228.4	5.3, 262.7	5.4, 179.7	5.4, 222.7	5.3, 118.0	5.3, 156.7

Parameter	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Number of Cycles								
Mean (Std Dev)	10.7 (6.20)	13.2 (7.75)	10.4 (6.56)	12.8 (8.11)	14.7 (9.85)	16.0 (11.54)	9.6 (4.16)	12.5 (6.18)
Median	10.0	14.0	10.0	13.0	12.0	12.0	10.0	14.0
Range	1, 38	1, 45	1, 43	1, 51	1, 38	1, 45	1, 22	1, 29
Dose Intensity [d] (mg/kg/3 weeks)								
Mean (Std Dev)	5.05 (0.561)	5.00 (0.592)	5.04 (0.560)	5.00 (0.588)	4.96 (0.603)	4.95 (0.625)	5.07 (0.549)	5.02 (0.584)
Median	5.30	5.26	5.30	5.25	5.20	5.20	5.30	5.30
Range	2.6, 5.6	2.5, 5.6	2.6, 5.7	2.5, 5.7	3.0, 5.6	3.0, 5.6	2.6, 5.6	2.5, 5.6
Relative Dose Intensity [e]								
Mean (Std Dev)	93.40 (10.363)	92.60 (10.987)	93.26 (10.341)	92.49 (10.912)	91.93 (11.160)	91.68 (11.578)	93.81 (10.130)	92.85 (10.840)
Median	97.80	97.35	97.70	97.20	96.15	96.10	98.20	97.60
Range	47.2, 104.1	46.1, 104.1	47.2, 104.8	46.1, 104.8	55.3, 104.1	55.3, 104.1	47.2, 103.3	46.1, 103.7

Parameter	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Relative Dose Intensity Categories [e] n (%)								
≥90%	183 (78.2)	174 (74.4)	209 (76.0)	200 (72.7)	36 (72.0)	36 (72.0)	147 (79.9)	138 (75.0)
<90% to ≥80%	22 (9.4)	30 (12.8)	31 (11.3)	38 (13.8)	7 (14.0)	6 (12.0)	15 (8.2)	24 (13.0)
<80% to ≥60%	26 (11.1)	25 (10.7)	32 (11.6)	32 (11.6)	6 (12.0)	7 (14.0)	20 (10.9)	18 (9.8)
<60%	3 (1.3)	5 (2.1)	3 (1.1)	5 (1.8)	1 (2.0)	1 (2.0)	2 (1.1)	4 (2.2)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the study or pool; Std Dev = standard deviation

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.

[a] Treatment duration (months) = (date of the last dose – date of the first dose + 21)/30.44; 1 month = 365.25/12 = 30.44 days

[b] Patient-years of exposure = sum (duration of exposure [months])/12.

[c] Cumulative dose level = sum (the actual dose level received).

[d] Dose intensity (mg/kg/3 weeks) = cumulative dose level (mg/kg) / duration of treatment (days)/21.

[e] Relative dose intensity (%) = dose intensity / assigned dose level (mg/kg/3 weeks).

Source: Appendix 1 Table 1

The median duration of exposure to trastuzumab deruxtecan for the all tumor types safety pool (herein after ATT pool) (n=275) was 9.43 months (range: 0.7-37.9) and 9.82 months (range: 0.7-37.1) for the HER2+MBC pool (n=234) (Update safety DCO 01 Aug 2019). 66% of the patients in the ATT pool had exposure of more than 6 months and 28% were exposed for more than 12 months.

The dose intensity was high and similar in both pools, with 5.25 mg (range: 2.5-5.7) for the ATT pool. This corresponds to more than 70% of the patients having had 90% or more of the planned dose of 5.4 mg/kg, which is acceptable and considered a relevant exposure for a tumour response.

Adverse events

Table 46: Summary of Subject Disposition (Safety Analysis Set)

Reason for Discontinuation	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Subjects Who Discontinued Study Drug for Any Reason	114 (48.7)	148 (63.2)	143 (52.0)	183 (66.5)	40 (80.0)	43 (86.0)	74 (40.2)	105 (57.1)
Progressive Disease [a]	58 (24.8)	75 (32.1)	81 (29.5)	100 (36.4)	20 (40.0)	22 (44.0)	38 (20.7)	53 (28.8)
Adverse Event	24 (10.3)	38 (16.2)	25 (9.1)	42 (15.3)	9 (18.0)	10 (20.0)	15 (8.2)	28 (15.2)
Withdrawal by Subject	11 (4.7)	12 (5.1)	12 (4.4)	14 (5.1)	4 (8.0)	4 (8.0)	7 (3.8)	8 (4.3)
Death	8 (3.4)	8 (3.4)	9 (3.3)	9 (3.3)	1 (2.0)	1 (2.0)	7 (3.8)	7 (3.8)
Clinical Progression [b]	5 (2.1)	5 (2.1)	7 (2.5)	7 (2.5)	5 (10.0)	5 (10.0)	0	0
Other	8 (3.4) [c]	10 (4.3) [d]	9 (3.3)	11 (4.0)	1 (2.0)	1 (2.0)	7 (3.8)	9 (4.9)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the study or pool; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

Percentages are calculated using the number of subjects in the Safety Analysis Set as the denominator.

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

[a] Based on RECIST v1.1

[b] Per investigator assessment

[c] As of the CSR DCOs, this included 4 subjects discontinued due to physician decision, 3 due to subject decision, and 1 due to Grade 3 troponin.

[d] As of the Safety Update DCO, this included 5 subjects discontinued due to physician decision, 4 due to subject decision, and 1 due to Grade 3 troponin.

Source: Appendix 1 Table 3

Table 47: Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

Parameter	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Subjects with Any TEAE	233 (99.6)	233 (99.6)	273 (99.3)	273 (99.3)	50 (100.0)	50 (100.0)	183 (99.5)	183 (99.5)
Drug-related TEAEs [a]	232 (99.1)	233 (99.6)	271 (98.5)	272 (98.9)	50 (100.0)	50 (100.0)	182 (98.9)	183 (99.5)
TEAEs with Worst CTCAE ≥Grade 3 [b]	117 (50.0)	128 (54.7)	138 (50.2)	149 (54.2)	23 (46.0)	23 (46.0)	94 (51.1)	105 (57.1)
Drug-related TEAEs with Worst CTCAE ≥Grade 3 [a,b]	95 (40.6)	107 (45.7)	111 (40.4)	125 (45.5)	18 (36.0)	18 (36.0)	77 (41.8)	89 (48.4)
Serious TEAEs	47 (20.1)	54 (23.1)	54 (19.6)	61 (22.2)	11 (22.0)	12 (24.0)	36 (19.6)	42 (22.8)
Drug-related Serious TEAEs [a]	20 (8.5)	27 (11.5)	23 (8.4)	30 (10.9)	4 (8.0)	4 (8.0)	16 (8.7)	23 (12.5)
TEAEs Associated with Discontinuation of Study Drug	22 (9.4)	36 (15.4)	22 (8.0)	39 (14.2)	7 (14.0)	8 (16.0)	15 (8.2)	28 (15.2)
Drug-related TEAEs Associated with Discontinuation of Study Drug [a]	19 (8.1)	33 (14.1)	19 (6.9)	35 (12.7)	5 (10.0)	6 (12.0)	14 (7.6)	27 (14.7)

Parameter	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
TEAEs Associated with Dose Reduction	42 (17.9)	48 (20.5)	50 (18.2)	56 (20.4)	5 (10.0)	5 (10.0)	37 (20.1)	43 (23.4)
Drug-related TEAEs Associated with Dose Reduction [a]	38 (16.2)	44 (18.8)	44 (16.0)	50 (18.2)	4 (8.0)	4 (8.0)	34 (18.5)	40 (21.7)

Parameter	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
TEAEs Associated with Drug interruption	78 (33.3)	87 (37.2)	96 (34.9)	106 (38.5)	21 (42.0)	22 (44.0)	57 (31.0)	65 (35.3)
Drug-related TEAEs Associated with Drug interruption [a]	63 (26.9)	68 (29.1)	75 (27.3)	81 (29.5)	15 (30.0)	15 (30.0)	48 (26.1)	53 (28.8)
TEAEs Associated with Outcome of Death [c]	12 (5.1)	12 (5.1)	12 (4.4)	12 (4.4)	3 (6.0)	3 (6.0)	9 (4.9)	9 (4.9)
Drug-related TEAEs Associated with Outcome of Death [a,c]	3 (1.3)	3 (1.3)	3 (1.1)	3 (1.1)	1 (2.0)	1 (2.0)	2 (1.1)	2 (1.1)

BC = breast cancer; ; CSR = clinical study report; DCO = data cut-off; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the study or pool; TEAE = treatment-emergent adverse event
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019
The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.
[a] If relationship was missing, the adverse event was considered to be related to the drug.
[b] A subject was counted once at the maximum severity, if he/she reported at least 1 adverse event. If a subject had both missing and non-missing CTCAE grades for a TEAE, the worst CTCAE grade was based on non-missing grade.
[c] For specific TEAEs associated with outcome of death.
Source: Appendix 1 Table 7

Table 48: Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in the HER2-positive Breast Cancer 5.4 mg/kg Pool as of the Safety Update DCO, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term/ Grouped Term	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Subjects with Any TEAE	233 (99.6)	233 (99.6)	273 (99.3)	273 (99.3)	50 (100.0)	50 (100.0)	183 (99.5)	183 (99.5)
Nausea	185 (79.1)	187 (79.9)	213 (77.5)	216 (78.5)	43 (86.0)	44 (88.0)	142 (77.2)	143 (77.7)
Fatigue	112 (47.9)	115 (49.1)	127 (46.2)	131 (47.6)	24 (48.0)	24 (48.0)	88 (47.8)	91 (49.5)
Vomiting	111 (47.4)	114 (48.7)	124 (45.1)	127 (46.2)	28 (56.0)	30 (60.0)	83 (45.1)	84 (45.7)

MedDRA Preferred Term/ Grouped Term	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Alopecia	107 (45.7)	108 (46.2)	117 (42.5)	118 (42.9)	19 (38.0)	19 (38.0)	88 (47.8)	89 (48.4)
Constipation	81 (34.6)	84 (35.9)	94 (34.2)	97 (35.3)	18 (36.0)	18 (36.0)	63 (34.2)	66 (35.9)
Decreased appetite	76 (32.5)	81 (34.6)	91 (33.1)	97 (35.3)	23 (46.0)	24 (48.0)	53 (28.8)	57 (31.0)
Anaemia [a]	72 (30.8)	79 (33.8)	83 (30.2)	90 (32.7)	24 (48.0)	24 (48.0)	48 (26.1)	55 (29.9)
Neutrophil count decrease [b]	69 (29.5)	76 (32.5)	75 (27.3)	83 (30.2)	12 (24.0)	12 (24.0)	57 (31.0)	64 (34.8)
Diarrhoea	67 (28.6)	72 (30.8)	79 (28.7)	84 (30.5)	18 (36.0)	18 (36.0)	49 (26.6)	54 (29.3)
Platelet count decrease [c]	47 (20.1)	54 (23.1)	56 (20.4)	63 (22.9)	15 (30.0)	15 (30.0)	32 (17.4)	39 (21.2)
Cough	46 (19.7)	50 (21.4)	50 (18.2)	55 (20.0)	14 (28.0)	15 (30.0)	32 (17.4)	35 (19.0)
White blood cell count decrease [d]	45 (19.2)	48 (20.5)	53 (19.3)	56 (20.4)	9 (18.0)	9 (18.0)	36 (19.6)	39 (21.2)
Abdominal pain [e]	42 (17.9)	44 (18.8)	44 (16.0)	47 (17.1)	13 (26.0)	13 (26.0)	29 (15.8)	31 (16.8)
Headache	42 (17.9)	44 (18.8)	46 (16.7)	49 (17.8)	8 (16.0)	8 (16.0)	34 (18.5)	36 (19.6)

MedDRA Preferred Term/ Grouped Term	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Aspartate aminotransferase increased	32 (13.7)	35 (15.0)	36 (13.1)	39 (14.2)	9 (18.0)	9 (18.0)	23 (12.5)	26 (14.1)
Stomatitis [f]	32 (13.7)	35 (15.0)	37 (13.5)	40 (14.5)	7 (14.0)	7 (14.0)	25 (13.6)	28 (15.2)
Dyspnoea	31 (13.2)	34 (14.5)	35 (12.7)	38 (13.8)	7 (14.0)	7 (14.0)	24 (13.0)	27 (14.7)
Dyspepsia	29 (12.4)	33 (14.1)	32 (11.6)	36 (13.1)	7 (14.0)	7 (14.0)	22 (12.0)	26 (14.1)
Epistaxis	30 (12.8)	33 (14.1)	33 (12.0)	36 (13.1)	8 (16.0)	9 (18.0)	22 (12.0)	24 (13.0)
ILD [g]	21 (9.0)	31 (13.2)	22 (8.0)	36 (13.1)	7 (14.0)	7 (14.0)	14 (7.6)	24 (13.0)
Asthenia	29 (12.4)	30 (12.8)	29 (10.5)	30 (10.9)	4 (8.0)	4 (8.0)	25 (13.6)	26 (14.1)
Hypokalaemia	28 (12.0)	30 (12.8)	33 (12.0)	35 (12.7)	9 (18.0)	9 (18.0)	19 (10.3)	21 (11.4)
Upper respiratory tract infection	25 (10.7)	30 (12.8)	26 (9.5)	31 (11.3)	9 (18.0)	10 (20.0)	16 (8.7)	20 (10.9)
Dry eye	26 (11.1)	27 (11.5)	29 (10.5)	30 (10.9)	6 (12.0)	6 (12.0)	20 (10.9)	21 (11.4)
Lymphocyte count decrease [h]	23 (9.8)	26 (11.1)	23 (8.4)	26 (9.5)	0	0	23 (12.5)	26 (14.1)
Alanine aminotransferase increased	24 (10.3)	25 (10.7)	26 (9.5)	27 (9.8)	7 (14.0)	7 (14.0)	17 (9.2)	18 (9.8)

Table 49: Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in the HER2-positive Breast Cancer 5.4 mg/kg Pool as of the Safety Update DCO, by Preferred Term (Safety Analysis Set) (Continued)

MedDRA Preferred Term/ Grouped Term	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Dizziness	24 (10.3)	25 (10.7)	27 (9.8)	29 (10.5)	8 (16.0)	8 (16.0)	16 (8.7)	17 (9.2)
Oedema peripheral	20 (8.5)	25 (10.7)	26 (9.5)	32 (11.6)	10 (20.0)	11 (22.0)	10 (5.4)	14 (7.6)
Pyrexia	23 (9.8)	25 (10.7)	27 (9.8)	31 (11.3)	10 (20.0)	11 (22.0)	13 (7.1)	14 (7.6)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, v20.1; N = total number of subjects in the study or pool; PT = preferred term; TEAE = treatment-emergent adverse event

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

If a subject had multiple occurrences of the same preferred term, the subject was counted once for that preferred term.

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.

[a] Anaemia (grouped term) includes PTs of haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased

[b] Neutrophil count decrease (grouped term) includes PTs of neutrophil count decreased and neutropenia

[c] Platelet count decrease (grouped term) includes PTs of platelet count decreased and thrombocytopenia

[d] White blood cell count decrease (grouped term) includes PTs of white blood cell count decreased and leukopenia

[e] Abdominal pain (grouped term) includes PTs of abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper

[f] Stomatitis (grouped term) includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering

[g] Interstitial lung disease (grouped term) includes PTs of interstitial lung disease, pneumonitis, organising pneumonia, and acute interstitial pneumonitis

[h] Lymphocyte count decrease (grouped term) includes PTs of lymphocyte count decreased and lymphopenia

Source: Appendix 1 Table 9

Table 50: Treatment-emergent Adverse Events of at Least Grade 3 Reported in at Least 5% of Subjects in the HER2-positive Breast Cancer 5.4 mg/kg Pool at the Safety Update DCO, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term / Grouped Term	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Subjects with Any TEAE ≥Grade 3	117 (50.0)	128 (54.7)	138 (50.2)	149 (54.2)	23 (46.0)	23 (46.0)	94 (51.1)	105 (57.1)
Neutrophil count decrease [a]	38 (16.2)	44 (18.8)	41 (14.9)	48 (17.5)	6 (12.0)	6 (12.0)	32 (17.4)	38 (20.7)
Anaemia [b]	17 (7.3)	21 (9.0)	23 (8.4)	27 (9.8)	5 (10.0)	5 (10.0)	12 (6.5)	16 (8.7)
Nausea	16 (6.8)	16 (6.8)	17 (6.2)	17 (6.2)	2 (4.0)	2 (4.0)	14 (7.6)	14 (7.6)
Fatigue	12 (5.1)	13 (5.6)	13 (4.7)	14 (5.1)	2 (4.0)	2 (4.0)	10 (5.4)	11 (6.0)
White blood cell count decrease [c]	10 (4.3)	13 (5.6)	12 (4.4)	15 (5.5)	1 (2.0)	1 (2.0)	9 (4.9)	12 (6.5)
Lymphocyte count decrease [d]	10 (4.3)	12 (5.1)	10 (3.6)	12 (4.4)	0	0	10 (5.4)	12 (6.5)

BC = breast cancer; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, v20.1; N = total number of subjects in the study or pool; PT = preferred term; TEAE = treatment-emergent adverse event

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

If a subject had both missing and non-missing CTCAE grades for a TEAE, the worst CTCAE grade was based on non-missing grade.

