30 January 2025
EMA/CHMP/78522/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Datroway

International non-proprietary name: datopotamab deruxtecan

Procedure No. EMEA/H/C/006547/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	Aspartate aminotransferase
AUCtau	Area under curve (for the plasma concentration-time curve during dosing interval)
BC	Breast cancer
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
CBR	Clinical benefit rate
CDK4/6i	Cyclin-dependent kinases 4 and 6 inhibitors
CI	Confidence interval
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
Dato-DXd	Datopotamab deruxtecan (formerly DS 1062a)
DCO	Data cut-off
DCR	Disease control rate
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DoR	Duration of response
DP	Drug product
DXd	MAAA-1181a (payload); the drug component of Dato-DXd,
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer

ER	Estrogen receptor
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration
FL-DP	Frozen-liquid drug product
GCP	Good Clinical Practice
geoCV%	Geometric mean coefficient of variation
GHS	Global health status
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HR+	Hormone receptor positive
IA1	Interim analysis 1
IA2	Interim analysis 2
ICC	Investigator's choice of chemotherapy
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IRR	Infusion-related reaction
ISH	In situ hybridisation
ISS	Integrated Summary of Safety
IV	Intravenous
Lyo-DP	Lyophilised powder drug product
mAb	Monoclonal antibody
MATE	Multidrug and toxin extrusion
MedDRA	Medical dictionary for regulatory activities
MRP	Multidrug resistance protein
ms	Milliseconds
MTD	Maximum tolerated dose
N	Number of patients
nAb	Neutralising antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NE	Not evaluable
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PDCO	Paediatric Committee
PFS	Progression-free survival
PFS2	Time from randomisation to second progression
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PR	Progesterone receptor
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
Q3W	Once every 3 weeks
QLQ-C30	Quality of life questionnaire (core 30-items)
QoL	Quality of life
QT	Time on an ECG wave between the start of the Q wave and the end of the T wave
QTc	QT interval of electrocardiogram corrected for heart rate
RECIST 1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
SAE	Serious adverse event
sBR	Structured benefit risk
SD	Stable disease
SMQ	Standardised MedDRA Queries
SOC	Standard of care
t1/2	Half-life
T-DXd	Trastuzumab deruxtecan (DS-8201a)
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent therapy

TNBC	Triple negative breast cancer
TROP2	Trophoblast cell surface antigen 2
TSST	Time to second subsequent therapy
TTD	Time to deterioration
TTR	Time-to-response
UGT	Uridine diphosphate glucuronosyltransferases
ULN	Upper limit of normal
US	United States of America
Vss	Volume of distribution at steady state
ΔQTc	Change from baseline in QTc

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Daiichi Sankyo Europe GmbH submitted on 12 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Datroway, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Datroway as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have progressed on and are not suitable for endocrine therapy and received at least one additional systemic therapy for unresectable or metastatic disease.

1.2. Legal basis, dossier content

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).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002976-PIP02-21 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.4.2. New active substance status

The applicant requested the active substance datopotamab 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.

1.5. 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
22/07/2021	EMA/SA/0000060979	Aaron Emmanuel Sosa Mejia and Elena Wolff-Holz
19/05/2022	EMA/SA/0000082333	Jens Reinhardt and Dieter Deforce

The scientific advice pertained to the following quality and clinical aspects:

- The stability studies to support the proposed shelf lives for the commercial Mab, drug substance, and drug product and proposed temperature control range; the extractable and Leachable assessment strategy to qualify the drug product container closure system; the proposed tests to support the commercial specifications for the Mab, drug substance and drug product.
- The design of the phase 3 study to support registration of Dato-DXd for the treatment of adult patients with inoperable or metasatic HR positive / HER2-negative breast cancer with disease progression following chemotherapy in the metastatic setting, in particular with regards to patient population, stratification factors, comparator and planned safety measures, sample size and statistical approach to evaluate the efficacy endpoints, patient-reported outcome assessment.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: Peter Mol

The application was received by the EMA on	12 February 2024
The procedure started on	1 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 May 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 October 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2024

The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 November 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 January 2025
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 Datroway on	30 January 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	30 January 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Claimed therapeutic indication:

Datroway as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have progressed on and are not suitable for endocrine therapy and received at least one additional systemic therapy for unresectable or metastatic disease.

2.1.2. Epidemiology

Breast cancer is the most common cancer in the world, with an estimated 2.3 million new cases of female BC in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer globally, with an estimated 685,000 deaths (GLOBOCAN 2020). In Europe, an estimated 531,000 patients were diagnosed with BC in 2020, and 141,765 died from the disease (GLOBOCAN 2020). The estimate for the prevalence of subjects with ER+/HER2- breast cancer is 1497 patients (IARC 2021).

2.1.3. Biologic features

Clinical practice typically uses a surrogate classification of 3 BC subtypes, based on molecular characteristics: HER2 positive, HR positive but HER2 negative, and TNBC. Approximately 70% of all BCs are of the subtype HR-positive, HER2-negative (Howlader et al 2014). Traditionally HER2-negative definition is IHC 0, IHC 1+ or IHC 2+/ISH- as per the ASCO/CAP criteria; however, based on emerging data and recent approvals, HER2-low BC (IHC 1+ or IHC 2+/ISH-) is potentially a new classification (Modi et al 2022).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Despite advances in the diagnosis and treatment of BC, around 5% to 10% of women diagnosed with BC have metastatic disease at the time of diagnosis, and up to 30% of women with early-stage non-metastatic BC will develop metastatic disease (Cardoso et al 2018, O'Shaughnessy 2005, OECD 2021).

For the targeted patient population and the proposed setting, the prognosis is reflected by data from the recent approvals of trastuzumab deruxtecan and sacituzumab govitecan. Hence, survival rates remain low, with a median OS of less than 2 years (23.9 months) for the HR positive patient cohort in the DESTINY Breast-04 study for trastuzumab deruxtecan, and less than 18 months for the physician's choice of chemotherapy (see EPAR Enhertu II/0022). The median OS in the TROPiCS-02 study was 14.4 months for sacituzumab govitecan and 11.2 months for the chemotherapy arm (Rugo et al 2022).