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.

If a subject had multiple occurrences of the same preferred term, the subject was counted once for the specific preferred term.

[a] Neutrophil count decrease (grouped term) includes PTs of neutrophil count decreased and neutropenia

[b] Anaemia (grouped term) includes PTs of haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased

[c] White blood cell count decrease (grouped term) includes PTs of white blood cell count decreased and leukopenia

[d] Lymphocyte count decrease (grouped term) includes PTs of lymphocyte count decreased and lymphopenia
Source: Appendix 1 Table 11

Almost all of the patients experienced at least one AE in the pivotal study U201 (HER2+ BC) at safety update DCO, and 57.1% experienced a ≥grade 3 AE. SAEs were observed in 22.8% of the patients, of which 4.9% had an SAE leading to death. The overall discontinuation rate due to AEs was 15.2%. Common AEs in the BC pool were nausea (77.7%), fatigue (49.5%), vomiting (45.7%), and constipation (35.9%). As expected with an antibody-drug conjugate (ADC), such as trastuzumab deruxtecan, the haematological toxicity was also common with anaemia (29.9%) and neutrophil count decrease (34.8%). However, febrile neutropenia was only reported in 1.7% of patients and grade 3 anaemia (8.7%), white blood cell count decrease (6.5%), and neutrophil count decrease (7.6%) were within an acceptable level. Other common grade 3 AEs were nausea (7.6%) and fatigue (6.0%), also of an acceptable level.

Adverse drug reactions – treatment-related AEs

Table 51: Adverse Drug Reactions Reported in the HER2-positive Breast Cancer 5.4 mg/kg Pool as of the Safety Update DCO, by MedDRA System Organ Class and Preferred Term/Grouped Term

MedDRA System Organ Class Preferred Term or Grouped Term	Number (%) of Subjects as of the Safety Update DCO (N=234)	
	Any Grade	CTCAE Grade 3-4
Blood and lymphatic system disorders		
Anaemia [a]	79 (33.8)	21 (9.0)
Neutropenia [b]	76 (32.5)	44 (18.8)
Thrombocytopenia [c]	54 (23.1)	10 (4.3)
Leukopenia [d]	48 (20.5)	13 (5.6)
Lymphopenia [e]	26 (11.1)	12 (5.1)
Febrile neutropenia	4 (1.7)	4 (1.7)
Eye disorders		
Dry eye	27 (11.5)	1 (0.4) [f]
Gastrointestinal disorders		
Nausea	187 (79.9)	16 (6.8)
Vomiting	114 (48.7)	10 (4.3)
Constipation	84 (35.9)	2 (0.9)
Diarrhoea	72 (30.8)	6 (2.6)
Abdominal pain [g]	46 (19.7)	3 (1.3)
Stomatitis [h]	35 (15.0)	2 (0.9)
Dyspepsia	33 (14.1)	0
General disorders and administration site conditions		
Fatigue [i]	141 (60.3)	15 (6.4)
Infections and infestations		
Upper respiratory tract infection [j]	43 (18.4)	0
Injury, poisoning and procedural complications		
Infusion related reaction [k]	6 (2.6)	0

MedDRA System Organ Class Preferred Term or Grouped Term	Number (%) of Subjects as of the Safety Update DCO (N=234)	
	Any Grade	CTCAE Grade 3-4
Investigations		
Aspartate aminotransferase increased	35 (15.0)	2 (0.9)
Alanine aminotransferase increased	25 (10.7)	3 (1.3)

MedDRA System Organ Class Preferred Term or Grouped Term	Number (%) of Subjects as of the Safety Update DCO (N=234)	
	Any Grade	CTCAE Grade 3-4
Metabolism and nutrition disorders		
Decreased appetite	81 (34.6)	3 (1.3)
Hypokalaemia	30 (12.8)	8 (3.4)
Nervous system disorders		
Headache [l]	47 (20.1)	0
Dizziness	25 (10.7)	0
Respiratory, thoracic and mediastinal disorders		
Cough	50 (21.4)	0
Dyspnoea	34 (14.5)	4 (1.7)
Epistaxis	33 (14.1)	0
Interstitial lung disease [m]	32 (13.7)	1 (0.4) [n]
Skin and subcutaneous tissue disorders		
Alopecia	108 (46.2)	1 (0.4) [o]
Rash [p]	30 (12.8)	1 (0.4)

CTCAE = Common Terminology Criteria for Adverse Events, version 4.03; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; IRR = infusion related reaction; MedDRA = Medical Dictionary for Regulatory Activities, version 20.1; N=number of subjects exposed; n (%) = number and percentage of subjects who experienced the adverse event; PT = preferred term

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

[a] Anaemia (grouped term) includes PTs of haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased

[b] Neutropenia (grouped term) includes PTs of neutrophil count decreased and neutropenia.

[c] Thrombocytopenia (grouped term) includes PTs of platelet count decreased and thrombocytopenia.

[d] Leukopenia (grouped term) includes PTs of white blood cell count decreased and leukopenia.

[e] Lymphopenia (grouped term) includes PTs of lymphocyte count decreased and lymphopenia

[f] This Grade 4 event was reported by the investigator. Per CTCAE v.4.03, the highest grade for dry eye is Grade 3.

[g] Abdominal pain (grouped term) includes PTs of abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain.

[h] Stomatitis (grouped term) includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

[i] Fatigue (grouped term) includes PTs of fatigue and asthenia.

[j] Upper respiratory tract infection (grouped term) includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.

[k] Cases of IRR include infusion related reaction (n=4), flushing (n=1), and hypersensitivity (n=1).

[l] Headache (grouped term) includes PTs of headache, migraine, and sinus headache.

[m] Interstitial lung disease includes events adjudicated as ILD and related to use of trastuzumab deruxtecan: pneumonitis, interstitial lung disease, respiratory failure, organising pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

[n] In addition to 1 subject with a Grade 3 event, 6 subjects had Grade 5 events.

[o] This Grade 3 severity was reported by the investigator. Per CTCAE v.4.03, the highest grade for alopecia is Grade 2.

[p] Rash (grouped term) includes PTs of rash, rash maculo-papular, and rash pustular.

Sources: Appendix 1 Table 23; Safety Update Table 1.2.2.3

Adverse events of special interest

Table 52: Selected Preferred Terms in Adverse Events of Special Interest

Category	Selected Preferred Terms for Review
Interstitial lung disease	Interstitial lung disease Pneumonitis Organising pneumonia Acute interstitial pneumonitis
Left ventricular ejection fraction decrease	Acute left ventricular failure Acute right ventricular failure Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive Chronic left ventricular failure Chronic right ventricular failure Ejection fraction decreased Left ventricular failure Right ventricular failure Ventricular failure
QT prolongation	Electrocardiogram QT prolonged Electrocardiogram QT interval abnormal Torsade de pointes Sudden cardiac death Sudden death Syncope Ventricular arrhythmia Ventricular fibrillation Ventricular flutter Ventricular tachycardia Ventricular tachyarrhythmia Seizure
Infusion-related reaction (defined as any of these pre-selected preferred terms within the same day of an infusion at any cycle)	Infusion related reaction Flushing Anaphylactic reaction Dyspnoea Hypotension Wheezing Hypersensitivity Bronchospasm Pruritus Angioedema Urticaria Skin exfoliation Oedema Rash

Interstitial Lung Disease/pneumonitis

At the time of the start of the clinical program, ILD was considered to be an important potential risk for trastuzumab deruxtecan. After the first suspected fatal ILD case occurred, the Sponsor established an external ILD Adjudication Committee for the program that adjudicated all events of potential ILD reported by investigators on an ongoing basis. Events of potential ILD from all clinical studies of trastuzumab deruxtecan were closely monitored. In Jan 2018, in response to the observed ILD events, ILD was determined to be an important identified risk. In the spring of 2019, a global ILD awareness campaign was initiated to educate both investigators and patients, with the goal of reducing the risk of severe ILD (including fatal cases) by proactively detecting and intensively managing ILD at an early stage. While there was an increase in the frequency of subjects with adjudicated drug-related ILD at the time of the Safety Update DCO (13.7% vs. the 9.4% as of the CSR DCOs), most events reported were Grade 1 or Grade 2, with no new events of Grade 4 or Grade 5 reported after the DCOs for the individual studies (01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201). An analysis of all events of potential ILD that were adjudicated by the AC from Study J101 and Study U201 pooled data

is presented below, based on the 44 PTs listed in the ILD AC Charter. In addition, a comprehensive exploratory analysis to evaluate the potential risk factors for ILD was performed based on the 5-study pool.

Table 53: ILD Events by Adjudicated Outcome and Adjudicated Grade (Safety Analysis Set)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee [a]	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Adjudicated as ILD	24 (10.3)	35 (15.0)	25 (9.1)	40 (14.5)
Grade 1	4 (1.7)	6 (2.6)	4 (1.5)	7 (2.5)
Grade 2 [b]	13 (5.6)	21 (9.0)	14 (5.1)	24 (8.7)
Grade 3	0	1 (0.4)	0	2 (0.7)
Grade 4	1 (0.4) [c]	0	1 (0.4) [c]	0
Grade 5	6 (2.6) [d]	7 (3.0)	6 (2.2) [d]	7 (2.5)

Adjudicated Outcome / CTCAE Grade Reported by Adjudication Committee [a]	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Adjudicated as Drug-related ILD	22 (9.4)	32 (13.7)	23 (8.4)	37 (13.5)
Grade 1	4 (1.7)	6 (2.6)	4 (1.5)	7 (2.5)
Grade 2 [b]	12 (5.1)	19 (8.1)	13 (4.7)	22 (8.0)
Grade 3	0	1 (0.4)	0	2 (0.7)
Grade 4 [c]	1 (0.4)	0	1 (0.4)	0
Grade 5 [c]	5 (2.1)	6 (2.6)	5 (1.8)	6 (2.2)
Adjudicated as Not Drug-related ILD	2 (0.9)	3 (1.3)	2 (0.7)	3 (1.1)
Grade 1	0	0	0	0
Grade 2	1 (0.4)	2 (0.9)	1 (0.4)	2 (0.7)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5 [d]	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)

AC = Adjudication Committee; BC = breast cancer; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; DCO = data cut-off; GC = gastric/ gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; TEAE = treatment-emergent adverse event

Percentages were calculated using the number of subjects with non-missing ILD grade as the denominator.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

If a subject had multiple ILD events, the CTCAE grade is shown for the event with the worst grade.

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201.

[a] The ILD AC assigned grades to those events that were determined to be ILD.

[b] Includes 3 events in Study J101 that occurred >28 days after the last dose, per investigator-reported onset date, including Subject No. 10104029 in the HER2-positive BC 5.4 mg/kg Pool, Subject No [redacted] in the All Tumor Types 5.4 mg/kg Pool (HER2-low GC), and Subject No [redacted] in the All Tumor Types ≥6.4 mg/kg Pool (HER2-positive GC 6.4 mg/kg)

[c] One subject in Study U201 had a TEAE of respiratory failure and subsequently died; the death was adjudicated as being due to ILD (after the database lock, the severity was updated from Grade 4 to Grade 5, following ILD AC re-adjudication of the event). As of the CSR DCO, the database reflected this as a Grade 4 event; the database as of 01 Aug 2019 reflects it as a Grade 5 event.

[d] One subject in Study U201 had an event adjudicated as not related to trastuzumab deruxtecan, with death not due to ILD. The ILD AC commented that "This is ARDS [acute respiratory distress syndrome] related to pneumococcal sepsis."

Sources: ISS Table 1.2.2.19; Safety Update Table 1.2.2.19

Table 54: Overview of Adjudicated Drug-related ILD Events (Safety Analysis Set)

Parameter	Number (%) of Subjects by Pool			
	HER2-positive BC 5.4 mg/kg		All Tumor Types 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Adjudicated drug-related ILD	22 (9.4) [a]	32 (13.7) [a]	23 (8.4) [b]	37 (13.5) [b]
ILD CTCAE ≥Grade 3 [c]	6 (2.6)	7 (3.0)	6 (2.2)	8 (2.9)
Serious ILD	8 (3.4)	12 (5.1)	8 (2.9)	13 (4.7)
ILD Associated with Discontinuation of Study Drug	15 (6.4)	22 (9.4)	16 (5.8)	24 (8.7)
ILD Associated with Dose Reduction	2 (0.9)	4 (1.7)	2 (0.7)	4 (1.5)
ILD Associated with Drug Interruption	5 (2.1)	6 (2.6)	5 (1.8)	7 (2.5)
ILD Associated with Outcome of Death	6 (2.6)	6 (2.6)	6 (2.2)	6 (2.2)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; CTCAE = Common Terminology Criteria for Adverse Events, version 4.03; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of subjects in the pool
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019
The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201.
[a] One event occurred >28 days after the last dose, per investigator-reported onset date
[b] Two events occurred >28 days after the last dose, per investigator-reported onset date
[c] A subject was counted once at the maximum severity, if he/she reported at least 1 AE.
Source: Appendix 1 Table 21

Table 55: Outcome of Events Adjudicated as Drug-related ILD (Safety Analysis Set)

Outcome	Number (%) of Subjects by Pool			
	HER2-positive BC 5.4 mg/kg		All Tumor Types 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Number of Subjects with Adjudicated Drug-related ILD	22	32	23	37
Recovered/Resolved	6 (27.3)	8 (25.0)	6 (26.1)	12 (32.4)
Recovering/Resolving	1 (4.5)	2 (6.3)	1 (4.3)	2 (5.4)
Recovered/Resolved with Sequelae	0	1 (3.1)	0	1 (2.7)
Not Recovered/Not Resolved	9 (40.9)	13 (40.6)	10 (43.5)	14 (37.8)
Fatal	6 (27.3)	6 (18.8)	6 (26.1)	6 (16.2)
Missing	0	2 (6.3) [a]	0	2 (5.4)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; N = total number of subjects in the pool
[a] Two subjects from Study U201 had events of adjudicated drug-related ILD with no outcome reported.
Percentages were calculated using the number of subjects who had adjudicated drug-related ILD as the denominator.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019
The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201.
Sources: ISS Table 1.2.2.16, Safety Update Table 1.2.2.16

10.2 Follow-up Information for Previously Unresolved Cases of Adjudicated Drug-related ILD, from Safety Update DCO of 1 Aug 2019 to 13 March 2020