2.1.5. Management

The standard first-line treatment for patients with locally advanced/metastatic HR positive, HER2-negative BC is the combination of CDK4/6i (palbociclib, abemaciclib, or ribociclib) with endocrine therapy (usually an aromatase inhibitor or fulvestrant) based on the results of several Phase III trials and current clinical guidelines (Burstein et al 2021, ESMO 2023, NCCN 2023). For patients with metastatic HR-positive, HER2-negative BC, who have exhausted other lines of endocrine therapy (e.g. fulvestrant monotherapy, everolimus based combinations, elacestrant in patients with tumoural ESR-1 mutations, alpelisib + fulvestrant in patients with PIK3CA mutations) (Orserdu EPAR 2024, Piqray EPAR 2023) or are not suitable for endocrine therapy, single-agent chemotherapy is the SOC, such as eribulin, capecitabine, gemcitabine, vinorelbine, taxanes (Cardoso et al 2018, ESMO 2023, NCCN 2023).

Recently, ADCs have been approved for the treatment of BC. Enhertu (trastuzumab deruxtecan) is a HER2-directed ADC approved in 2022 as a treatment for adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH−) BC, who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (see EPAR Enhertu II/0022). Trodelvy (sacituzumab govitecan) is a TROP2-directed ADC approved in 2023 as a treatment for adult patients with unresectable locally advanced or metastatic HR-positive, HER2-negative BC, who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting (see EPAR Trodelvy II/0020). Current treatment guidelines now include sacituzumab govitecan and trastuzumab deruxtecan as systemic therapy options for patients with HR-positive and HER2 negative/HER2-low breast cancer, respectively (ESMO 2023, Moy et al 2022, NCCN 2023).

Unmet medical need

At the time of initiation of the pivotal study (TB01) and throughout the active enrolment period, for patients who developed resistance to endocrine therapy (with or without combination with targeted agents), sequential single-agent chemotherapy was the SOC. However, chemotherapy is associated with poor response rates, suboptimal disease control, and confers toxicity, including cytopenias and neuropathy (Bidard et al 2022, Kalinsky et al 2022, Lindeman et al 2021, Rugo et al 2022a, Tolaney et al 2023).

Despite advances including trastuzumab deruxtecan and sacituzumab govitecan, there is still an unmet medical need. Trastuzumab deruxtecan has been approved for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) BC, however, this only accounts for 60% of the HER2-negative metastatic BCs overall (Schettini et al 2021, Tarantino et al 2020), leaving 40% of HER2-negative patients without this option. Furthermore, though sacituzumab govitecan has been approved

to treat adult patients with unresectable locally advanced or metastatic HR positive, HER2-negative BC, it is approved for patients who have received endocrine-based therapy and at least 2 additional systemic therapies in the advanced setting (Trodelvy EPAR 2023, Rugo et al 2022a). Despite available therapies, there remains a high unmet medical need for new therapeutic options that would provide a clinically meaningful delay in time to progression and improved survival.

Therefore, there remains an unmet medical need for therapies with improved efficacy and tolerability, in patients with HR-positive, HER2-negative metastatic BC that have progressed after one prior line of systemic therapy.

2.2. About the product

Datopotamab deruxtecan is a TROP2-directed antibody-drug conjugate. The antibody is a humanised anti-TROP2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd) bound by a tetrapeptide-based cleavable linker. The antibody-drug conjugate is stable in plasma. The antibody binds to TROP2 expressed on the surface of certain tumour cells. After binding, datopotamab deruxtecan undergoes internalisation into the tumour cells. Subsequently, the release of DXd results in DNA damage and apoptotic cell death via topoisomerase I inhibition. Datopotamab deruxtecan may also exhibit indirect cytotoxicity as shown in vitro through mechanisms of antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and bystander cytotoxicity of DXd against TROP2 expressing tumour cells and neighbouring cells.

The finally approved indication was:

Datroway as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

Datroway should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products.

Patients for treatment of unresectable or metastatic HR-positive, HER2-negative breast cancer should be selected on the basis of a documented HER2-negative result assessed by a CE marked IVD if available, or an alternative validated test.

The recommended dose of Datroway is 6 mg/kg (up to a maximum of 540 mg for patients ≥90 kg) of body weight given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

The infusion rate of Datroway should be slowed or interrupted if the patient develops an infusion-related reaction. Datroway should be permanently discontinued in case of life-threatening infusion-related reactions.

Management of adverse reactions may require dose delay, dose reduction, or treatment discontinuation per guidelines provided in Tables 1 and 2.

Datroway dose should not be re-escalated after a dose reduction is made.

Table 1 Dose reductions for adverse reactions

Recommended starting dose	6 mg/kg (up to a maximum of 540 mg for patients ≥90 kg)
First dose reduction	4 mg/kg (up to a maximum of 360 mg for patients ≥90 kg)
Second dose reduction	3 mg/kg (up to a maximum of 270 mg for patients ≥90 kg)

Table 2: Dose modifications for adverse reactions

Adverse reaction	Severity*	Dose modification
Interstitial lung disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	Delay dose until resolved to Grade 0#, then: • if resolved in 28 days or less from date of onset, maintain dose. • if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1). • consider corticosteroid treatment as soon as ILD/pneumonitis is suspected.
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	• Permanently discontinue. • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected.
Keratitis	Grade 2	• Delay dose until resolved to Grade 1 or less, then maintain dose.
	Grade 3	• Delay dose until resolved to Grade 1 or less, then reduce the dose by 1 level (see Table 1).
	Grade 4	• Permanently discontinue.
Stomatitis	Grade 2	• Delay dose until resolved to Grade 1 or less. • Restart at the same dose for first occurrence. • Consider restarting at reduced dose level (see Table 1) if recurrent.
	Grade 3	• Delay dose until resolved to Grade 1 or less. • Restart at reduced dose level (see Table 1).
	Grade 4	• Permanently discontinue.

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Grade 0 refers to full resolution of ILD/pneumonitis, including the disappearance of radiological findings associated with active ILD/pneumonitis. Residual scarring or fibrosis following recovery of ILD/pneumonitis is not considered to be active disease.

2.3. Type of application and aspects on development

This is a complete independent application.

The Dato DXd clinical program has been designed to evaluate the overall benefits and risks of Dato DXd in various tumour types, stages of disease, and lines of treatment. However, Dato-DXd is not yet approved for any tumour type. The primary efficacy and safety claims that support the use of Dato DXd in the proposed indication are based on the ongoing, pivotal Phase III clinical study TROPION-Breast01 (TB01). The objective of the TB01 study is to assess the efficacy and safety of Dato DXd 6 mg/kg IV Q3W when compared with ICC in patients with inoperable or metastatic HR positive, HER2 negative BC who have been treated with one or 2 prior lines of systemic chemotherapy.

2.4. Quality aspects

2.4.1. Introduction

The active substance datopotamab deruxtecan is an antibody-drug conjugate (ADC). It contains a humanised anti-trophoblast cell surface antigen 2 (TROP2) immunoglobulin G1 (IgG1) monoclonal antibody (MAb) produced by mammalian Chinese Hamster Ovary (CHO) cells, covalently linked to DXd, an exatecan derivative and a topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Approximately 4 molecules of deruxtecan are attached to each antibody molecule.

The finished product is presented as a powder for concentrate for solution for infusion in a vial containing 100 mg of datopotamab deruxtecan as active substance. It 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 blue flip off crimp cap.

Datopotamab 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.

2.4.2. Active substance

Datopotamab deruxtecan active substance results from the conjugation of the following intermediates:

- Datopotamab MAb;

- A drug-linker (MAAA-1162a) comprised of a topoisomerase I inhibitor derivative of exatecan (MAAA-1181a, also referred to as DXd) and a tetrapeptide-based cleavable linker (MFAH).

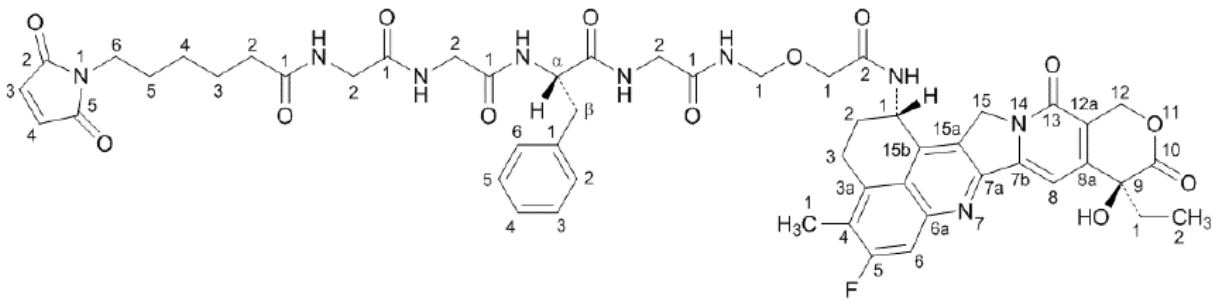
The ADC is stable in plasma. The antibody binds to TROP2 expressed on the surface of certain tumour cells. After binding, datopotamab deruxtecan then undergoes internalisation into the tumour cells. Subsequently, the release of DXd results in DNA damage and apoptotic cell death via topoisomerase I inhibition. Datopotamab deruxtecan may also exhibit indirect cytotoxicity as shown in vitro through mechanisms of antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and bystander cytotoxicity of DXd against TROP2 expressing tumour cells and neighbouring cells.

2.4.2.1. Drug-linker intermediate (MAAA-1162a)

2.4.2.1.1. General information

The molecular structure of the MAAA-1162a drug-linker is shown in Figure 1.

Figure 1 Molecular structure of the MAAA-1162a



2.4.2.1.2 Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

The manufacturing process and process controls for the MAAA-1162a drug-linker are described in detail. The MAAA-1162a drug-linker manufacturing consists of several chemical synthesis steps.

MAAA-1162a is synthesised by coupling drug intermediate and linker intermediate.

Control of materials

The controls of materials including starting materials, reagents, solvents, catalysts and other auxiliary materials are appropriate. Adequate justifications of starting materials have been provided as well as discussions on the observed impurities. No animal-derived materials are used in the process.

Control of critical steps and intermediates

The control of critical steps and specifications of intermediates are deemed 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), process validation data is not provided in this submission and the process validation will be completed prior to commercialisation. This is acceptable.

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. Comparability studies were performed to qualify the changes introduced in the process. This is acceptable.

Characterisation

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. The methods employed are appropriate for structure elucidation of MAAA-1662a.

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 (including nitrosamines) for MAAA-1162a was provided. With reference to ICH Q3A (R2) "Impurities in New Active 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. Observed impurities in each isolated intermediate were identified based upon testing according to their specifications. The Applicant provided a risk assessment confirming that there is no risk in relation to nitrosamine impurities.

2.4.2.1.3. Specification

The specifications of MAAA-1162a include 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.

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 data are provided. All batches complied with the specifications. The reference standard has been adequately described and qualified.

Batch analysis

Batch analysis data are provided from the MAAA-1162a drug-linker batches manufactured to support non-clinical studies, clinical studies, and commercial supply. The batch analysis data are reported against the specification in place at the time of testing.

Reference standard

MAAA-1162a batches are manufactured, characterised and qualified as MAAA-1162a reference to support routine analytical testing for in-process, release, and stability testing.

Container closure system

MAAA-1162a is suitably packaged. Materials in contact with the product comply with relevant EU requirements. 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.

2.4.2.1.4. 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.

2.4.2.2. Datopotamab intermediate

2.4.2.2.1. General information

Datopotamab is a recombinant humanised anti-TROP2 IgG1 MAb. Datopotamab consists of 2 heavy chains and 2 kappa light chains each containing intrachain disulphide bonds, covalently linked through interchain disulphide bonds. The molecular mass not accounting glycans is approximately 145.3 kDa.

2.4.2.2.2. Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

The manufacturing process and process controls for the datopotamab intermediate are described in detail. The datopotamab process consists of thawing of the working cell bank (WCB) and upscaling of the cells, expression of datopotamab in the production bioreactor, harvesting, clarification, series of chromatography steps viral inactivation, viral filtration, ultra-diafiltration (UF/DF), final filtration and filling.

Control of materials

Raw materials are described and adequately controlled. Compositions of culture media and buffers are provided. The generation of the recombinant cell clone expressing datopotamab is described. A two-tiered cell bank system consisting of a master cell bank (MCB) and WCB has been generated. The cell banks have been properly qualified, including testing on end-of-production cells. Also, genetic stability of the cell bank was demonstrated. Apart from the WCB cells, no animal-derived materials are used in the process. The Applicant has removed the *in vivo* viral assay from the qualification specifications of future WCBs. A protocol for renewal of WCBs is described in the dossier.