Country	Subject Number	Dose (mg/kg)	Tumor Type	Subject Trial Status	Subject Survival Status	ILD Highest Grade	Resolved/ Not Resolved	Details
Study DS8201-A-U201								
France		5.4	Breast cancer	In survival follow-up	Alive as of 17 Dec 2019	Grade 2 (AESI start date 27 Mar 2019)	Resolved	Resolved as of 25 Jul 2019
France		5.4	Breast cancer	In survival follow-up	Alive as of 16 Aug 2019	Grade 3 (AESI start date 26 Apr 2019)	Unknown-Not assessed	Not resolved
Japan		5.4	Breast cancer	In survival follow-up	Alive as of 05 Nov 2019	Grade 2 (AESI start date 26 Dec 2018)	Not resolved	Improved to Grade 1 on 25 Feb 2019 Ongoing at Grade 1 as of 18 Feb 2020
Japan		5.4	Breast cancer	In survival follow-up	Alive as of 12 Feb 2020	Grade 1 (AESI start date 04 Jul 2019)	Not resolved	Ongoing at Grade 1 as of 17 Feb 2020
Japan		5.4	Breast cancer	In survival follow-up	Alive as of 22 Nov 2019	Grade 1 (AESI start date 05 Feb 2019)	Not resolved	Ongoing at Grade 1 as of 27 Feb 2020
Japan		5.4	Breast cancer	In survival follow-up	Alive as of 27 Jan 2020	Grade 1 (AESI start date 04 Jun 2019)	Not resolved	Ongoing at Grade 1 as of 27 Jan 2020
Japan		5.4	Breast cancer	In treatment	On treatment as of 12 Feb 2020	Grade 1 (AESI start date 01 Aug 2019	Resolved	Resolved as of 27 Aug 2019
Republic of Korea		5.4	Breast cancer	In survival follow-up	Alive as of 10 Sep 2019	Grade 1 (AESI start date 10 May 2019)	Not resolved	Ongoing at Grade 1 as of 20 Feb 2020
United Kingdom		5.4	Breast cancer	In survival follow-up	Alive as of 02 Oct 2019	Grade 2 (AESI start date 18 Sep 2018)	Resolved	Resolved as of 6 Dec 2019
United States		5.4	Breast cancer	Study discontinued	Dead 23 Mar 2019 (cause: Unknown)	Grade 1 (AESI start date 13 Sep 2018)	Not resolved (resolving)	Resolving pneumonitis as of 4 Oct 2018
United States		5.4	Breast cancer	Study discontinued	Dead 18 Jul 2019 (cause: disease progression)	Grade 2 (AESI start date 10 Jan 2019)	Resolved	Resolved as of 7 May 2019
United States		5.4	Breast cancer	In survival follow-up	Alive as of 02 Jul 2019	Grade 2 (AESI start date 28 May 2019, worsened on 28 Jun2019)	Resolved	Resolved as of 27 Jan 2020
Study DS8201-A-J101								
Japan		5.4	Breast cancer	Study discontinued	Lost to follow-up	Grade 1	Resolved	Resolved as of 18 Jan 2019
Japan		5.4	Breast cancer	In survival follow-up		Grade 1	Not resolved	Not resolved
United States		5.4	Breast cancer	In survival follow-up		Grade 1	Resolved	Resolved as of May 2019

AESI = adverse event of special interest; ILD = interstitial lung disease

Table 56: Potential ILD Risk Factors by Adjudicated ILD Status, Across All Tumor Types and Doses in the Combined Five Studies as of the CSR DCOs (Safety Analysis Set)

Comorbidity/Potential Risk Factor	Number (%) of Subjects with ILD Events [a]
Age group [b]	
<65	52/455 (11.4)
≥65	20/190 (10.5)
Sex	
Male	7/81 (8.6)
Female	65/564 (11.5)
Race	
White	18/214 (8.4)
Asian	51/398 (12.8)
Other	3/28 (10.7)

Comorbidity/Potential Risk Factor	Number (%) of Subjects with ILD Events [a]
Missing	0/5
Country	
Japan	51/316 (16.1)
Non-Japan	21/329 (6.4)
Region	
Asia	51/377 (13.5)
Non-Asia	21/268 (7.8)

Comorbidity/Potential Risk Factor	Number (%) of Subjects with ILD Events [a]
Tumor type	
Breast cancer	62/517 (12.0)
Gastric cancer	4/41 (9.8)
Other cancer	6/87 (6.9)
Lung cancer or metastasis/lymphangitis carcinomatosis at baseline	
Yes	32/315 (10.2)
No	40/330 (12.1)
Prior chest/lung radiotherapy	
Yes	19/139 (13.7)
No	53/506 (10.5)
Comorbidity or history of lung disease [c]	
Yes	5/40 (12.5)
No	67/605 (11.1)
Number of prior chemotherapy/targeted therapies received	
<10	51/530 (9.6)
≥10	21/115 (18.3)
Time since initial disease diagnosis [d]	
< median (62.8 months)	28/322 (8.7)
≥ median (62.8 months)	44/323 (13.6)
Dose (mg/kg)	
5.4	25/315 (7.9)
≥6.4	47/321 (14.6)

CSR = clinical study report; DCO = data cut-off; ILD = interstitial lung disease
The 5 studies include Study J101, Study U201, Study A103, Study A104, and Study J102.
[a] 72 subjects had adjudicated drug-related ILD.
[b] Age in years was calculated using the informed consent date and the birth date.
[c] Lung comorbidities included chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, pleural effusion, and radiation pneumonitis.
[d] Time since disease diagnosis was calculated as (date of diagnosis of primary cancer – date of the first dose + 1).
Source: ISS Table 1.2.2.28

Table 57: Odds Ratio of Risk Factors as of the CSR DCOs (Safety Analysis Set)

Risk Factor	Odds Ratio (95% CI)	p-value
Country: Japan vs. Non-Japan	3.1 (1.8, 5.3)	<0.001
Number of Prior Targeted Therapies: ≥10 vs. <10	2.4 (1.4, 4.3)	0.002

CI = confidence interval; CSR = clinical study report; DCO = data cut-off; ILD = interstitial lung disease
Stepwise logistic regression was used to explore the correlation between ILD events and potential risk factors. The stepwise selection used an entry criteria p-value<0.05 and exit criteria p-value=0.10. Only factors remaining in the final selected model were included.
Subjects from 5 studies were included in the model: Study J101, Study U201, Study J102, Study A103, Study A104
Source: ISS Table 1.2.2.26

Adverse events of special interest included ILD/pneumonitis, left ventricular dysfunction, QT prolongation, and infusion-related reactions. Below, the AESI of ILD/pneumonitis is assessed.

35/234 (15%) patients in the HER2-positive BC 5.4 mg/kg Pool had an ILD event and of these, 32 patients (13.7%) had treatment-related events of grade 1 in 6/234 (2.6%) patients, grade 2 in 19/234 (8.1%), grade 3 in 1/234 (0.4%), grade 4 in 0, and fatal outcome (grade 5) was observed in 6 patients (2.6%). 3 patients had ILD that was not deemed treatment-related and one was a fatal event of ARDS related to pneumococcal sepsis.

Compared to the HER2-positive BC ≥6.4 mg/kg Pool, the incidence of treatment-related ILD was lower in the HER2-positive 5.4 mg/kg Pool: 32/234 (13.7%) vs. 34/137 (24.8%). The median time to onset of ILD was 134.0 days (range: 35-338) and the median duration of the first event of ILD was 31.5 days (range: 3-261). Trastuzumab deruxtecan was discontinued due to treatment-related ILD in 22/234 (9.4%) patients, while the dose was reduced in 4/234 (1.7%) patients and dosing was interrupted in 6/234 (2.6%) patients. The outcome of the worst event of treatment-related ILD (further updated) was as follows: Not recovered/Not resolved: 7/32 (21.9%); Recovered/Resolved: 15/32 (46.9%); fatal: 6/32 (18.8%); Recovered/Resolving: 2/32 (6.3%) and Recovered/Resolved with sequelae: 1/32 (3.1%). Reported outcome were missing for 1 patient.

Relatively more patients from Japan experienced treatment-related ILD (12/51 [23.5%] vs. 20/183 [10.9%] non-Japan) and some of the difference was driven by low grade events (grade 1 [7.8%]) Japan vs. 2 [1.1%] non-Japan or grade 2 ([15.7%] Japan vs. [6.0%] non-Japan).

The Applicant has analysed at potential risk factors for ILD across all tumor types and doses in the combined five studies as of the CSR DCOs among the 645 treated patients. Of all the variables tested, only country (Japan vs. non-Japan) and number of prior regimens (<10 vs. ≥10) were statistically significant, i.e. patients from Japan had a higher incidence of treatment-related ILD (any grade) than patients from outside Japan did and patients with ≥10 prior regimens experienced a higher incidence than those who received <10 prior regimens, adjusting for all other factors.

The chosen factors which were analysed are deemed clinically relevant, but the presented analysis does not find any clinically relevant risk factors that can be used for the prescriber, since the applied indication is not for patients treated with more than 10 prior regimens and the increased number of events in Japanese were mostly of low grade; hence, no regulatory consequences are warranted for this finding. The Applicant informs that they plan to continue investigating trastuzumab deruxtecan related ILD/pneumonitis in ongoing and future clinical studies and they will submit the results of these analyses post-authorization in the Periodic benefit risk evaluation reports. The plans for further investigation of ILD/pneumonitis risk factors and prognostic factors are endorsed.

LVEF decrease

The Sponsor reviewed the selected PTs in the AESI of LVEF decrease (listed in Table 2.21) to determine whether the event was related to LVEF per echocardiogram (ECHO)/multigated acquisition (MUGA) scan and determined that LVEF decrease is not a risk for trastuzumab deruxtecan. Only the PT of ejection fraction decreased was determined to indicate actual LVEF decrease.

One additional subject reported a PT of ejection fraction decreased as of the Safety Update DCO (3/234 [1.3%] compared with 2/234 [0.9%] reported as of the CSR DCOs). Of these 3 subjects, 1 had a grade 2 event that was associated with drug interruption and resolved; 1 had a grade 3 event (reported the same day as Grade 1 mitral valve incompetence) that was associated with drug interruption and resolved; and the additional subject as of the Safety Update DCO had 3 grade 2 events, none of which required any action with regard to study treatment and all of which resolved.

No new events of cardiac failure were reported as of the Safety Update DCO. As reported as of the CSR DCOs, 2 subjects in the HER2-positive BC 5.4 mg/kg Pool from Study U201 had events of PTs other than ejection fraction decreased: a grade 2 SAE of cardiac failure congestive that led to the withdrawal of the study drug and resolved (LVEF value of 63% at baseline and 66%-70% during the study); and a grade 1 cardiac failure on Day 1 that was not resolved at the DCO (LVEF value of 52% at baseline and 57%-60% during the study).

One new subject with a PT of asymptomatic troponin I increased (grade 3) was reported in the HER2-positive BC 5.4 mg/kg Pool as of the Safety Update DCO. The event resolved, with no action taken regarding study drug. At the time of the Safety Update DCO, a PT of troponin increased was reported

as a TEAE in 3/234 (1.3%) subjects (1 grade 1 event and 2 grade 3 events), and troponin I increased was reported as a TEAE in 4/234 (1.7%) subjects (2 grade 1 events and 2 grade 3 events) in the HER2 positive BC 5.4 mg/kg Pool, with all events being asymptomatic.

The AESI of LVEF decrease included many PTs (Table 2.21) and the Applicant found that 'Left ventricular dysfunction' could be related to treatment with trastuzumab deruxtecan and this is an 'Important potential risk' in the list of safety concerns.

LVEF decrease is a known risk for Trastuzumab, but the Applicant states that after reviewing the selected PTs in the AESI of LVEF decrease it was determined that LVEF decrease is not a risk for trastuzumab deruxtecan. The definition of LVEF decrease should include patients with a reported AE of cardiac failure or LVEF decrease and/or a laboratory value of LVEF decrease.

The Applicant provided an update on TEAEs of LVEF decease (grouped PTs) and LVEF laboratory abnormalities through EMA DCO. The number TEAE reported within the grouped preferred terms (PTs) for left ventricular ejection fraction (LVEF) was limited, with 4 patients (2.2%) reporting ejection fraction decreased through EMA DCO. All were considered treatment related by the investigator and resolved without study drug discontinuation.

QT prolongation

The Sponsor reviewed the 12 selected PTs in the AESI of QT prolongation (listed in Table 2.21). Of these 12 selected PTs, events of electrocardiogram (ECG) QT prolonged (14/234 [6.0%] subjects, compared to 12/234 [5.6%] as of the CSR DCOs) and seizure (1/234 [0.4%] subject), were reported in the HER2 -positive BC 5.4 mg/kg Pool. The SAE of seizure was in a subject who had a history of brain metastases and brain irradiation; the event was not associated with QT prolongation. No symptomatic QT prolongation, Torsade de pointes, or severe arrhythmic events were reported. Compared to results as of the CSR DCOs, 1 new asymptomatic event of ECG QT prolonged (Grade 3) was reported during this period in the HER2-positive BC 5.4 mg/kg Pool. The event resolved with no action taken regarding study drug. Based on ECG data, 8/234 (3.4%) subjects in the HER2-positive BC 5.4 mg/kg Pool had a maximum change from baseline in QT interval corrected for heart rate by Fridericia's formula (QTcF) >60 msec, which was unchanged from the results seen at the individual DCOs.

Infusion-related reactions

The Sponsor reviewed the 14 selected PTs in the AESI of potential IRR (listed in Table 2.21). No new events of IRR were reported as of the Safety Update DCO. A total of 18/234 (7.7%) subjects in the HER2-positive BC 5.4 mg/kg Pool had events of potential IRR. After review, events of potential IRR in 12 of the 18 cases were considered not to be IRR, due to alternative etiologies. Hence, six (2.6%) of the 234 subjects in the HER2-positive BC 5.4 mg/kg Pool had events of IRR after review:

• An SAE of Grade 1 hypersensitivity was reported in 1/234 (0.4%) subject.

• The other 5/234 (2.1%) subjects had PTs of Grade 1 flushing (n=1) or Grade 2 infusion related reaction (n=4)

• No subject had study drug discontinued or dose reduction due to a TEAE of IRR.

• Dosing was interrupted in 1/234 (0.4%) subject who had a PT of infusion related reaction.

• At the time of the DCO, the IRR had resolved in 5 subjects and resolved with sequelae in 1 subject, who had a second event approximately 6 months later that resolved on the day of onset (Day 178).

• Prophylactic medication was allowed at the investigator's discretion but was not mandated by protocol.

The available data did not allow for differentiation between prophylactic use and management of IRR; however, as stated above, no subject had study drug discontinued or dose reduction due to a TEAE of IRR.

Serious adverse event/deaths/other significant events

SAEs

Table 58: Treatment-emergent Serious Adverse Events Reported in at Least 1% of Subjects in the HER2-positive Breast Cancer 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects in Pool			
	HER2-positive 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Subjects with Any Serious TEAE	47 (20.1)	54 (23.1)	54 (19.6)	61 (22.2)
Pneumonitis	4 (1.7)	6 (2.6)	4 (1.5)	6 (2.2)
Pneumonia	5 (2.1)	5 (2.1)	7 (2.5)	7 (2.5)
Respiratory failure	5 (2.1)	5 (2.1)	5 (1.8)	5 (1.8)
Vomiting	4 (1.7)	4 (1.7)	4 (1.5)	4 (1.5)
Cellulitis	3 (1.3)	4 (1.7)	4 (1.5)	5 (1.8)
Hypokalaemia	3 (1.3)	3 (1.3)	3 (1.1)	3 (1.1)
Intestinal obstruction	3 (1.3)	3 (1.3)	3 (1.1)	3 (1.1)
Nausea	3 (1.3)	3 (1.3)	3 (1.1)	3 (1.1)
Pleural effusion	2 (0.9)	3 (1.3)	2 (0.7)	3 (1.1)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, v20.1; N = total number of subjects in the pool; PT = preferred term; TEAE = treatment-emergent adverse event
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019
If a subject had multiple occurrences of the same PT, the subject was counted once for that preferred term.
The 2 pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
Sources: ISS Table 1.2.1.3; Safety Update Table 1.2.1.3

In the all tumor types pool, 22.2% had an SAE and most commonly pertaining to pneumonia (2.5%), pneumonitis (2.2%), respiratory failure and cellulitis (1.8% each). Hence, 23 patients (8.4%) had an SAE related to the respiratory system. Treatment-emergent SAEs were reported in 23.1% of patients in the HER2-positive BC 5.4 mg/kg Pool and the following PTs were reported in ≥1% of patients: 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%).

Deaths

Table 59: Primary Cause of Any Deaths and On-study Deaths (Safety Analysis Set)

Primary Cause	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Any Death	28 (12.0)	39 (16.7)	40 (14.5)	55 (20.0)	9 (18.0)	14 (28.0)	19 (10.3)	25 (13.6)

Primary Cause	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive BC 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Disease Progression	16 (6.8)	25 (10.7)	24 (8.7)	35 (12.7)	5 (10.0)	9 (18.0)	11 (6.0)	16 (8.7)
Adverse Event	7 (3.0) [a]	7 (3.0) [a]	8 (2.9)	8 (2.9)	2 (4.0)	2 (4.0)	5 (2.7)	5 (2.7)
Other	2 (0.9) [b]	2 (0.9) [b]	3 (1.1)	3 (1.1)	0	0	2 (1.1)	2 (1.1)
Unknown	3 (1.3)	5 (2.1)	5 (1.8)	9 (3.3)	2 (4.0)	3 (6.0)	1 (0.5)	2 (1.1)
On-study Death [c]	10 (4.3)	10 (4.3)	10 (3.6)	10 (3.6)	3 (6.0)	3 (6.0)	7 (3.8)	7 (3.8)
Adverse Event	5 (2.1) [d]	5 (2.1) [d]	5 (1.8) [d]	5 (1.8) [d]	2 (4.0)	2 (4.0)	3 (1.6)	3 (1.6)
Disease Progression	4 (1.7)	4 (1.7)	4 (1.5)	4 (1.5)	1 (2.0)	1 (2.0)	3 (1.6)	3 (1.6)
Other	1 (0.4) [e]	1 (0.4) [e]	1 (0.4) [e]	1 (0.4) [e]	0	0	1 (0.5)	1 (0.5)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the study or pool

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.