Control of Critical steps and intermediates

An overview is provided of all critical process parameters (CPPs) and key process parameters (KPPs) as well as of all IPCs. It is confirmed that any harvest test result that is positive for mycoplasma or virus contamination will result in rejection of the corresponding batch of datopotamab. Quality of intermediates is adequately controlled.

Process validation

The manufacturing process of the datopotamab MAb has been appropriately validated. Process performance qualification (PPQ) data from validation batches showed that the CPP results were within the acceptance ranges and that all IPCs and release test results complied with the specifications.

Also, temperature-conditioned transport of the datopotamab MAb has been validated.

Reprocessing of the viral filtration and final filtration were validated. The Applicant is recommended to submit the validation reports of the studies for the reprocessing of viral filtration and final filtration to the Agency with the next forthcoming variation impacting the datopotamab MAb intermediate section (see Recommendation).

The reuse of UF membrane and of the resins used in the protein A chromatography and CEX chromatography has been validated at small scale. The small-scale process has been extensively and adequately qualified. Both reprocessing and column/UF lifetime will also be verified at commercial scale. Validation protocols have been provided and are deemed acceptable.

Overall, the datopotamab manufacturing process is considered validated.

Manufacturing process development

The Applicant has described the control strategy for critical quality attributes (CQAs) of datopotamab which is comprised of multiple control elements that were established based on process development

experiments and data generated during the process characterisation studies. Findings from these studies were used to define a commercial manufacturing process, including CPPs, KPPs and IPCs. An overview was provided of all process variants used during clinical development. Extensive comparability studies were performed which confirmed that datopotamab from all process variants was highly similar.

Characterisation

Extensive characterisation has been performed for datopotamab using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Physico-chemical characterisation included analysis of primary structure, disulphide bonds, glycosylation, charge variants, size variants including low molecular weight species (LMWS) and high molecular weight species (HMWS), protein concentration, secondary and tertiary structure.

Biological characterisation was performed. including ADCC, complement-dependent cytotoxicity (CDC), cell growth inhibition, antigen binding activity, FcgammaRIIIa binding, FcRn binding and C1q binding. Datopotamab does not show any CDC activity or cell growth inhibitory activity. *In vitro* ADCC activity was observed for datopotamab; however, no *in vivo* ADCC activity was detected when using an *in vivo* model, thereby indicating that ADCC is not relevant for the mechanism of action of the finished product.

Impurities have been investigated in detail. itIt is agreed that impurities are efficiently removed to levels that are very low and safe. Clearance studies have been performed.

The Applicant provided a risk assessment confirming that there is no risk for nitrosamine impurities.

2.4.2.2.3. Specification

The specifications for datopotamab include control of identity, purity, potencyand other general tests. The proposed tests are deemed sufficient for the release testing of datopotamab and the acceptance criteria are considered acceptable.

Analytical methods

All release testing methods have been described. Non-compendial methods were appropriately validated.

Batch analysis

Batch data are provided for clinical lots, PPQ lots and the commercial batches produced thus far. Release test results are very consistent between batches and confirm compliance with the specifications.

Reference standard

The Applicant has provided detailed information on the reference materials used during clinical development and those intended for commercial product testing. A two-tiered system has been established consisting of a primary and secondary reference standard. All reference standards have been properly qualified. Protocols have been included to produce and qualify future primary and secondary reference standards. The qualification protocols and specifications are deemed acceptable.

Container closure

The Applicant provided a detailed description of the container used for datopotamab storage. Specifications are provided. The materials in contact with the datopotamab comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed but did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab.

2.4.2.2.4. Stability

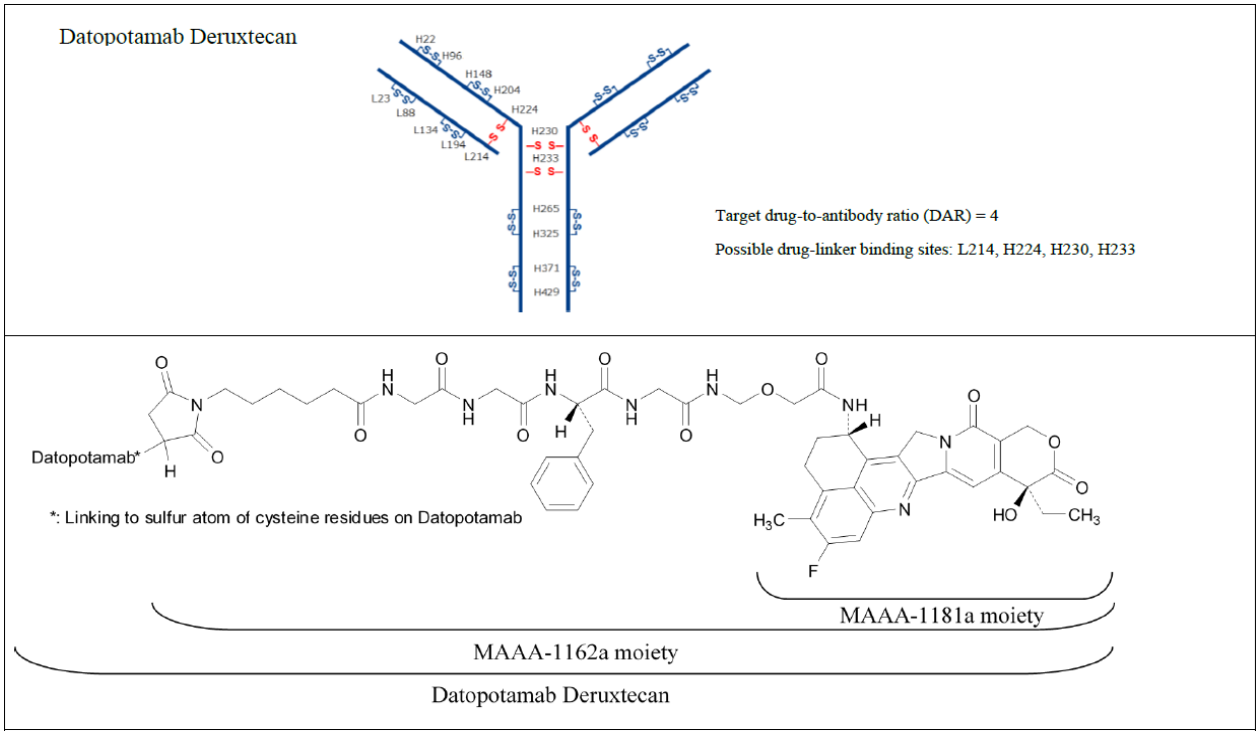
Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. The currently available stability data justify the proposed shelf life for datopotamab intermediate when stored under the long-term storage condition.

2.4.2.3. Datopotamab deruxtecan

2.4.2.3.1. General information

Datopotamab deruxtecan is an ADC comprised of a recombinant humanised anti-TROP2 IgG1 MAb, datopotamab, covalently conjugated to a drug-linker, MAAA-1162a, via thioether bonds. The structure is shown in Figure 2.

Figure 2 Schematic Structures of Datopotamab Deruxtecan



2.4.2.3.2. Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Datopotamab deruxtecan is manufactured at Daiichi Sankyo Chemical Pharma Co., Ltd., (DSCP) Onahama Plant, 389-4, Izumimachi Shimokawa, Aza, Otsurugi, Iwaki, Fukushima, 971-8183, Japan. All sites involved in the manufacture and control of the active substance and intermediates operate in accordance with GMP.

The manufacturing process and process controls for the datopotamab deruxtecan active substance are described in detail. The active substance manufacturing process includes thawing of datopotamab intermediate, reduction of datopotamab, conjugation of reduced datopotamab with MAAA-1162a drug-linker, quenching of reaction mixture, purification, concentration, formulation, filtration and filling.

Control of materials

Starting materials are the datopotamab MAb intermediate and the MAAA-1162a drug-linker intermediate, for which detailed information on their synthesis and control has been provided. Raw materials are described and are adequately controlled. No animal-derived materials are used in the process.

Control of critical steps and intermediates

An overview is provided of all CPPs and KPPs as well as of all IPCs. The overall control strategy has been explained and is deemed acceptable.

Process validation

Process validation was successfully performed. All process parameter results fell within the acceptance criteria; active substance test results complied with the IPC and release specifications and confirmed the high consistency of the active substance quality. Extensive hold time studies were performed which confirmed that the proposed hold times can be considered as properly validated. The lifetime of the UF/DF membrane has been adequately validatedAlso transport of the active substance has been adequately validated.

Manufacturing process development

The development of the active substance manufacturing process and the different process variants have been described. Comparability analyses have been performed to justify the process changes introduced during clinical development. Comparability test results confirmed that Phase 3 clinical lots from the clinical site and finished product lots from the commercial site were highly comparable.

Extensive process characterisation has been performed to identify the CPPs and to establish an appropriate control strategy for the active substance manufacturing process. The proposed strategy and the combination of IPC and release testing is deemed acceptable.

Characterisation

In-depth characterisation has been performed for datopotamab deruxtecan using a combination of different analytical methods to reveal the structural, physico-chemical properties and biological activity of the molecule. See above for details.

2.4.2.3.3. Specification

The specifications for the datopotamab deruxtecan active substance 3 include control of identity, purity, potency, drug-to-antibody ratio (DAR) and other general tests. Specifications limits have been sufficiently justified.
3

Analytical procedures

Analytical methods for active substance release testing are described and were adequately validated.

Batch analysis

Batch analysis data are provided for clinical active substance lots and PPQ active substance lots. All test results comply with the specifications and confirm the high consistency of the active substance quality.

Reference standard

The Applicant has provided detailed information on the reference materials. A two-tiered system has been established consisting of a primary and secondary standard. All standards have been properly qualified. Protocols have been included to produce and qualify future primary and secondary standards. The qualification protocols and specifications are deemed acceptable.

Container closure

The Applicant provided a detailed description of the container for datopotamab deruxtecan active substance, which is a single-use bag. Specifications are provided. The materials in contact with the active substance comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed and did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab deruxtecan active substance.

2.4.2.3.4. Stability

Long-term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. Under the long-term storage conditions, it was observed that datopotamab deruxtecan active substance remains stableNo trends were observed for any of the quality parameters. Datopotamab deruxtecan active substance also remained stable at accelerated conditions. Some degradation was observed under stressed conditions. The currently available stability data justify the proposed active substance shelf life when stored under the long-term storage condition.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The composition of the finished product (100 mg datopotamab deruxtecan) has been provided. All excipients - L-histidine and L-histidine hydrochloride monohydrate, sucrose and polysorbate 80 - are of compendial grade. No excipients derived from human or animal origin are used and no novel excipients are included.

Datopotamab deruxtecan is a powder for solution for infusion. The finished product is presented as a lyophilised powder in a glass vial without preservatives. Each vial is intended for reconstitution with 5 mL of water for injections to provide a solution of 20 mg/mL datopotamab deruxtecan.
4

Pharmaceutical development

The pharmaceutical development of datopotamab deruxtecan finished product is described in detail. Early phase clinical trials were performed using a liquid formulation. A lyophilised presentation was developed for later stage clinical trials and commercial production. Comparability analyses have

demonstrated comparability of finished product manufactured during development. Formulation studies were performed to justify the composition of the finished product. Process development studies were performed to define the optimal process parameters. CPPs were identified.

The use of an in-line filter is recommended for administration and compatibility of this filter has been properly validated.

A description was provided for the container closure system and its compatibility was demonstrated. Extractables and leachables studies were performed which did not reveal any compounds of concern.

2.4.3.2. Manufacture of the product and process controls

Manufacture

The manufacturer response for EU batch release is Daiichi Sankyo Europe GmbH, Luitpoldstrasse 1, 85276 Pfaffenhofen, Germany. All sites involved in the manufacture and control of the finished product operate in accordance with GMP.

A detailed description has been provided for the manufacturing process and process controls for the datopotamab deruxtecan finished product. The finished product process consists of active substance thawing, mixing, sterile filtration, filling, lyophilisation, vial capping, visual inspection, labelling and secondary packaging. No animal-derived materials are used in the process. Quality of intermediates is adequately controlled by IPCs.

Process validation

The finished product manufacturing process was appropriately validated. Supporting validation studies were provided.