[a] In addition to the subjects listed in footnote "d," 2 subjects in Study U201 had adverse event as primary cause of death, but the event occurred after the on-study treatment period.

[b] Other primary causes of deaths were recorded for 2 subjects in Study U201 (acute organ failure in Subject No. and alteration of the general condition in relation to his cancer in Subject No.) (Safety Update Listing 1.5.2).

[c] On-study death was defined as any death that occurred from the date of the first dose up to 28 days (for Study J101) or up to 47 days (for Study U201) after the last dose of study drug.

[d] Includes DS8201-A-J101 Subject Nos. (respiratory failure), (respiratory failure); DS8201-A-U201 Subject Nos. (shock haemorrhagic), (general physical health deterioration), (pneumonia) (Safety Update Listing 1.5.2).

[e] Other death was Study U201 Subject No. who experienced Grade 5 acute hepatic failure and acute kidney injury that occurred 34 days after the subject's last dose and were attributed to disease progression (Study U201 CSR Section 10.3.1.1).

Source: Appendix 1 Table 13

Table 60: Treatment-emergent Adverse Events Associated with Outcome of Death, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of Subjects in Pool				Number (%) of Subjects in Study			
	HER2-positive 5.4 mg/kg Pool		All Tumor Types 5.4 mg/kg Pool		Study J101 HER2-positive BC 5.4 mg/kg		Study U201 HER2-positive BC 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)	CSR DCO (N=50)	Safety Update DCO (N=50)	CSR DCO (N=184)	Safety Update DCO (N=184)
Subjects with Any TEAE Associated with Outcome of Death	12 (5.1)	12 (5.1)	12 (4.4)	12 (4.4)	3 (6.0)	3 (6.0)	9 (4.9)	9 (4.9)
Respiratory failure	3 (1.3)	3 (1.3)	3 (1.1)	3 (1.1)	2 (4.0)	2 (4.0)	1 (0.5)	1 (0.5)
Disease progression	2 (0.9)	2 (0.9)	2 (0.7)	2 (0.7)	1 (2.0)	1 (2.0)	1 (0.5)	1 (0.5)
Acute hepatic failure [a]	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
Acute kidney injury [a]	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
Acute respiratory failure	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
General physical health deterioration	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
Lymphangitis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
Pneumonia	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
Pneumonitis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)
Shock haemorrhagic	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.5)	1 (0.5)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, v20.1; N = total number of subjects in the study or pool; TEAE = treatment-emergent adverse event

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

The 2 pooled analysis groups were based on tumor type and assigned dose for subjects in Study J101 and Study U201. The individual studies include all treated subjects with HER2-positive BC who were assigned to receive 5.4 mg/kg in Study J101 or Study U201.

A death could be associated with multiple preferred terms.

[a] Acute hepatic failure and acute kidney injury were both reported as TEAEs associated with an outcome of death in Study U201 Subject No., with both attributed to disease progression (liver metastases).

Sources: Appendix 1 Table 15; Study U201 CSR Section 10.3.1.1

A total of 12 (4.7%) patients had at least 1 TEAE associated with a fatal outcome and narratives for all subjects who died on-study are provided. For 4 of the 12 patients (1 in the 7.4 mg/kg dose cohort and 3 in the 5.4 mg/kg dose cohort), the TEAEs with a fatal outcome were adjudicated as study drug-related Grade 5 ILD by the ILD AC. An additional subject in the 5.4 mg/kg cohort had an event of ILD adjudicated as study drug-related Grade 4 ILD ; the patient subsequently died before DCO and the death was adjudicated as being due to ILD (for a total of 5 deaths due to study drug-related ILD events). In addition, one Subjectin the 5.4 mg/kg cohort had an event adjudicated as ILD but not related to study drug. Death was attributed instead to acute respiratory distress syndrome related to pneumococcal sepsis by the ILD AC.

- **Subject No.** (7.4 mg/kg), a 67-year-old white female subject, started treatment with DS-8201a on 03 Apr 2018 and received the last dose on Day 246. A TEAE of grade 1 pneumonitis started on Day 253, which was considered to be study drug related by the investigator. Dosing was not modified, and the subject continued on treatment. On Day 266, the subject experienced Grade 3 hypoxia and the event led to treatment discontinuation. Death from study drug-related Grade 5 pneumonitis occurred on Day 285 from first dose. The event was adjudicated as Grade 5 study drug-related ILD by the ILD AC.
- **Subject No.** (5.4 mg/kg), a 45-year-old white female, started treatment with DS-8201a on 25 Jul 2018 and received the last dose on Day 65. A Grade 5 event of acute respiratory failure occurred on Day 83 with death on Day 91. The event was adjudicated as Grade 5 study drug-related ILD by the ILD AC.
- **Subject No.** (5.4 mg/kg), a 62-year-old white female, started treatment with DS-8201a on 21 Aug 2018 and received the last dose on Day 43. The event of Grade 5 lymphangitis started on Day 63 and led to death on Day 72. The event was initially reported as pneumonitis before the study site updated the event to lymphangitis. The event was adjudicated as Grade 5 study drug-related ILD by the ILD AC.
- **Subject No.** (5.4 mg/kg), a 64-year-old white female, started treatment with DS-8201a on 13 Sep 2018 and received the last dose on Day 127. Grade 1 cough and Grade 1 dyspnoea started on Day 120, which were considered to be drug-related by the investigator; dosing was not modified, and no treatment was administered. These TEAEs remained ongoing and on Day 148, a diagnosis of pneumonitis was made and DS-8201a was withdrawn due to the event. Death from study drug-related Grade 5 pneumonitis occurred on Day 190 from first dose. The event was adjudicated as Grade 5 study drug-related ILD by the ILD AC.
- **Subject No.** (5.4 mg/kg), a 33-year-old white female, started treatment with DS-8201a on 29 Aug 2018 and received the last dose on Day 85. A Grade 1 TEAE of pneumonitis (asymptomatic per verbatim term) was reported on Day 86, which the investigator considered to be study drug-related and for which dosing was interrupted and treatment with oral methylprednisolone (48 mg) was started on Day 106. The event worsened to Grade 2 on Day 134 and was associated with Grade 1 hypoventilation. Treatment of pneumonitis with methylprednisolone continued and DS-8201a was withdrawn due to the event on Day 134. Both events of pneumonitis and hypoventilation remained ongoing. A TEAE of respiratory failure was reported as starting on Day 137, with death from study drug-related Grade 5 respiratory failure occurring on Day 145. The event was adjudicated as Grade 4 study drug-related ILD by the ILD AC.
- **Subject No.** (5.4 mg/kg), a 48-year-old white female, started treatment with DS-8201a on 26 Jul 2018 and received the last dose on Day 156. The event of Grade 5 pneumonia started on Day 167 with death from the event on Day 180. The event was adjudicated as Grade 5 ILD not

related to DS-8201a by the ILD AC. The event was attributed instead to acute respiratory distress syndrome related to pneumococcal sepsis by the ILD AC.

In 6 of the 12 patients with TEAEs associated with a fatal outcome, death was not considered to be study drug-related by the investigators: 2 subjects with disease progression, these 2 subjects are not described below. Based on the protocol, when a subject died from PD with no other immediate causes, disease progression was to be reported as an SAE; and 1 subject each with shock haemorrhagic , asthenia, acute hepatic failure and acute kidney injury, and general physical health deterioration.

- **Subject No.** (5.4 mg/kg), a 69-year-old white female, started treatment with DS-8201a on 08 May 2018 and received the last dose on Day 45. A Grade 5 shock haemorrhagic occurred on Day 87 and the subject died the same day. No laboratory test results were available for the time of the event.
- **Subject No.** (6.4 mg/kg), a 78-year-old white female, started treatment with DS-8201a on 03 May 2018 and received the last dose on Day 99. The TEAE of Grade 5 asthenia started on Day 113. The subject had ongoing Grade 2 anemia. After the start of the event of asthenia, the subject experienced Grade 2 pleural effusion and Grade 1 ascites and was hospitalized on 30 Aug 2018. Treatment with DS-8201a was discontinued on Day 119 due to physical deterioration. Death due to asthenia occurred on Day 153 and was considered to be unrelated to study drug.
- **Subject No.** (5.4 mg/kg), a 53-year-old white female, started treatment with DS-8201a on 23 Aug 2018 and received the last dose on Day 85. Study drug was interrupted on Day 104 due to a TEAE of blood bilirubin increased. Events of Grade 1 abdominal distension, peripheral swelling, chromaturia, and dyspnea, and Grade 2 fatigue started on Day 117. Ultrasound results at the time showed hepatic metastatic disease and cholelithiasis without evidence of cholecystitis. The subject received 5 cycles of study drug and discontinued due to progressive disease. The TEAEs of Grade 5 acute hepatic failure and acute kidney injury started on Day 119 and were attributed to disease progression (liver metastases) with death from the events on Day 125.
- **Subject No.** (5.4 mg/kg), a 66-year-old white female, started treatment with DS-8201a on 20 Jun 2018 and received the last dose on Day 190. The subject was diagnosed with pneumonia based on radiological findings and was hospitalized; during this time, general condition worsened, with an ECOG PS of 3 reported. The event of Grade 5 general physical health deterioration started on Day 196, for which DS-8201a was interrupted. Death due to the event occurred on Day 219 from first dose.
- **Subject:** 61-year-old female initially diagnosed with breast cancer on 22 OCT 2014. She enrolled in the DS8201-A-U201 clinical study and was assigned to the dose level of 5.4 mg/kg in Part 2 Cohort 2a. At study entry, the subject had stage IV breast cancer with disease progression. Her last anti-cancer regimen prior to participating in this study included trastuzumab and capecitabine (15 JAN 2018 to 09 JUL 2018). The tumor was HER2 IHC 2+, ISH positive. The subject had ECOG PS of 1 and had received 5 prior anti-cancer regimens, including anti-HER2 agents. Relevant prior radiation therapy included femoral neck stereotactic radiotherapy (JUL 2017). Relevant medical history included asthenia (ongoing from 2018) and ascites (ongoing from 2018). On 12 NOV 2018 (Day 98), the subject was diagnosed with Grade 3 hyperkalaemia, considered a serious adverse event as it required hospitalization. The last dose of DS-8201a (5.4 mg/kg) the subject received prior to onset of the event of hyperkalaemia was on 09 OCT 2018 (Day 64). The subject's potassium was reported as 8.8 mmol/L (reference range: 3.4 to 4.5 mmol/L); 9 L of fluid was removed by paracentesis on the

same day. There were no ECG signs of hyperkalemia. The subject improved with intravenous medications of insulin/glucose QD and polystyrene sulfonate QD and oral furosemide QD (12 NOV 2018 to 13 NOV 2018) for Hyperkalemia. On 13 NOV 2018 (Day 99), laboratory result showed normal potassium. On 15 NOV 2018 (Day 101), the event of hyperkalaemia resolved with potassium of 4.16 mmol/L. The action taken with DS-8201a as a result of the event hyperkalaemia was not applicable as DS-8201a had been previously interrupted. Relevant concomitant medications the subject was taking at the time of the event of hyperkalaemia included morphine, enoxaparin sodium, and prednisolone. DS-8201a was permanently discontinued due to the Investigator's decision on 22 NOV 2018 (Day 108). The subject received a total of 4 doses of DS-8201a. On 03 DEC 2018 (Day 119), the subject died due to deterioration of her general condition caused by her cancer. It is unknown whether an autopsy was performed. The Investigator considered the event of hyperkalaemia unrelated to DS-8201a. This is agreed.

Laboratory findings

Haematology

Table 61: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Anaemia (Haemoglobin Decreased) as of the Safety Update DCO (Safety Analysis Set)

Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
HER2-positive BC (5.4 mg/kg) (N=234)	Normal	24 (10.3)	84 (36.2)	23 (9.9)	5 (2.2)	0	136 (58.6)
	1	0	26 (11.2)	40 (17.2)	6 (2.6)	0	72 (31.0)
	2	0	0	14 (6.0)	8 (3.4)	0	22 (9.5)
	3	0	0	2 (0.9)	0	0	2 (0.9)
	4	0	0	0	0	0	0
	Total	24 (10.3)	110 (47.4)	79 (34.1)	19 (8.2)	0	232 (100.0)
	Missing	0	1	0	1	0	2
All Tumor Types (5.4 mg/kg) (N=275)	Normal	26 (9.5)	88 (32.2)	29 (10.6)	6 (2.2)	0	149 (54.6)
	1	0	34 (12.5)	52 (19.0)	7 (2.6)	0	93 (34.1)
	2	0	0	16 (5.9)	13 (4.8)	0	29 (10.6)
	3	0	0	2 (0.7)	0	0	2 (0.7)
	4	0	0	0	0	0	0
	Total	26 (9.5)	122 (44.7)	99 (36.3)	26 (9.5)	0	273 (100.0)
	Missing	0	1	0	1	0	2

BC = breast cancer; DCO = data cut-off; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Percentages were based on the number of subjects in the Safety Analysis Set for each pool with a baseline and at least 1 post-baseline assessment.
Safety Update DCO = 01 Aug 2019
Bolded values represent worsening from baseline.
The pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
Source: Safety Update Table 1.3.1.1

Table 62: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Platelet Count (Decrease) as of the Safety Update DCO (Safety Analysis Set)

Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
HER2-positive BC 5.4 mg/kg (N=234)	Normal	101 (43.7)	66 (28.6)	11 (4.8)	6 (2.6)	0	184 (79.7)
	1	2 (0.9)	28 (12.1)	13 (5.6)	3 (1.3)	0	46 (19.9)
	2	1 (0.4)	0	0	0	0	1 (0.4)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	104 (45.0)	94 (40.7)	24 (10.4)	9 (3.9)	0	231 (100.0)
	Missing	1	2	0	0	0	3
All Tumor Types 5.4 mg/kg (N=275)	Normal	115 (42.3)	79 (29.0)	13 (4.8)	8 (2.9)	0	215 (79.0)
	1	3 (1.1)	33 (12.1)	16 (5.9)	4 (1.5)	0	56 (20.6)
	2	1 (0.4)	0	0	0	0	1 (0.4)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	119 (43.8)	112 (41.2)	29 (10.7)	12 (4.4)	0	272 (100.0)
	Missing	1	2	0	0	0	3

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the Pool
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Percentages were based on the number of subjects in the Safety Analysis Set for each pool with a baseline and at least 1 post-baseline assessment.
Safety Update DCO = 01 Aug 2019
Bolded values represent worsening from baseline.
The pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
Source: Safety Update Table 1.3.1.1

Table 63: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Neutrophils, by Pool (Safety Analysis Set)

Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
HER2-positive BC 5.4 mg/kg (N = 234)	Normal	75 (32.5)	36 (15.6)	67 (29.0)	31 (13.4)	2 (0.9)	211 (91.3)
	1	0	2 (0.9)	6 (2.6)	6 (2.6)	2 (0.9)	16 (6.9)
	2	1 (0.4)	1 (0.4)	0	0	0	2 (0.9)
	3	0	2 (0.9)	0	0	0	2 (0.9)
	4	0	0	0	0	0	0
	Total	76 (32.9)	41 (17.7)	73 (31.6)	37 (16.0)	4 (1.7)	231 (100.0)
	Missing	1	0	1	1	0	3
All Tumor Types 5.4 mg/kg (N = 275)	Normal	97 (35.7)	37 (13.6)	80 (29.4)	34 (12.5)	3 (1.1)	251 (92.3)
	1	0	2 (0.7)	6 (2.2)	7 (2.6)	2 (0.7)	17 (6.3)
	2	1 (0.4)	1 (0.4)	0	0	0	2 (0.7)
	3	0	2 (0.7)	0	0	0	2 (0.7)
	4	0	0	0	0	0	0
	Total	98 (36.0)	42 (15.4)	86 (31.6)	41 (15.1)	5 (1.8)	272 (100.0)
	Missing	1	0	1	1	0	3

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Percentages were based on the number of subjects in the Safety Analysis Set for each pool with a baseline and at least 1 post-baseline assessment.
Bolded values represent worsening from baseline.
The pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
Source: Safety Update Table 1.3.1.1

Table 64: Summary of Shifts from Baseline to Worst Post-Baseline CTCAE Grade in Lymphocytes, by Pool (Safety Analysis Set)

Pool	Baseline CTCAE Grade	Number (%) of Subjects with Worst Post-baseline CTCAE Grade					
		Normal	1	2	3	4	Total
HER2-positive BC5.4 mg/kg (N = 234)	Normal	88 (38.1)	12 (5.2)	70 (30.3)	16 (6.9)	0	186 (80.5)
	1	0	0	3 (1.3)	3 (1.3)	0	6 (2.6)
	2	3 (1.3)	0	8 (3.5)	20 (8.7)	0	31 (13.4)
	3	0	0	0	5 (2.2)	2 (0.9)	7 (3.0)
	4	0	0	1 (0.4)	0	0	1 (0.4)
	Total	91 (39.4)	12 (5.2)	82 (35.5)	44 (19.0)	2 (0.9)	231 (100.0)
	Missing	1	0	1	1	0	3
All Tumor Types 5.4 mg/kg (N = 275)	Normal	98 (36.0)	13 (4.8)	85 (31.3)	21 (7.7)	1 (0.4)	218 (80.1)
	1	0	0	5 (1.8)	4 (1.5)	0	9 (3.3)
	2	3 (1.1)	0	9 (3.3)	21 (7.7)	1 (0.4)	34 (12.5)
	3	0	0	0	8 (2.9)	2 (0.7)	10 (3.7)
	4	0	0	1 (0.4)	0	0	1 (0.4)
	Total	101 (37.1)	13 (4.8)	100 (36.8)	54 (19.9)	4 (1.5)	272 (100.0)
	Missing	1	0	1	1	0	3

BC = breast cancer; CTCAE = Common Terminology Criteria for Adverse Events, v4.03; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool
Baseline value was defined as the last non-missing value prior to the first dose of study drug.
Percentages were based on the number of subjects in the Safety Analysis Set for each pool with a baseline and at least 1 post-baseline assessment.
Bolded values represent worsening from baseline.
The pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
Source: Safety Update Table 1.3.1.1

The level of haematological toxicity is acceptable and seems manageable. All events were more frequent in the higher dose pool.