2.4.3.3. Product specification

Finished product specifications and acceptance limits as well as corresponding analytical methods have been described5. The specification for datopotamab deruxtecan includes control of identity, purity and impurities, potency, quantity and other general tests. The general tests for release includes appearance before and after reconstitution (color and clarity), osmolality, pH, water content, reconstitution time as well as tests for safety (visible particles, subvisible particulate matter, bacterial endotoxins and sterility). The tests are performed according to compendial requirements and/or by visual observation. Specification acceptance criteria have been sufficiently justified and are considered acceptable.
5

Analytical procedures

Analytical methods have been adequately validated.

Batch analysis

Finished product batch data were provided. The results complied with the specifications.

Reference materials

The Applicant has described the reference materials that are used during finished product release testing.

Characterisation of impurities

A risk assessment for the presence of elemental impurities in the active substance and finished product was conducted in accordance with ICH Q3D. No elemental impurity exceeding levels stated in ICH Q3D were detected.

A risk assessment to assess the potential presence of nitrosamines in datopotamab, the active substance and the finished product was provided. It can be concluded that the risk of contamination by N-nitrosamines in the finished product is negligible.

Container closure

The container closure system for the lyophilised finished product is a Type I glass amber vial, closed with a fluoro-resin laminated butyl rubber stopper and secured with an aluminium seal with polypropylene flip-off cap. Vial and stopper materials are compliant with respective Ph. Eur. monographs.

2.4.3.4. Stability of the product

The Applicant provided long-term, accelerated and stressed stability data of representative finished product lots. The available stability data support the proposed shelf life of 36 months for the finished product when stored at 2-8°C (unopened vial).

Regarded the reconstituted solution, chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

As for the diluted solution, it is recommended that it is used immediately. If not used immediately, the diluted solution may be stored at room temperature ($\leq 25^0$C) for up to 4 hours or in a refrigerator at 2^0C to 8^0C for up to 24 hours, protected from light.

The maximum time from reconstitution of the vial through the end of administration should not exceed 24 hours. The product should be discarded if storage time exceeds these limits.

2.4.3.5. Post-approval change management protocol(s)

The Applicant has presented 2 post-approval change management protocols (PACMPs) for introducing additional manufacturing sites of the datopotamab antibody intermediate and the datopotamab deruxtecan active substance. A comparability analysis will be performed according to ICH Q5E to demonstrate equivalence of the material form the registered site(s) and the new site(s). Material from the new site will be included in stability studies. Analytical methods will be transferred to the new sites; compendial methods will be verified; non-compendial methods will be partially revalidated. The proposed PACMPs for the datopotamab intermediate and datopotamab deruxtecan active substance have been revised following questions asked during the procedure. All information and data that are expected to be included in Module 3 for a new production site have now been properly referred to in the PACMPs. The current PACMPs are deemed acceptable.

2.4.3.6. Adventitious agents

The Applicant has implemented comprehensive approaches to guarantee the viral safety of datopotamab. Potential viral contamination at the level of MCB and WCB was investigated. During the

manufacturing process, extensive testing of the unprocessed bulk for presence of adventitious agents is performed.

Safety assessment confirmed that there is no risk for TSE/BSE.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

MAAA-1162a drug-linker intermediate

The manufacturing process and process controls for the MAAA-1162a drug-linker are described in detail. The MAAA-1162a drug-linker manufacturing consists of several chemical synthesis steps. The control of materials including starting materials, reagents, solvents, catalysts and other auxiliary materials are appropriate. Adequate justifications of starting materials have been provided as well as discussions on the observed impurities. No animal-derived materials are used in the process. The control of critical steps and specifications of intermediates are deemed adequate and IPCs and operational controls are suitably justified.

The manufacturing process was optimised during development to improve the manufacturing efficiency while maintaining the desired quality of the drug-linker. Comparability studies were performed to qualify the changes introduced in the process.

The structure of MAAA-1162a was confirmed using elemental analysis, IR, UV, ^{1}H and ^{13}C NMR, MS and single crystal X-ray structure analysis. Impurities were evaluated in detail.

The specification of MAAA-1162a includes tests for description, identification by IR, specific optical rotation, assay and related substances by RP-HPLC and residual solvents by GC. The proposed limits are acceptable and are based on ICH Q3A, ICH Q6A and batch data. The Applicant provided a risk assessment confirming that there is no risk in relation to nitrosamine impurities.

Suitably described and validated analytical methods are used and are adequate to control MAAA-1162a on a routine basis. Batch analysis data are provided. All batches complied with the specifications. The reference standard has been adequately described and qualified.

MAAA-1162a is suitably packaged. Materials in contact with the product comply with relevant EU requirements.

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.

Datopotamab monoclonal antibody intermediate

The manufacturing process and process controls for the datopotamab intermediate are described in detail. The datopotamab process consists of thawing of the WCB and upscaling of the cells, expression of datopotamab in the production bioreactor, harvesting, clarification, series of chromatography steps, viral inactivation, viral filtration, UF/DF, final filtration and filling. Quality of intermediates is adequately controlled by in-process controls.

Raw materials are described and properly controlled. Compositions of culture media and buffers are provided. The generation of the recombinant cell clone expressing datopotamab is described. A two-tiered cell bank system consisting of a MCB and WCB has been generated. The cell bank has been

properly qualified, including testing on end-of-production cells. Also, genetic stability of the cell bank was demonstrated. Apart from the WCB cells, no animal-derived materials are used in the process.

An overview is provided of all critical and key process parameters as well as of all IPCs.

The manufacturing process of the datopotamab monoclonal antibody has been appropriately validated. The Applicant is recommended (see below) to submit the validation reports of the studies for the reprocessing of viral filtration and final filtration for Datopotamab with the next forthcoming variation impacting the Datopotamab intermediate section.

An overview was provided of all process variants used during clinical development. Comparability studies were performed which confirmed that datopotamab from all process variants was highly similar.

Extensive characterisation has been performed for datopotamab using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Also, biological characterisation was performed. Datopotamab does not show any CDC activity or cell growth inhibitory activity. *In vitro* ADCC activity was observed for datopotamab; however, no *in vivo* ADCC activity was detected when using an *in vivo* model, thereby indicating that ADCC is not relevant for the mechanism of action of the finished product.

Impurities have been investigated in detail. Product-related impurities are controlled via the release specifications of datopotamab. Process-related impurities include HCP, host cell DNA, residual protein A and residual cell culture components The other impurities were shown to be efficiently removed to levels that are very low and safe present and therefore do not require routine testing. The Applicant also provided a risk assessment confirming that there is no risk for nitrosamine impurities.