Blood chemistry

Table 65: Abnormal Clinical Chemistry Parameters, All Grades and At Least Grade 3 (Safety Analysis Set)

Clinical Chemistry Parameter	HER2-positive BC (5.4mg/kg) (N = 234) n (%)		HER2-positive BC (6.4, 7.4, and 8.0 mg/kg) (N = 137) n (%)		All tumor types (5.4 mg/kg) (N = 275) n (%)		All tumor types (6.4, 7.4, and 8.0 mg/kg) (N = 258) n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Creatinine increased	48 (20.5)	0	65 (47.4)	1 (0.7)	85 (30.9)	0	179 (69.4)	2 (0.8)
Hypercalcemia	9 (3.8)	2 (0.9)	12 (8.8)	0	12 (4.4)	3 (1.1)	21 (8.1)	2 (0.8)
Hypocalcemia	35 (15.0)	1 (0.4)	50 (36.5)	0	57 (20.7)	1 (0.4)	126 (48.8)	0
Hypermagnesemia	17 (7.3)	0	14 (10.2)	2 (1.5)	20 (7.3)	0	18 (7.0)	3 (1.2)
Hypomagnesemia	21 (9.0)	1 (0.4)	18 (13.1)	0	28 (10.2)	1 (0.4)	41 (15.9)	1 (0.4)
Hyperkalemia	14 (6.0)	1 (0.4)	9 (6.6)	0	19 (6.9)	3 (1.1)	31 (12.0)	1 (0.4)
Hypokalemia	70 (29.9)	9 (3.8)	65 (47.4)	11 (8.0)	86 (31.3)	14 (5.1)	119 (46.1)	21 (8.1)
Hypernatremia	20 (8.5)	0	16 (11.7)	0	23 (8.4)	0	30 (11.6)	1 (0.4)
Hyponatremia	37 (15.8)	2 (0.9)	36 (26.3)	6 (4.4)	53 (19.3)	4 (1.5)	90 (34.9)	16 (6.2)
Hypoalbuminemia	74 (31.6)	0	79 (57.7)	2 (1.5)	109 (39.6)	1 (0.4)	190 (73.6)	6 (2.3)
Alkaline phosphatase increased	153 (65.4)	5 (2.1)	98 (71.5)	1 (0.7)	182 (66.2)	6 (2.2)	177 (68.6)	5 (1.9)
Alanine aminotransferase increased	130 (55.6)	1 (0.4)	89 (65.0)	4 (2.9)	142 (51.6)	1 (0.4)	153 (59.3)	9 (3.5)
Aspartate aminotransferase increased	193 (82.5)	2 (0.9)	120 (87.6)	5 (3.6)	224 (81.5)	5 (1.8)	213 (82.6)	13 (5.0)
Blood bilirubin increased	38 (16.2)	1 (0.4)	29 (21.2)	2 (1.5)	50 (18.2)	1 (0.4)	56 (21.7)	5 (1.9)

Percentages were based on the number of subjects in the Safety Analysis Set.
Safety Update DCO = 01 Aug 2019.
The pooled analysis groups are based on tumor type and first dose received for subjects in Studies DS8201-A-J101 and DS8201-A-U201.
Source: EU MAA LoQ Safety Analyses Table 10.20.

Updated blood chemistry is assessed for the relevant dosing group (ATT pool, n=235) and showed very common all grade events, but very seldom the events were of grade 3 or more, hypokalaemia and alkaline phosphatase increased being the two most common grade≥3 events in 5.1% and 2.2% of the patients, respectively. Hence, shifts in blood chemistry were acceptable and manageable.

Table 66: Hepatic Function Abnormalities as of the Safety Update DCO, by Pool (Safety Analysis Set)

Laboratory Parameter	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg (N = 234)	HER2-positive BC 6.4, 7.4, 8.0 mg/kg (N = 137)	All Tumor Types 5.4 mg/kg (N = 275)	All Tumor Types 6.4, 7.4, 8.0 mg/kg (N = 258)
Alanine Aminotransferase (ALT)				
Non-missing n [a]	232	136	273	257
Baseline ≥ULN	41 (17.7)	33 (24.3)	48 (17.6)	56 (21.8)
Maximum Post-baseline Value				
≥3 x ULN	8 (3.4)	14 (10.3)	11 (4.0)	27 (10.5)
≥5 x ULN	1 (0.4)	4 (2.9)	1 (0.4)	9 (3.5)
≥8 x ULN	1 (0.4)	2 (1.5)	1 (0.4)	4 (1.6)
≥10 x ULN	1 (0.4)	1 (0.7)	1 (0.4)	2 (0.8)
≥20 x ULN	0	0	0	1 (0.4)
Aspartate Aminotransferase (AST)				
Non-missing n [a]	232	136	273	257
Baseline ≥ULN	102 (44.0)	62 (45.6)	119 (43.6)	104 (40.5)
Maximum Post-baseline Value				
≥3 x ULN	10 (4.3)	18 (13.2)	15 (5.5)	40 (15.6)
≥5 x ULN	3 (1.3)	6 (4.4)	6 (2.2)	14 (5.4)
≥8 x ULN	1 (0.4)	2 (1.5)	1 (0.4)	4 (1.6)
≥10 x ULN	1 (0.4)	2 (1.5)	1 (0.4)	4 (1.6)
≥20 x ULN	1 (0.4)	0	1 (0.4)	1 (0.4)
ALT or AST				
Non-missing n [a]	232	136	273	257
Baseline ≥ULN	105 (45.3)	67 (49.3)	122 (44.7)	111 (43.2)
Maximum Post-baseline Value				
≥3 x ULN	15 (6.5)	23 (16.9)	21 (7.7)	49 (19.1)
≥5 x ULN	3 (1.3)	7 (5.1)	6 (2.2)	17 (6.6)
≥8 x ULN	1 (0.4)	3 (2.2)	1 (0.4)	5 (1.9)
≥10 x ULN	1 (0.4)	2 (1.5)	1 (0.4)	4 (1.6)
≥20 x ULN	1 (0.4)	0	1 (0.4)	1 (0.4)

Table 67: Hepatic Function Abnormalities as of the Safety Update DCO, by Pool (Safety Analysis Set) (Continued)

Laboratory Parameter	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg (N = 234)	HER2-positive BC 6.4, 7.4, 8.0 mg/kg (N = 137)	All Tumor Types 5.4 mg/kg (N = 275)	All Tumor Types 6.4, 7.4, 8.0 mg/kg (N = 258)
Total Bilirubin (TBL)				
Non-missing n [a]	234	136	275	257
Baseline ≥ULN	7 (3.0)	4 (2.9)	9 (3.3)	8 (3.1)
Maximum Post-Baseline value				
≥1.5 x ULN	12 (5.1)	11 (8.1)	16 (5.8)	21 (8.2)

Laboratory Parameter	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg (N = 234)	HER2-positive BC 6.4, 7.4, 8.0 mg/kg (N = 137)	All Tumor Types 5.4 mg/kg (N = 275)	All Tumor Types 6.4, 7.4, 8.0 mg/kg (N = 258)
≥2 x ULN	4 (1.7)	6 (4.4)	4 (1.5)	13 (5.1)
≥3 x ULN	1 (0.4)	2 (1.5)	1 (0.4)	6 (2.3)
Alkaline Phosphatase (ALP)				
Non-missing n [a]	234	137	275	258
Baseline ≥ULN	85 (36.3)	48 (35.0)	99 (36.0)	89 (34.5)
Maximum Post-Baseline value				
≥1.5 x ULN	90 (38.5)	58 (42.3)	108 (39.3)	110 (42.6)
≥2 x ULN	47 (20.1)	32 (23.4)	55 (20.0)	66 (25.6)
Concurrent TBL Elevation with ALT or AST Elevation [b]				
Non-missing n [a]	232	136	273	257
ALT or AST ≥3 x ULN and TBL >2 x ULN	1 (0.4)	3 (2.2)	1 (0.4)	8 (3.1)
Concurrent TBL Elevation with ALT or AST Elevation and ALP <2 x ULN [b]				
Non-missing n [a]	232	136	273	257
ALT or AST ≥3 x ULN and TBL >2 x ULN and ALP <2 x ULN	1 (0.4)	0	1 (0.4)	0

BC = breast cancer; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; N = total number of subjects in the pool; n = number of subjects with both baseline and post-baseline values; ULN = upper limit of normal
Percentages were calculated using the non-missing n as the denominator.
Safety Update DCO = 01 Aug 2019
Each subject was counted for only the worst case observed post-baseline.
The 4 pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
[a] Non-missing n is the number of subjects with both baseline and post-baseline data.
[b] "Concurrent" is defined as these abnormalities occurred within a 28-day window.
Source: Safety Update Table 1.3.1.2

In the ATT pool, the patients commonly had increased ALT (17.6%), AST (43.6%), or ALP (36%) compared to baseline.

Safety in special populations

Age

Subjects were categorized into age groups of <65 or ≥65 years and <75 and ≥75 years of age at baseline. Since only 11 subjects in the HER2-positive BC 5.4 Pool were ≥75 years of age, no meaningful comparison between subjects <75 and ≥75 years of age could be made.

The following differences of at least 10 pp or a doubling in incidence were noted when comparing subjects <65 years of age (N=173) and subjects ≥65 years of age (N=61):

- A higher proportion of subjects ≥65 years than subjects <65 years had ≥Grade 3 TEAEs: 38/61 (62.3%) vs. 90/173 (52.0%).
- A higher proportion of subjects ≥65 years than subjects <65 years had ≥Grade 3 events of fatigue (8/61 [13.1%] vs. 5/173 [2.9%]), and febrile neutropenia (4/61 [6.6%] vs. 0%).

Compared to data as of the CSR DCOs, overall TEAEs and PTs of anaemia and neutrophil count decreased were no longer notably different (ie, no longer had a >10-pp difference or a doubling between the 2 age subgroups).

Race

The following differences were noted when comparing Asian subjects (N=97) and White subjects (N=119) in the HER2-positive BC 5.4 mg/kg Pool. Since over 90% of subjects in each pool were either Asian or White, differences in other races were not evaluated.

- SAEs occurred more frequently in White vs Asian subjects: 34/119 (28.6%) vs. 18/97 (18.6%).
- TEAEs associated with outcome of death occurred more frequently in White subjects (10/119 [8.4%] vs. 2/97 [2.1%] Asian subjects); this difference was driven primarily by the deaths due to adjudicated drug-related ILD in 5/119 (4.2%) White subjects compared to 1/97 (1.0%) Asian subject.
- TEAEs associated with drug interruption occurred more frequently in Asian subjects than White subjects: 43/119 (44.3%) vs. 37/97 (31.1%).
- A higher proportion of Asian vs White subjects had an event of neutrophil count decrease: 42/97 (43.3%) vs. 28/119 (23.5%) subjects, with values ≥Grade 3 in 27/97 (27.8%) vs. 15/119 (12.6%), and WBC count decrease (grouped term): 30/97 (30.9%) vs. 15/119 (12.6%) subjects, with values ≥Grade 3 in 7/97 (7.2%) vs. 6/119 (5.0%).
- A lower proportion of Asian vs White subjects experienced ≥Grade 3 AEs in the Gastrointestinal disorders SOC (8/97 [8.2%] vs. 23/119 [19.3%]), and the following TEAEs:
    - Nausea: ≥Grade 3 in 2/97 (2.1%) Asian vs. 13/119 (10.9%) White subjects
    - Abdominal pain (grouped term): 11/97 (11.3%) vs. 31/119 (26.1%) subjects, with values ≥Grade 3 in 2 (2.1%) vs. 1 (0.8%)
    - Vomiting: 37/97 (38.1%) vs. 67/119 (56.3%) subjects
    - Diarrhea: 17/97 (17.5%) vs. 50/119 (42.0%) subjects
    - Dyspnea: 6/97 (6.2%) vs. 25/119 (21.0%) subjects, with values ≥Grade 3 in 1/97 (1.0%) vs. 3/119 (2.5%)
    - Fatigue: 37/97 (38.1%) vs. 68/119 (57.1%) subjects

The differences between Asian and White subjects reported as of the CSR DCOs remained in the Safety Update DCO, with only anemia no longer showing a 10-pp difference between races.

Country

The following differences were noted between subjects in Japan (N=51) and subjects in other countries (N=183) in the HER2-positive BC 5.4 mg/kg Pool.

- A higher proportion of subjects in Japan were ≥65 years (18/51 [35.3%] Japan vs. 43/183 [23.5%] non-Japan).
- Subjects in Japan had longer median treatment duration (10.58 months; range: 0.7-37.1) than non-Japan subjects (9.69 months; range: 0.7-26.3), and lower median relative dose intensity (94.3% vs. 97.6%). A higher proportion of subjects in Japan had a treatment duration >12 months (19/51 [37.3%] vs. 50 [27.3%] non-Japan).
- A higher proportion of subjects in Japan experienced adjudicated drug-related ILD (12/51 [23.5%] vs. 20/183 [10.9%]). This difference was driven primarily by events of Grade 1 (4/51 [7.8%]) Japan vs. 2/183 [1.1%] non-Japan) or Grade 2 (8/51 [15.7%] vs. 11/183 [6.0%]). (No event was adjudicated as drug-related ≥Grade 3 ILD in Japan in this pool.)

- A lower proportion of subjects in Japan experienced TEAEs associated with an outcome of death (1/51 [2.0%] Japan vs. 11/183 [6.0%] non-Japan). A similar difference was also seen based on race (Asian vs. White).
- A higher proportion of subjects in Japan discontinued due to TEAEs (13/51 [25.5%] Japan vs. 23/183 [12.6%] non-Japan).
- A higher proportion of subjects in Japan had drug interruption due to TEAEs (27/51 [52.9%] Japan vs. 60/183 [30.2%] non-Japan).

The differences observed between the country subgroups were similar as of the CSR DCOs and the Safety Update DCO.

Geographic Region

The following differences were noted between subjects in Europe (N=68), North America (N=82), and Asia (N=84) in the HER2-positive BC 5.4 mg/kg Pool.

- Median treatment duration in the HER2-positive BC 5.4 mg/kg Pool was lower in the European subgroup (9.25 months vs. 9.74 months in North America and 10.78 months in Asia), primarily due to the timing of study initiation in the various geographical regions.
- Compared with the North America subgroup, the European subgroup had a higher proportion of subjects with asthenia (23/68 [33.8%] vs. 6/82 [7.3%]), dyspnea (18/68 [26.5%] vs. 12/82 [14.6%]), and lymphocyte count decrease (grouped term) (11/68 [16.2%] vs. 5/82 [6.1%]); and a lower proportion of subjects with fatigue (28/68 [41.2%] vs. 59/82 [72.0%]), alopecia (27/68 [39.7%] vs. 41/82 [50.0%]), diarrhea (22 [32.4%] vs. 36 [43.9%]), and cough (11/68 [16.2%] vs. 28/82 [34.1%]).
- The European subgroup had a higher proportion of subjects with a TEAE associated with an outcome of death than either of the 2 other geographical regions (7/68 [10.3%] vs. 4/82 [4.9%] North America, 1/84 [1.2%] Asia). Each of the 7 subjects in the European subgroup had death associated with a different PT (acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, and respiratory failure).
- The European subgroup had a higher proportion of subjects with a serious TEAE than either of the other 2 geographical regions (23/68 [33.8%] vs. 17/82 [20.7%] North America, 14/84 [16.7%] Asia). The most common serious TEAE in all 3 subgroups was ILD (4/68 [5.9%] Europe, 3/82 [3.7%] North America, and 1/84 [1.2%] Asia), with no PT or grouped term accounting for a preponderance of serious TEAEs.
- The European subgroup had a higher proportion of subjects with TEAEs of ILD (11/68 [16.2%]) than the North America subgroup (7/82 [8.5%]).

More patients of ≥65 years of age had a grade ≥3 treatment emergent AEs (38/61 (62.3%) vs. 90/173 (52.0%), especially regarding fatigue (8/61 [13.1%] vs. 5/173 [2.9%]), and febrile neutropenia (4/61 [6.6%] vs. 0%).

Renal function at baseline

In the HER2-positive BC 5.4 mg/kg Pool, 113 subjects entered the study with normal renal function, 91 with mild impairment (39%; creatinine clearance ≥60 and <90 mL/min), 29 with moderate impairment (12%; creatinine clearance ≥30 and <60 mL/min), and 1 with severe impairment (creatinine clearance ≥15 and <30 mL/min). No subject entered the study with end-stage renal disease.

A higher proportion of subjects with moderate renal impairment at baseline had study drug discontinuation for TEAEs and drug-related TEAEs (24.1% overall, 20.7% drug related) than subjects with normal renal function at baseline (13.3% overall, 11.5% drug related) or mild renal impairment (14.3% overall, all drug related).

Furthermore, a higher proportion of subjects with moderate renal impairment at baseline had events of adjudicated drug-related ILD (9/29; 31.0%) compared to subjects with normal renal function (12/113; 10.6%) or mild renal impairment (10/91; 11.0%) at baseline.

Hepatic function at baseline

In the HER2-positive BC 5.4 mg/kg Pool, 132 subjects entered the study with normal hepatic function (56%), 99 with mild impairment (42%), and 1 with moderate impairment. No subject entered the study with severe hepatic impairment. The safety profile was similar between subjects with normal hepatic function and those with mild hepatic impairment, except for ≥Grade 3 TEAEs, which were reported in 59.8% of subjects with normal hepatic function and 46.5% of subjects with mild hepatic impairment.

Table 68: Age by Pooled Groups for Older Subjects (Safety Analysis Set)

	Age 65-74 (Older subjects number / total number) n (%)	Age 75-84 (Older subjects number / total number) n (%)	Age 85+ (Older subjects number / total number) n (%)
HER2+ BC (5.4 mg/kg) (N = 234)	50 (21.4)	8 (3.4)	3 (1.3)
HER2+ BC (6.4, 7.4, and 8.0 mg/kg) (N = 137)	32 (23.4)	3 (2.2)	0
All tumor types (5.4 mg/kg) (N = 275)	66 (24.0)	12 (4.4)	3 (1.1)
All tumor types (6.4, 7.4, and 8.0 mg/kg) (N = 258)	67 (26.0)	12 (4.7)	0

Note: Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
The 4 pooled analysis groups were based on tumor type and first dose received for subjects in Studies J101 and U201.
DCO = 01 Aug 2019
Source: Safety Update EU Analysis Table 1.

Table 69: Summary of Adverse Events by Pooled Group and Age (Safety Analysis Set)

MedDRA Terms	HER2+ BC (5.4 mg/kg) (N=234) n (%)				HER2+ BC (6.4, 7.4, and 8.0 mg/kg) (N=137) n (%)				All Tumor Types (5.4 mg/kg) (N=275) n (%)				All Tumor Types (6.4, 7.4, and 8.0 mg/kg) (N=258) n (%)			
	Age <65 N=173	Age 65-74 N=50	Age 75-84 N=8	Age 85+ N=3	Age <65 N=102	Age 65-74 N=32	Age 75-84 N=3	Age 85+ N=0	Age <65 N=194	Age 65-74 N=66	Age 75-84 N=12	Age 85+ N=3	Age <65 N=179	Age 65-74 N=67	Age 75-84 N=12	Age 85+ N=0
Total AEs	172 (99.4)	50 (100)	8 (100)	3 (100)	102 (100)	32 (100)	3 (100)	0	192 (99.0)	66 (100)	12 (100)	3 (100)	179 (100)	67 (100)	12 (100)	0
Serious AEs - Total	38 (22.0)	13 (26.0)	2 (25.0)	1 (33.3)	22 (21.6)	10 (31.3)	2 (66.7)	0	41 (21.1)	17 (25.8)	2 (16.7)	1 (33.3)	45 (25.1)	21 (31.3)	8 (66.7)	0
Serious AEs - with fatal outcome	9 (5.2)	3 (6.0)	0	0	3 (2.9)	2 (6.3)	1 (33.3)	0	9 (4.6)	3 (4.5)	0	0	9 (5.0)	3 (4.5)	3 (25.0)	0
AE associated with treatment discontinuation	26 (15.0)	10 (20.0)	0	0	36 (35.3)	9 (28.1)	1 (33.3)	0	27 (13.9)	12 (18.2)	0	0	53 (29.6)	16 (23.9)	2 (16.7)	0
Psychiatric disorders	24 (13.9)	4 (8.0)	2 (25.0)	1 (33.3)	25 (24.5)	6 (18.8)	1 (33.3)	0	25 (12.9)	5 (7.6)	2 (16.7)	1 (33.3)	32 (17.9)	11 (16.4)	3 (25.0)	0
Nervous system disorders	83 (48.0)	23 (46.0)	2 (25.0)	1 (33.3)	54 (52.9)	17 (53.1)	2 (66.7)	0	93 (47.9)	33 (50.0)	2 (16.7)	1 (33.3)	88 (49.2)	27 (40.3)	7 (58.3)	0
Accidents and injuries	9 (5.2)	4 (8.0)	2 (25.0)	0	9 (8.8)	2 (6.3)	1 (33.3)	0	12 (6.2)	5 (7.6)	2 (16.7)	0	14 (7.8)	4 (6.0)	1 (8.3)	0
Cardiac disorders	13 (7.5)	6 (12.0)	1 (12.5)	2 (66.7)	11 (10.8)	4 (12.5)	0	0	16 (8.2)	8 (12.1)	1 (8.3)	2 (66.7)	14 (7.8)	6 (9.0)	1 (8.3)	0
Vascular disorders	22 (12.7)	9 (18.0)	3 (37.5)	0	14 (13.7)	3 (9.4)	0	0	23 (11.9)	10 (15.2)	3 (25.0)	0	31 (17.3)	4 (6.0)	1 (8.3)	0
Cerebrovascular disorders	2 (1.2)	0	0	0	3 (2.9)	0	0	0	2 (1.0)	0	0	0	4 (2.2)	0	1 (8.3)	0
Infections and infestations	78 (45.1)	30 (60.0)	5 (62.5)	1 (33.3)	53 (52.0)	15 (46.9)	2 (66.7)	0	83 (42.8)	36 (54.5)	8 (66.7)	1 (33.3)	87 (48.6)	32 (47.8)	8 (66.7)	0
Anticholinergic syndrome	66 (38.2)	20 (40.0)	3 (37.5)	1 (33.3)	48 (47.1)	17 (53.1)	2 (66.7)	0	72 (37.1)	26 (39.4)	3 (25.0)	1 (33.3)	80 (44.7)	29 (43.3)	5 (41.7)	0
Quality of life decreased	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sum of Postural hypotension, Falls, Black outs, Syncope, Dizziness, Ataxia, Fractures	22 (12.7)	8 (16.0)	2 (25.0)	0	13 (12.7)	3 (9.4)	1 (33.3)	0	24 (12.4)	12 (18.2)	2 (16.7)	0	26 (14.5)	6 (9.0)	4 (33.3)	0

AE = adverse event; BC = breast cancer; HER2 = human epidermal growth factor receptor 2
Note: AE summary only included treatment-emergent adverse events.
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
Safety update DCO = 01 Aug 2019
The 4 pooled analysis groups were based on tumor type and first dose received for subjects in studies J101 and U201.
MedDRA terms 'Psychiatric disorders', 'Nervous system disorders', 'Cardiac disorders', 'Vascular disorders', and 'Infections and infestations' are system organ classes. 'Accidents and injuries', 'Cerebrovascular disorders', and 'Anticholinergic syndrome' are standard MedDRA queries.
'Quality of life decreased' is a MedDRA preferred term and is the sum of 'Postural hypotension', 'Falls', 'Black outs', 'Syncope', 'Dizziness', and 'Ataxia'.
Fractures' are searched based on preferred terms 'Orthostatic hypotension', 'Fall', 'Loss of consciousness', 'Syncope', 'Dizziness', 'Ataxia', and 'Fracture'.
Source: Safety Update EU Analysis Table 2.

The provided tables above show that in the HER2-positive BC 5.4 mg/kg Pool, the distribution of patients in each age subgroup were as follows: <65 years, N=173; 65 to 74 years, N=50; 75 to 84 years, N=8; and ≥85 years, N=3. This reflects the patient population but limits any firm conclusions for the age group patients who are more than 75 years of age due to small numbers.

It is noted that there are more serious AEs (26% vs 22%), AEs associated with discontinuations (20% vs 15%), cardiac disorders (12% vs 7.5%) and infections (60% vs 45.1%) in the 65-74 years of age group compared to patients <65 years.

Immunological events

Antidrug Antibody-related Adverse Events study U201

Thirteen (5.1%) of 253 subjects had a positive ADA sample at baseline. Of these 13 subjects, 5 (2.0%) subjects had positive ADA samples while on treatment. Of these 5 subjects: 3 subjects were positive both at baseline and post-baseline; 1 subject who tested ADA-negative at baseline was ADA-positive post-baseline; and 1 subject with no detectable ADAs at baseline was positive post-baseline. One subject (No. 81090001), who was ADA-positive at baseline experienced a TEAE of Grade 2 IRR at Cycle 1 Day 1. In the ADA evaluations, no subject shifted from ADA negative at baseline to ADA positive after baseline. One subject who received trastuzumab deruxtecan and itraconazole shifted from ADA-positive at baseline to ADA-negative after baseline.

Information on ADAs are collected in the ongoing phase 3 studies with trastuzumab deruxtecan, see Table below.

Table 70: Immunogenicity Sampling Strategy for Trastuzumab Deruxtecan Clinical Development Program

	ADA and NAb Sampling Points						
Study	C1D1 BI	C1D8	C2D1 BI	C4D1 BI	Later Cycles	EOT	Follow-up Visits
DS8201-A-J101	X	X	X	X	C6D1 BI (every 2 cycles)	X	D40 and as needed
DS8201-A-J102	X	X	X	X	C6D1 BI (every 2 cycles)	X	D40 and as needed
DS8201-A-A103	X	X	X	X	C6D1 BI (every 2 cycles)	X	D40 and as needed
DS8201-A-A104	X		X	X	C6D1 BI (every 2 cycles)	X	D40 and as needed
DS8201-A-U201	X		X	X	C8D1 BI (every 4 cycles)		D40 and as needed
DS8201-A-U301	X		X	X	C8D1 BI (every 4 cycles)	X	D40 and as needed
DS8201-A-U302	X		X	X	C8D1 BI (every 4 cycles)	X	D40 and as needed
DS8201-A-U303	X		X	X	C8D1 BI (every 4 cycles)		D40 and as needed

ADA = anti-drug antibody; BI = before infusion; C = cycle; D = day; EOT = end of treatment; NAb = neutralizing antibody.

Safety related to drug-drug interactions and other interactions

The PK results of the DDI study DS8201 A A104 are summarized in previous section, please see clinical pharmacology for details. The conclusions of this study were as follows:

• Concomitant use of trastuzumab deruxtecan with ritonavir (dual inhibitor of OATP1B/CYP3A) or itraconazole (strong inhibitor of CYP3A) resulted in increases of 22% and 18% in AUC17d of MAAA-1181a, respectively.

• Concomitant use of ritonavir and itraconazole did not affect the exposure of trastuzumab deruxtecan.

• Trastuzumab deruxtecan in combination with ritonavir or itraconazole showed a similar safety profile as observed in other trastuzumab deruxtecan studies.

Discontinuation due to adverse events

Table 71: Treatment-emergent Adverse Events Associated with Study Drug Discontinuation Reported in Any Subject in the HER2-positive Breast Cancer 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg		All Tumor Types 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Any TEAE Associated with Study Drug Discontinuation	22 (9.4)	36 (15.4)	22 (8.0)	39 (14.2)
ILD [a]	13 (5.6)	21 (9.0) [b]	13 (4.7)	22 (8.0)
Alveolitis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Cardiac failure congestive	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Dyspnoea	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Neuropathy peripheral	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Osteonecrosis of jaw	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Performance status decreased	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Pleural effusion	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Pneumonia	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Thrombocytopenia	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Troponin increased	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Platelet count decrease [c]	1 (0.4)	2 (0.9)	1 (0.4)	2 (0.9)
Acute hepatitis B	0	1 (0.4)	0	1 (0.4)

Table 72: Treatment-emergent Adverse Events Associated with Study Drug Discontinuation Reported in Any Subject in the HER2-positive Breast Cancer 5.4 mg/kg Pool, by Preferred Term (Safety Analysis Set) (Continued)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg		All Tumor Types 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Cough	0	1 (0.4)	0	1 (0.4)
Diarrhoea	0	1 (0.4)	0	1 (0.4)
Gamma-glutamyltransferase increased	0	1 (0.4)	0	1 (0.4)
Hypoxia	0	1 (0.4)	0	1 (0.4)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities, v20.1; N = total number of subjects in the pool; PT = preferred term; TEAE = treatment-emergent adverse event

Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.

CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019

The 4 pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.

[a] ILD (grouped term) includes PTs of interstitial lung disease, pneumonitis, organising pneumonia, and acute interstitial pneumonitis

[b] 14/234 (6.0%) subjects from the HER2-positive BC 5.4 mg/kg Pool discontinued due to the PT of pneumonitis, 6/234 (2.6%) due to the PT of ILD, and 1/234 (0.4%) due to the PT of organising pneumonia

[c] Platelet count decrease (grouped term) includes PTs of platelet count decreased and thrombocytopenia

Sources: ISS Tables 1.2.1.5, 1.2.1.5b, 1.2.2.9; Safety Update Tables 1.2.1.5, 1.2.1.5b, 1.2.2.9

Dose reductions

Table 73: Treatment-emergent Adverse Events Associated with Dose Reduction Reported in at Least 1% of Subjects in the HER2-positive Breast Cancer 5.4 mg/kg Pool, by Pool (Safety Analysis Set)

MedDRA Preferred Term or Grouped Term	Number (%) of Subjects in Pool			
	HER2-positive BC 5.4 mg/kg		All Tumor Types 5.4 mg/kg	
	CSR DCO (N=234)	Safety Update DCO (N=234)	CSR DCO (N=275)	Safety Update DCO (N=275)
Subjects with Any TEAE Associated with Dose Reduction	42 (17.9)	48 (20.5)	50 (18.2)	56 (20.4)
Fatigue	7 (3.0)	8 (3.4)	8 (2.9)	9 (3.3)
Nausea	7 (3.0)	8 (3.4)	8 (2.9)	9 (3.3)
Neutrophil count decrease [a]	5 (2.1)	8 (3.4)	6 (2.2)	9 (3.3)
Blood bilirubin increased	4 (1.7)	4 (1.7)	4 (1.5)	4 (1.5)
Vomiting	3 (1.3)	3 (1.3)	3 (1.1)	3 (1.1)
Weight decreased	3 (1.3)	3 (1.3)	4 (1.5)	4 (1.5)

BC = breast cancer; CSR = clinical study report; DCO = data cut-off; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities, v20.1; N = total number of subjects in the pool; PT = preferred term; TEAE = treatment-emergent adverse event
Percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator.
CSR DCO = 01 Feb 2019 for Study J101 and 21 Mar 2019 for Study U201; Safety Update DCO = 01 Aug 2019
The 2 pooled analysis groups were based on tumor type and first dose received for subjects in Study J101 and Study U201.
[a] Neutrophil count decrease (grouped term) includes PTs of neutrophil count decreased and neutropenia.