The Applicant has proposed specifications and acceptance limits for datopotamab. The proposed tests are deemed sufficient for the release testing of datopotamab. All release testing methods have been described. Non-compendial methods were appropriately validated. Batch data are provided for clinical lots, PPQ lots and the commercial batches produced thus far. Release test results are very consistent between batches and confirm compliance with the specifications.

The Applicant has provided detailed information on the reference materials used during clinical development and those intended for commercial product testing.

The container used for datopotamab storage is a single-use bag. Specifications are provided. The materials in contact with the datopotamab comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed but did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab.

Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. Under the long-term storage conditions, it was observed that datopotamab remains stable. The currently available stability data justify the proposed shelf life for datopotamab intermediate when stored under the long-term storage condition.

Datopotamab deruxtecan active substance

The manufacturing process and process controls for the datopotamab deruxtecan active substance are described in detail. The active substance manufacturing process includes thawing of datopotamab intermediate, reduction of datopotamab, conjugation of reduced datopotamab with MAAA-1162a drug-linker, quenching of reaction mixture, purification, concentration, formulation, filtration and filling. Starting materials are the datopotamab mAb and the MAAA-1162a drug-linker, for which detailed information on their synthesis and control has been provided in separate sections. Raw materials are

described and are adequately controlled. No animal-derived materials are used in the process. An overview is provided of all critical and key process parameters as well as of all IPCs.

Process validation was successfully performed. All process parameter results fell within the acceptance criteria; active substance test results complied with the IPC and release specifications and confirmed the high consistency of the active substance quality. Also hold timesand active substance transport have been adequately validated.

Extensive process characterisation has been performed to identify the CPPs and to establish an appropriate control strategy for the active substance manufacturing process. The development of the active substance manufacturing process and the different process variants have been described. Comparability analyses confirmed that active substance from different process variants ere comparable.

In-depth characterisation has been performed for datopotamab deruxtecan using a combination of different analytical methods to reveal the structural and physico-chemical properties of the molecule. Also biological characterisation was performed. The active substance shows *in vitro* ADCC activity that is similar to that of datopotamab MAb. However, ADCC is not considered as an important mechanism of action of the active substance or finished product since only datopotamab deruxtecan was able to reduce tumor growth in an *in vivo* model whereas datopotamab mAb showed no inhibitory effect on tumor growth *in vivo*. Product-related impurities as well as active substance without conjugated drug-linker are controlled via the release specification. Process-related impurities include residual MAAA-1162a drug-linker as well as reagents, by-products and degradation products. The most important impurities have been described. Overall, all impurities are adequately controlled during manufacturing and/or release testing.

The Applicant has proposed specifications and acceptance limits for the datopotamab deruxtecan active substance. Analytical methods used for active substance release testing are described and have been adequately validated. Batch analysis data are provided for clinical active substance lots and PPQ active substance lots. All test results comply with the specifications and confirm the high consistency of the active substance quality. The Applicant also provided detailed information on the reference materials.

The container used for datopotamab deruxtecan active substance storage is a single-use bag. Specifications are provided. The materials in contact with the active substance comply with the respective Ph. Eur requirements. Extractables and leachables testing were performed and did not reveal any compounds of concerns. The proposed containers are properly qualified and deemed acceptable for storage of datopotamab deruxtecan active substance.

Long term stability studies have been performed, as well as stability studies under accelerated and stressed conditions. Under the long-term storage conditions, it was observed that datopotamab deruxtecan active substance remains stable. The currently available stability data justify the proposed active substance shelf life when stored at under long-term storage condition.

Datopotamab deruxtecan finished product

A detailed description has been provided for the manufacturing process and process controls for the datopotamab deruxtecan finished product. The finished product process consists of active substance thawing, mixing, sterile filtration, filling and lyophilisation. No animal-derived materials are used in the process. Quality of intermediates is adequately controlled by in-process controls.

The composition of the finished product has been provided. All excipients are of compendial grade. No excipients derived from human or animal origin are used and no novel excipients are included.

The pharmaceutical development of datopotamab deruxtecan finished product is described in detail. Early phase clinical trials were performed using a liquid formulation. A lyophilised presentation was

developed for later stage clinical trials and commercial production. Comparability analyses have demonstrated comparability of finished product manufactured during development. Formulation studies were performed to justify the composition of the finished product. Process development studies were performed to define the optimal process parameters. Critical process parameters were identified.

A description was provided for the container closure system and its compatibility was demonstrated. Extractables and leachables studies were performed which did not reveal any compounds of concern.

The finished product manufacturing process was appropriately validated. Supporting validation studies were provided including validation of aseptic processing and validation of sterile filtration. In addition, also validation of sterilisation of container components as well as validation of shipment was provided.

Finished product specifications and acceptance limits as well as corresponding analytical methods have been described. Methods have been adequately validated. finished product batch data were provided; the results complied with the specifications. The Applicant has also described the reference materials that are used during finished product release testing. Risk assessments were performed demonstrating that the risk for elemental impurities or nitrosamines can be considered negligible to non-existing.

The container closure system for the lyophilised finished product is a Type I glass amber vial, closed with a fluoro-resin laminated butyl rubber stopper and secured with an aluminium seal with polypropylene flip-off cap. Vial and stopper materials are compliant with respective Ph.Eur. monographs.

The Applicant provided long term, accelerated and stressed stability data of representative finished product lots. The available stability data support the proposed shelf life of 36 months for the finished product when stored at 2-8°C.

Safety assessment confirmed that there is no viral safety and TSE/BSE risks.

The Applicant has presented PACMPs for introducing additional manufacturing sites of the datopotamab antibody intermediate and the datopotamab deruxtecan active substance. The proposed PACMPs have been revised and contain now all essential information. The current PACMPs are deemed acceptable.

2.4.5. Conclusions on the 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 and intermediates is adequately described, controlled and validated. The active substance and intermediates are 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.

Overall, the quality of Datroway 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 Datroway is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The Applicant is recommended to submit the validation reports of the studies for the reprocessing of viral filtration and final filtration for Datopotamab with the next forthcoming variation impacting the Datopotamab intermediate section.