Post marketing experience

Trastuzumab deruxtecan was approved in the USA on 20 Dec 2019 and was first made available in the USA on 31 Dec 2019. Trastuzumab deruxtecan was also approved in Japan on 25 Mar 2020, but no post-marketing experience in Japan is available. The post marketing data are summarized below.

Since the approval of trastuzumab deruxtecan in the USA, the estimated cumulative post-marketing patient exposure through 13 Mar 2020 was 94 patient-years ([redacted]). A total of 111 AEs was reported in 50 patients during the post-marketing period from 20 Dec 2019 through 13 Mar 2020, including 16 serious events in 15 patients. The majority of events were non-serious (95 events in 38 patients). Gastrointestinal disorders were the MedDRA SOC with the highest proportion of AEs (37 of the 111 total events), with the majority (35/37) of these events being non-serious.

Sixteen serious AEs were reported in 15 patients 4 of these were reported to have a fatal outcome (neoplasm malignant, respiratory failure, death and malaise). 1 was reported as not recovered (deafness), 1 was reported as recovered (pneumonitis), and 10 had an unknown outcome (ILD, aphasia, ascites, general physical health deterioration, generalized tonic-clonic seizure, hospitalisation, hyponatraemia, infusion related reaction, nausea, neutropenia). There was 1 report of an SAE of neutropenia ([redacted]), and the outcome is yet unknown but additional follow up information is expected.

Death due to any cause was reported in 4 patients, with PTs of death (1), respiratory failure (1), neoplasm malignant (1) and malaise (1). All were medically confirmed reports and were deemed not-related to treatment.

Cumulatively, since the approval of Enhertu in December 2019, 3 patients treated in the post marketing setting were reported to have had a potential ILD AE: PTs were ILD (1 with unknown

outcome), pneumonitis (1 recovered), and respiratory failure (1 with a fatal outcome). All events were serious events. Two of the 3 AEs were medically confirmed reports and 1 was a consumer report.

2.6.1. Discussion on clinical safety

The safety populations of interest are patients with all tumor types (ATT pool, n=275) and the breast cancer patients (n=234) treated with the proposed dose of 5.4 mg/kg. The median duration of exposure to trastuzumab deruxtecan for the ATT pool was almost 10 months for both safety pools at the Update safety DCO of 01 Aug 2019. 66% of the patients in the ATT pool were exposed for more than 6 months, while 28% were exposed for more than 12 months. Hence, the median exposure is similar in both safety pools and considered acceptable for the applied CMA. Moreover, safety data from a phase 3 confirmatory study is expected as part of the special obligations for a CMA.

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study U201 at safety update DCO. In the HER2-positive breast cancer pool, gastrointestinal events were the most frequent AEs for trastuzumab deruxtecan, e.g. nausea (79.9%) and vomiting (48.7%). Other frequently reported GI events were constipation (35.9%) and diarrhea (30.8%). Haematological toxicity (anemia: 33.8%, neutrophil count decreased: 32.5% and platelet count decrease: 23.1%) was commonly observed. Although ≥grade 3 neutrophil count decreased was common (18.8% of patients), febrile neutropenia was reported for 1.7% patients. Both GI and haematological events are known side effects of for cytotoxic drugs such as topoisomerase inhibitors.

Treatment-related AEs or adverse drug reactions (ADRs) were similar to the AEs observed, both regarding all-grade events and grade 3-4 events. This is interpreted as most of these were due to the chemotherapy-like toxicity, which is also commonly observed with other ADCs. Although heavily pre-treated, the study population were of good performance status, had with relatively few severe symptoms of the underlying advanced breast cancer disease, and tolerated the treatment with trastuzumab deruxtecan with an acceptable level of toxicity.

Adverse events of special interest included ILD/pneumonitis, left ventricular dysfunction, QT prolongation, and infusion-related reactions. ILD/pneumonitis is an important identified risk with trastuzumab deruxtecan and the Applicant payed special attention to this AESI from the start. In the HER2-positive breast cancer pool, 18.1% of the patients had an ILD event while more than grade 3 events were observed in 3.7% and fatal outcome was observed in 6 patients (2.6%). The incidence of treatment-related ILD was lower in the 5.4 mg/kg Pool (13.7%) vs the 6.4 mg/kg pool 34/137 (24.8%), so there seems to be a dose-risk relationship favouring the lower proposed dose of 5.4 mg/kg. The median time to onset of ILD was 134.0 days (range: 35-338) and the median duration of the first event of ILD was 31.5 days (range: 3-261), so the timing of the event cannot be estimated from these data. At the updated DCO, almost half of the patients had recovered and only 1 patient with sequalae. The Applicant has analysed potential risk factors for ILD across all tumor types and doses among 645 treated patients and found that patients from Japan had a higher incidence of treatment-related ILD (any grade) than patients from outside Japan did. Moreover, patients with ≥10 prior regimens experienced a higher incidence than those who received <10 prior regimens. The chosen factors which were analysed are deemed clinically relevant, but the presented analysis does not find any clinically relevant risk factors that can be used for the prescriber, since the applied indication is not for patients treated with more than 10 prior regimens and the increased number of events in Japanese were mostly of low grade; hence, no regulatory consequences are warranted for this finding. The Applicant informs that they plan to continue investigating trastuzumab deruxtecan related ILD/pneumonitis in ongoing and future clinical studies and they will submit the results of these analyses post-authorization in the Periodic benefit risk evaluation reports. The plans for further investigation of ILD/pneumonitis risk factors and prognostic factors are endorsed. A precautionary

statement is included in section 4.4 of the SmPC, including a warning that patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis. Furthermore, measures are included in the RMP and educational material (see RMP). Overall, the risk of treatment-related ILD is the most serious toxicity of trastuzumab deruxtecan and the information about this in the SmPC, including the warning section, is acceptable at this point in time.

There were few events of cardiac failure which were not associated with a reduction in LVEF. The limited number of events is reassuring; however, as stated by the Applicant patients with LVEF less than 50% were excluded from the study. The Applicant added left ventricular dysfunction as important potential risk in the RMP and additional data will become available through PSURs and from the ongoing phase 3 trials. Assessment of causality is hampered by the lack of a control group, therefore results from the controlled settings will provide further information on causality. A conservative approach is needed in the absence of a control group and also given the known class-effect. The additional information in section 4.4 is acceptable. The Applicant provided additional information clarifying that no grade Grade 2 LVEF decrease (Resting LVEF 50% to 40%; 10% to 19% decrease from baseline) occurred, which explains why no dose modification was performed. The Applicant has agreed to include LVEF decrease in the ADR Table in section 4.8 of the SmPC, and to include left ventricular dysfunction as an important identified risk in the RMP.

6% of the patients had an AE of QT prolonged, and only one grade 3 event was symptomatic. 3.4% had QT interval prolongation on ECG of more than 60 msec. Overall, the incidence of QT prolongation is acceptable and manageable with trastuzumab deruxtecan.

After review, six patients (2.6%) had an infusion-related reaction (IRR), and all events have resolved with sequelae in one patient with 2 IRR events. No discontinuations or dose-reductions were necessary, so this event is manageable.

Overall, there were 12 **deaths** from any treatment emergent adverse event (4.4%), 3 patients (1.1%) died from other causes, and 9 patients (3.3%) died due to unknown causes in the ATT pool (n=275). Of the 39 deaths (16.7%) in the HER2-positive BC 5.4 mg/kg pool, the most frequent cause of death was disease progression (n=25, 10.7%). Four deaths were clarified to be treatment-related ILD.

In the ATT pool, 22.2% had **serious adverse events** (SAEs), most commonly pertaining to pneumonia (2.5%), pneumonitis (2.2%), respiratory failure, and cellulitis (1.8% each). In total, 23 patients (8.4%) had an SAE related to the respiratory system; however, the rate of SAEs with trastuzumab deruxtecan is acceptable considering the heavily treated study population as well as the targeted setting and patient population.

In the ATT pool, the patients commonly had increased ALT (17.6%), AST (43.6%), or ALP (36%) compared to baseline. However, these were rarely increased to very high levels, and no cases of potential Hy's Law were determined to be causally associated with trastuzumab deruxtecan. Overall, hepatotoxicity was within an acceptable level for most patients and is deemed manageable based on available data.

More patients of ≥65 years of age had a grade ≥3 treatment emergent AEs (38/61 (62.3%) vs. 90/173 (52.0%), especially regarding fatigue (8/61 [13.1%] vs. 5/173 [2.9%]), and febrile neutropenia (4/61 [6.6%] vs. 0%). This is often observed with advanced cancer patients treated with chemotherapy, and is within an acceptable level.

Increased toxicity in white vs Asian patients were observed regarding SAEs (28.6% vs 18.6%), grade 5 AEs (8.4% vs 2.1%), AEs leading to dose interruption (44.3% vs 31.1%), and neutrophil count decrease (43.3% vs 23.5%). Moreover, more white patients had GI toxicity (19.3% vs 8.2%). These differences are also reflected in the safety by country and geographic region shown above. However, even though the data indicate increased toxicity in white patients and those from the European region,

this may have been biased by differences in the reporting of adverse events between the regions among other things, so this is overall not considered problematic. It seems that the awareness of possible ILD/pneumonitis was increased in Japan, leading to more low-grade cases, which may then not progress into high grade or even fatal events. Hence, comprehensive information about this risk with trastuzumab deruxtecan is highly endorsed. The increased toxicity in elderly patients, especially regarding fatigue has also previously been shown in cancer trials, and data are adequately reflected in the SmPC, section 4.8. The increased toxicity in the patients aged 65 years or older is adequately reflected in the SmPC.

The Applicant stated that 1 subject with moderate hepatic impairment was included in study U201 and two additional patients were included in study U301 and U303; however, it is unknown whether these patients were treated with trastuzumab deruxtecan. The Applicant plans to obtain data from 10 subjects with moderate hepatic impairment treated with trastuzumab deruxtecan from several ongoing clinical studies for an overall assessment of the effect of moderate hepatic impairment on the PK and safety of trastuzumab deruxtecan. This is considered acceptable.

It is agreed that at this time, ADA formation does not seem to cause safety problems, not even serious infusion-related reactions. However, this may change with increased use of the drug and overall increased exposure, and the Applicant stated that information on ADAs are collected in the ongoing phase 3 studies with trastuzumab deruxtecan. This is acceptable.

Drug-drug interactions do not seem to have clinically meaningful effect on safety.

The overall **discontinuation rate** due to AEs in the ATT pool was 14.2%, and of these, 12.7% of the patients discontinued due to treatment-related AEs. This is similar to the discontinuation rate due to AEs in the breast cancer safety pool at safety update DCO (16.2%). Most common AEs leading to discontinuation were ILD/pneumonitis in both the BC (9%) and the ATT pool (8%), which reflects the safety profile of trastuzumab deruxtecan. Otherwise, only 1-2 patients discontinued per PT, which means that the known hematological toxicity rarely led to discontinuations, which is reassuring. Overall, the rate of discontinuations is acceptable for the proposed indication and targeted patient population. With currently available data, the AEs of ILD/pneumonitis is by far the greatest risk in the treatment with trastuzumab deruxtecan.

Dose reductions were common and the rates were similar in both the BC and the ATT pool at safety update DCO (~20%). Most frequent AEs leading to dose reductions were fatigue, nausea, and decreased neutrophil count, which is consistent with the safety profile of trastuzumab deruxtecan, since ILD/pneumonitis should lead to discontinuation of the drug. The overall rate of dose reductions is considered acceptable considering the heavily pre-treated study population and the targeted setting and patient population.

Post marketing data from the US is summarized above, and do not give rise to any new safety concerns with trastuzumab deruxtecan. The SAEs are considered to reflect the targeted patient population and disease. Moreover, the serious and potentially fatal ILD/pneumonitis cases induced are of focus for the Applicant, and relevant data about this known risk is adequately described in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional safety data needed in the context of a conditional MA

Submission of additional safety data from the ongoing randomised phase 3 U301 study, which is recommended as the confirmatory study for the CMA.

2.6.2. Conclusions on the clinical safety

Although heavily pre-treated, the study population were of good performance status, with relatively few severe symptoms of the underlying advanced breast cancer disease, and tolerated the treatment with trastuzumab deruxtecan with an acceptable level of toxicity. Hence, with currently available safety data, ILD/pneumonitis is by far the greatest risk in the treatment with trastuzumab deruxtecan. Moreover, safety data from the phase 3 confirmatory study as well as an updated analyses of risk factors and risk mitigation strategies for ILD/pneumonitis should be provided post-authorisation. Overall, the safety profile can be considered acceptable in the target population with limited treatment options and no major objections on safety are identified precluding marketing authorisation.

The CHMP considers the following measure (SOB) necessary to address the missing safety data in the context of a conditional MA:

Submission of interim efficacy and safety data from the ongoing randomised phase 3 U301 study, which is requested as a specific obligation to the CMA.

2.7. Risk Management Plan

Safety concerns

Table - Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Interstitial lung disease/Pneumonitis • Left ventricular dysfunction
Important potential risks	• Embryo-foetal toxicity • Product confusion-related medication errors
Missing information	• Use in patients with moderate or severe hepatic impairment • Long-term safety

Pharmacovigilance plan

Table - Ongoing and Planned Additional Pharmacovigilance Activities

Study: Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 - Required additional pharmacovigilance activities				
Prescriber Survey planned	EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis	ILD	Final Report	Q3 2023
Phase 2 or 3 studies planned	Collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies	Use in patients with moderate or severe hepatic impairment	Final report (for 10 subjects)	Q4 2023

EU = European Union; ILD = interstitial lung disease

Risk minimisation measures

Table 74 - Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Interstitial Lung Disease/Pneumonitis	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Patient Information Leaflet Section 4 Recommendations for ILD/pneumonitis monitoring and detecting early signs and symptoms of ILD/pneumonitis are included in SmPC Section 4.4. Dose modification guidance and recommendation for corticosteroid treatment for managing the risk of ILD/pneumonitis are included in SmPC Section 4.2. Additional risk minimisation activities: HCP Guide and Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: Prescriber survey
Left ventricular dysfunction	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Patient Information Leaflet Section 2 Recommendations for monitoring of left ventricular dysfunction are included in SmPC Section 4.4. Dose modification guidance for managing the risk of left ventricular dysfunction is included in SmPC Section 4.2. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: None
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 Patient Information Leaflet Section 2 Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6. Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Product confusion-related medication error	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 6.6 Pack and vials: specific livery for Enhertu on the packaging and specific colors for vial cap and bottle to distinguish from other trastuzumab containing products Additional risk minimisation activities: HCP Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Review of data from ongoing clinical studies Additional pharmacovigilance activities: Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

HCP = healthcare professional; ILD = interstitial lung disease; PK = pharmacokinetic; SmPC = Summary of Product Characteristics; PIL=Patient Information Leaflet

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR

cycle with the international birth date (IBD). The IBD is 20.12.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that trastuzumab deruxtecan has not been previously authorised in a medicinal product in the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Enhertu (trastuzumab deruxtecan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for trastuzumab deruxtecan is monotherapy 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.

3.1.2. Available therapies and unmet medical need

Metastatic HER2-positive breast cancer remains an uncurable disease. Although treatment with anti-HER2-based regimens has improved the disease outcomes for patients with unresectable locally-advanced or metastatic HER2-positive breast cancer, the disease invariably progresses.

There is no clearly defined standard of care (SOC) for patients with metastatic HER2-positive breast cancer after two or more anti-HER2-based regimens. Preferred regimens include continuation of HER2-targeted therapy with trastuzumab or lapatinib in combination with cytotoxic chemotherapy, such as capecitabine. However, efficacy outcomes from current treatments approved in the EU for previously treated patients with two or more anti-HER2-based regimens for HER2-positive metastatic breast

cancer are response rates in the range from 9% to 41%. Results from recent clinical studies (Rugo et al., 2019; Murthy et al., 2019) evaluating combination therapies in patients with HER2-positive metastatic breast cancer, who had received 2 or more prior anti-HER2-based regimens, underline the continued need for efficacy improvement for this patient population as the median PFS was below 6 months and median OS was reported to be 17.4 to 19.8 months. Therefore, there remains a significant unmet medical need for HER2+ metastatic breast cancer patients who have progressed despite receiving current standard of care, including 2 prior anti-HER2 agents.

3.1.3. Main clinical studies

The pivotal study U201 is a global, phase 2, open-label, multicentre, single-arm trial conducted at 72 study sites, which was fully recruited in approximately 1 year, and the median follow-up was 12.2 months at the time of the updated data cut-off. A third of the patients were enrolled in the geographic regions of either Asia, US or Europe, respectively; hence, predominantly from populations that are similar to the European populations. The patient population was heavily pretreated with a median number of 5 prior cancer regimens including at least 2 anti-HER2 based regimens at baseline, which is considered representative of the target population. The 184 patients with HER2-positive MBC treated with trastuzumab deruxtecan at the proposed dose are of main focus in this application.

3.2. Favourable effects

The primary endpoint of ORR by ICR was 60.3% at the initial data cut and this result was maintained at the updated DCO with 12.2 months of follow-up time i.e. 60.9% (95%CI: 53.4; 68). Update DCO show that 6% had a CR and 54.9% had a PR, while 36.4% of the patients had SD as best overall response.

The most recent update (DCO 8 June 2020) showed an ORR by IRC of 61.4% (95%CI: 54.0; 68.5).

The secondary endpoint of duration of response by IRC at update DCO show a median of 14.8 months (95%CI: 13.8, 16.9), while further updated DOR was 20.8 months (95%CI: 15; NE).

The latest updated PFS was 19.4 months (95%CI: 14.1; NE).

Updated OS data based on a DCO of 08 Jun 2020 with a median duration of follow-up of 20.5 months showed a median OS of 24.6 months (95%CI: 23.1, NE).

The results of the first-in-human study J101 (n=51) support the findings of the pivotal trial, ORR being 51.0% (95%CI: 36.6, 65.2) and median DoR of 12.7 months (95% CI: 6.7, NE) at time of primary data cut-off.

3.3. Uncertainties and limitations about favourable effects

The magnitude of response is considered clinically relevant for this heavily pre-treated study population, who have no standard of care. Although sensitivity analyses of ORR are consistent with the result of the primary endpoint, no comparative data is available at this point in time. This hampers the interpretability of PFS especially. For the same reason, subgroup analyses are also difficult to interpret (the ongoing Ph III study is expected to address these).

The number of patients with inactive brain metastases at baseline is limited (24/184). OS data were initially immature with only 10% deaths, but the Applicant has provided updated OS data up of 20.5 months and was recommended to provide the final OS data post-authorisation after the Study U201 closes. The interim efficacy data from the ongoing Phase 3 study U301 which are being requested as a

specific obligation to the marketing authorisation (see "Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation") are expected to address the above uncertainties.

3.4. Unfavourable effects

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study U201 at safety update DCO and most of these were treatment-related. Gastrointestinal events were the most frequent AEs for trastuzumab deruxtecan, with incidences of 79.9% for nausea and 48.7% for vomiting based on the pooled data at the safety update DCO. Other frequently reported gastrointestinal events were constipation (35.9%) and diarrhoea (30.8%). These occurred early upon treatment (nausea and vomiting within first week), were mostly grade 1 and 2 and resolved without dose modifications.

Next to GI events, hematological events (anemia: 33.8%, neutrophil count decreased: 32.5% and platelet count decrease: 23.1%) were commonly observed AEs. Most events occurred within the first 3 months and were grade 1 or 2. The highest frequency of ≥grade 3 events was neutrophil count decreased (18.8% of patients). Febrile neutropenia was reported for 1.7% patients. In general, haematological events were managed with dose interruptions and dose reductions or supportive management. Both GI and haematological events are known side effects of for cytotoxic drugs such as topoisomerase inhibitors.

≥Grade 3 events were reported in 54.7% of patients, predominantly neutrophil count decrease (18.8%) and anaemia (9.0%).

Adverse events of special interest of clinical interest included ILD/pneumonitis, LVEF decrease, QT prolongation and IRR in the HER2-positive breast cancer pool, which were selected based on class effects. A total of 15% of the patients had an ILD/pneumonitis event and fatal events were observed in 2.6%. In total, 16.9% of patients met the laboratory criteria for grade 2 LVEF decrease, and none were grade 3 or higher.

Overall, **serious adverse events** occurred in 23.2% of patients and there were 16.7% deaths during follow-up. Most frequently occurring SAEs were pneumonitis (2.6%), pneumonia, and respiratory failure (2.1% each). TEAEs were considered the primary cause of death in 3.0% of patients.

Treatment discontinuation due to TEAEs occurred in 16.2% of patients in the BC pool and the most common were ILD/pneumonitis in both the BC (9%) and the ATT pool (8%).

There were more ≥grade 3 events in patients ≥65 years, especially fatigue and febrile neutropenia.

3.5. Uncertainties and limitations about unfavourable effects

The median exposure in the HER2-positive BC 5.4 mg/kg Pool was 9.82 months (range: 0.7-37.1) for the HER2+MBC pool (n=234) (Update safety DCO 01 Aug 2019) with 69/234 (29.5%) being treated for > 12 months. Therefore, long-term safety data is limited. Causality assessment of unfavourable events is impaired by the single arm design of the studies.

The knowledge about ILD/pneumonitis is still limited regarding the recovery rate and clinically relevant risk factors. Moreover, patients with a history of noninfectious ILD/pneumonitis that required steroids were excluded from the trial due to a potential increased risk of ILD. Proposed mitigating strategies for ILD (section 4.2 and 4.4 SmPC, DHPC) appear adequate to reduce the risk of severe/fatal ILD for these patients.

No safety data are available in patients with severe renal impairment and safety data in patients >75 years is limited.

No safety data are available in patients with moderate/severe hepatic impairment whereas the safety profile may be different as the drug is primarily hepatically eliminated. Grade 1 and Grade 2 elevations in ALT and AST were frequently reported. Although no severe hepatic toxicities were observed, the impact may be more relevant in patients with moderate/severe hepatic impairment. Therefore, a PK and safety study in patients with moderate hepatic impairment is required (see RMP).

Long-term safety data is limited and a safety update with a focus on the AESI of ILD is expected with the efficacy update. In approximately 2 years' time, the interim PFS results will be available from the ongoing phase 3 randomised controlled study with trastuzumab deruxtecan versus investigator's choice ([redacted]), and it is considered that the benefits shown now could outweigh the risks of conditionally approving trastuzumab deruxtecan before comparative confirmatory data are available.

To address the limitations around safety data, interim safety data from the ongoing Phase 3 study [redacted] are being requested as a specific obligation to the marketing authorisation (see "Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation").

3.6. Effects Table

Table 75. Updated effects Table for Trastuzumab deruxtecan for HER2-positive breast cancer Study U201 (data cut-off: 08 June 2020).

Effect	Short Description	Unit	Treatment Trastuzumab deruxtecan N=184	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
ORR by IRC	Confirmed response rate	% 95%CI	61.4 54.0; 68.5	NA	N=169 with measurable disease at baseline	
DOR by IRC	Duration of response	Months 95%CI	20.8 15.0; NE	NA	N=112 with CR/PR	
PFS	Progression-free survival	Months 95%CI	19.4 14.1; NE	NA	38% PFS events	
OS	Overall survival	Months 95%CI	24.6 23.1; NE	NA	35.3% events	
Unfavourable Effects (HER2+ BC pool, n=184)						
Any AEs		%	99.6			
Grade ≥3 AEs		%	54.7			
SAEs		%	23.1			
AEs leading to discontinuation		%	16.2			

Effect	Short Description	Unit	Treatment Trastuzumab deruxtecan N=184	Control	Uncertainties/ Strength of evidence	Ref
AEs leading to death		%	5.1			

Abbreviations: ORR – Overall Response Rate, IRC – Independent Review Committee, AE – Averse Event, SAE – Serious Adverse Event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Trastuzumab deruxtecan monotherapy was studied in a single-arm phase 2 study with 184 advanced or metastatic breast cancer patients, who had received at least 2 lines of therapy. The study population is in general representative of the target population and the limited number of patients with brain metastases does not raise a major issue on efficacy.

As the basis for this application is a single-arm trial, several aspects need explicit consideration. In this respect, the natural course of the target disease as well as the target population are considered adequately defined. Updated efficacy results for trastuzumab deruxtecan based on a median follow-up of 20.5 months, confirm the initial analysis. The results showed a significant antitumor activity (ORR by IRC of 61.4%) that seems better than reported for currently used anti-HER2 based regimens in this setting with no clear SOC. Responses appear durable (updated median DoR: 20.8 months) and updated median PFS was 19.4 months. The obtained ORR and DoR should be compared to the fact, that there is no clear standard of care in the proposed setting, and efficacy of the available treatments used show limited efficacy with a reported median DoR of 6.0 -8.5 months and median PFS of 4.9 – 7.8 months (the NALA, SOPHIA, and HER2CLIMB studies). The substantial longer DoR together with the high ORR support a major therapeutic advantage despite the inherent limitations related to cross-study comparisons. The difference is as such that it is considered to overcome the remaining uncertainties related to indirect comparisons and high censoring rate.

Censoring rates remained high at the time of DCO 08 Jun 2020 with a median follow-up of 20.5 months, for DoR: 65.2% and for PFS: 62.0%. In order to reason out what the likely DoR for this study would be, sensitivity analyses were requested with clinical progression and investigator determined PD counted as events rather than censored, and the median DoR for the EMA DCO is estimated to be 14.6 months (95%CI 10.3, 18.2). Given that it is reasonable to presume that these patients may have showed signs of progression, an event based on investigator or ICR progression could be a better measure of efficacy, so this may be a more realistic estimate than the 20 months that was first estimated in the EMA DCO. However, a median DoR of 14 months in combination with an ORR of around 60% is just as well considered a major therapeutic advantage (MTA) over existing therapies in the target population.

As the initial results are to some extent confirmed by an update of efficacy data and various sensitivity analyses, the ORR and DoR are likely to translate into a clinically meaningful benefit for a population with median OS of 3 years. The clinical benefit in terms of survival and efficacy in patients with brain metastasis need to be confirmed by the ongoing phase III U301 trial proposed as specific obligations in case of a CMA.

Efficacy results need to be weighed against the safety profile, which is mainly characterised by gastrointestinal and haematological events, which were generally manageable and infrequently led to treatment discontinuation. Although the single arm trial design hampers a causality assessment of adverse events, the safety profile of trastuzumab deruxtecan largely resembles that of other trastuzumab-based regimens combined with chemotherapy. Grade 2 LVEF was observed and because decrease in LVEF is a class effect, left ventricular dysfunction was added as an important identified risk for trastuzumab deruxtecan in the RMP.

The major safety concern of trastuzumab deruxtecan is the risk of ILD/pneumonitis (13.7%), which frequently led to drug discontinuation and with fatal events being reported (2.6%). The incidence is higher than reported for other trastuzumab-based products and may be related both to the antibody and the released drug; however, when early recognised, low grade ILD/pneumonitis is manageable with dose modification and corticosteroid treatment in line with clinical treatment guidelines (see section 4.2 and 4.4 of the SmPC), more safety data will be available from the ongoing studies with trastuzumab deruxtecan, to better characterize the safety profile of trastuzumab deruxtecan within a reasonable timeframe. Further safety data such as long-term safety, a PK and safety study in patients with moderate hepatic impairment will be provided post authorisation (see RMP and Annex II).

To contextualize, the Applicant is seeking an indication in a setting, where there is no standard of care available and currently used treatment regimens show limited efficacy. Hence, there is a high unmet medical need for further treatment options for the targeted patient population in the proposed setting, and trastuzumab deruxtecan is considered to address this unmet need.

3.7.2. Balance of benefits and risks

The reported ORR and duration of response are considered promising in the target population that have already received two anti-HER2 based regimens and who have no clear SOC. The effect size is as such that it is sufficient to overcome the uncertainties related to the lack of an active comparator arm and thus the indirect comparisons. Overall, the results indicate a likely clinical benefit of trastuzumab deruxtecan in terms of time dependent endpoints.

The adverse events are mostly mild, reversible upon management and/or dose modifications and comparable to what is known from trastuzumab-based regimens combined with chemotherapy. Further PK and safety data in patients with moderate hepatic impairment will be obtained post-approval.

The benefit/risk balance is currently positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. Breast cancer is the most commonly diagnosed female cancer worldwide and the leading cause of cancer death in women.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed in Section 3.7.2. .
- It is likely that the applicant will be able to provide comprehensive data.

  The ongoing Phase 3 Study U301 is designed to demonstrate the efficacy and safety of trastuzumab deruxtecan vs Investigator's choice in patients with HER2-positive MBC previously treated with TDM1 (i.e. 3rd line treatment), n=600 planned, PFS projected Q1 2022. A total of 411 out of 600 subjects planned are enrolled as of 08 Jun 2020 in Study U301. Previously, 329/600 subjects planned were enrolled as of 13 Mar 2020, therefore 82 new patients were enrolled within a period of about 3 months. A total of 189 patients are needed to meet the planned 600 subjects. Therefore, the planning for the last subject to be enrolled (Feb 2021) is considered reasonable. It is expected that granting of a CMA will not impact the enrolment of the phase 3 study U301 and with an estimated DCO of Q3 2021, results are expected to be available in a reasonable time frame. Hence, Study U301 serves as a confirmatory study, with a study population similar to the currently evaluated study population from the pivotal Study U201.
- Unmet medical needs will be addressed, as

  there is no clearly defined SoC and reported ORRs of therapeutic regimens administered after 2 or more prior anti-HER2-based regimens range approximately from 9% to 41%, while trastuzumab deruxtecan showed a confirmed ORR of 60.9% (95% CI: 53.4, 68.0) in Study U201 with DoR of 14.8 months (95% CI: 13.8, 16.9). Additionally, the median PFS with currently available treatment options is in the range of 3.3 to 7.8 months and a need for better treatments exist that prolong PFS and ultimately OS. ORR and DoR are substantially higher/longer for trastuzumab deruxtecan than reported for other medicinal products in the target population with at least two prior lines of anti-HER2 treatment. The MTA is therefore considered demonstrated.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  ORR and DoR are substantially higher/longer for trastuzumab deruxtecan than reported for other medicinal products in the target population with at least two prior lines of anti-HER2 treatment. The difference is as such that it is considered to overcome the remaining uncertainties related to indirect comparisons and high censoring rate. The safety profile can be considered acceptable in the target population with limited treatment options. It is considered that the benefits shown now outweigh the risks of conditionally approving trastuzumab deruxtecan before comparative confirmatory data are available.

3.8. Conclusions

The overall B/R of Enhertu is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Enhertu is favourable in the following indication:

Enhertu as monotherapy 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.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Additional risk minimisation measures are necessary for the safe and effective use of the product.

I) **Healthcare Professional (HCP) Guide for ILD/pneumonitis**

The HCP Guide will contain the following key elements:

- Summary of important findings of trastuzumab deruxtecan-induced ILD/pneumonitis (eg, frequency, grade, time to onset) observed in the clinical trial setting
- Description of the appropriate monitoring and evaluation of ILD/pneumonitis in patients receiving trastuzumab deruxtecan
- Detailed description of management of ILD/pneumonitis in patients treated with trastuzumab deruxtecan including guidance on drug interruption, reduction and treatment discontinuation for ILD/pneumonitis

- Reminder to HCP that they should repeat the information about signs and symptoms of ILD/pneumonitis at each patient visit, including when the patient should seek attention from an HCP (eg, the symptoms to watch for; the importance to adhere to scheduled appointments).
- Reminder to HCP to provide the patient with the Patient Card (PC), including advice that the PC should be kept with the patient at all times.

Patient Card

The Patient Card will contain the following key elements:

- Description of the important risks of ILD/pneumonitis associated with the use of trastuzumab deruxtecan
- Description of key signs and symptoms of ILD/pneumonitis and guidance on when to seek attention from an HCP
- Contact details of the trastuzumab deruxtecan prescriber
- Cross-reference to Patient Information Leaflet

II) **Healthcare Professional Guide for prevention of medication errors**

The HCP Guide will contain the following key elements:

- Alert to HCPs about a potential risk of confusion between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla® (trastuzumab emtansine)
- Mitigation measures for prescribing errors due to similarities in active ingredient names and measures to avoid errors during prescription phase by physicians
- Comparison of commercial appearance between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla® (trastuzumab emtansine).
- Potential mitigation strategies to avoid errors during preparation phase by pharmacists
- Detailed Information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase by nurses

The Marketing Authorisation Holder shall agree the format and content of the above material with the National Competent Authority prior to launch in the Member State.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Enhertu 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, the MAH should submit the interim results of study DS-8201-A-U301, a phase 3, multicentre, randomised, open-label, active-controlled study of Enhertu versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pre-treated with prior standard of care HER2 therapies, including T-DM1.	March 2022

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that trastuzumab deruxtecan is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.