2.5. Non-clinical aspects

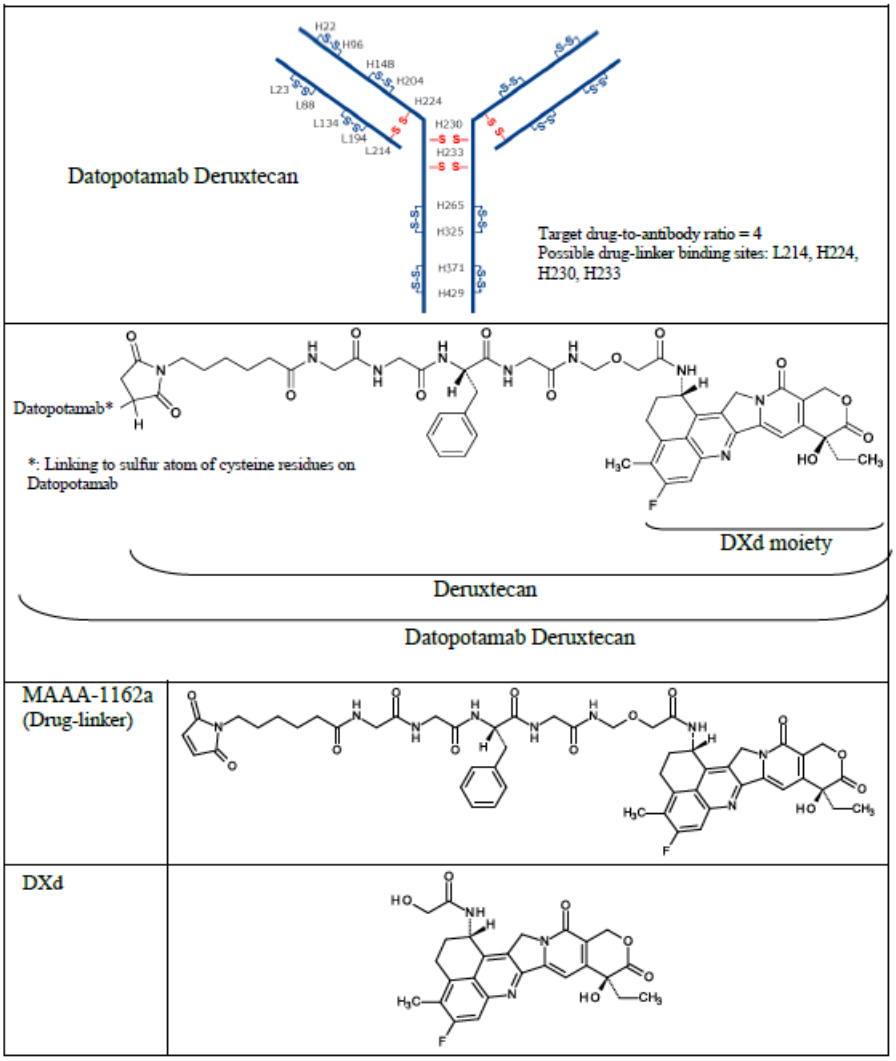
2.5.1. Introduction

Datopotamab deruxtecan is an antibody-drug conjugate (ADC) composed of a humanised anti-trophoblast cell surface antigen (TROP) 2 immunoglobulin G1 monoclonal antibody, datopotamab, covalently linked to the membrane-permeable deoxyribonucleic acid (DNA) topoisomerase I inhibitor DXd via a stable tetrapeptide-based linker. The average drug-to-antibody ration of Dato-DXd is four.

Deruxtecan, the drug-linker compound (MAAA-1162a) is similar to the one used in Enhertu (trastuzumab deruxtecan; publicly available EPAR: EMA/CHMP/636117/2022). Parts of the dossier for datopotamab deruxtecan are therefore identical to those previously submitted as part of the marketing authorisation application dossier for Enhertu.

The following mechanism of action was proposed for datopotamab deruxtecan (Dato-DXd): After binding of datopotamab deruxtecan (Dato-DXd) to TROP2, it undergoes internalisation and intracellular linker cleavage in the lysosomes to release the DXd (MAAA-1181a). DXd induces DNA damage and apoptotic cell death.

Figure 3 Structure of datopotamab deruxtecan (antibody-drug conjugate/Dato-DXd), deruxtecan (drug-linker/MAAA-1162a) and DXd (drug, MAAA-1181a). Please note that the average drug-to-antibody ration of datopotamab deruxtecan is 4.



The recommended dose of datopotamab deruxtecan is 6.0 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

The non-clinical pharmacology program for datopotamab deruxtecan was composed of several primary in vitro and in vivo pharmacodynamic studies to support the anticipated mechanism of action. Secondary pharmacodynamics for the DXd was addressed in vitro in an off-target panel of 86 receptors, channels, transporters or enzymes. Safety pharmacology was evaluated in two dedicated safety studies; a hERG study and an in vivo study in telemetered male cynomolgus monkeys assessing cardiovascular, respiratory and CNS endpoints. Both safety studies were GLP-compliant in accordance to guideline requirement (ICH S7A).

A list of terminology used in the non-clinical dossier is included in the below table.

Table 6 List of terminology specific to the non-clinical dossier.

TERM	DEFINITION
^{14}C-DXd	^{14}C-labeled DXd
Dato	MAAP-9001a; the antibody component of Dato-DXd, a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody, also known as datopotamab
Dato-DXd	DS-1062a; an antibody-drug conjugate comprised of a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug-linker, MAAA-1162a, via thioether bonds; the target drug-to-antibody ratio is 4, also known as datopotamab deruxtecan
DXd	MAAA-1181a; the drug component of Dato-DXd, a derivative of exatecan, a topoisomerase I inhibitor
MAAA-1162a	drug-linker, the complex of DXd and a maleimide tetrapeptide linker
MAAP-9002b	an antibody-drug conjugate comprised of same antibody, linker, and drug as those of Dato-DXd; the average drug-to-antibody ratio was approximately 7.
total anti-TROP2 antibody[a]	the sum of drug conjugated and unconjugated anti-TROP2 antibody

[a] Total anti-TROP2 antibody is referred to as total antibody in the nonclinical study reports.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro pharmacodynamic studies

Target binding activity and specificity of datopotamab deruxtecan (CR16-H0009-R01 and CR16-H0009-R02)

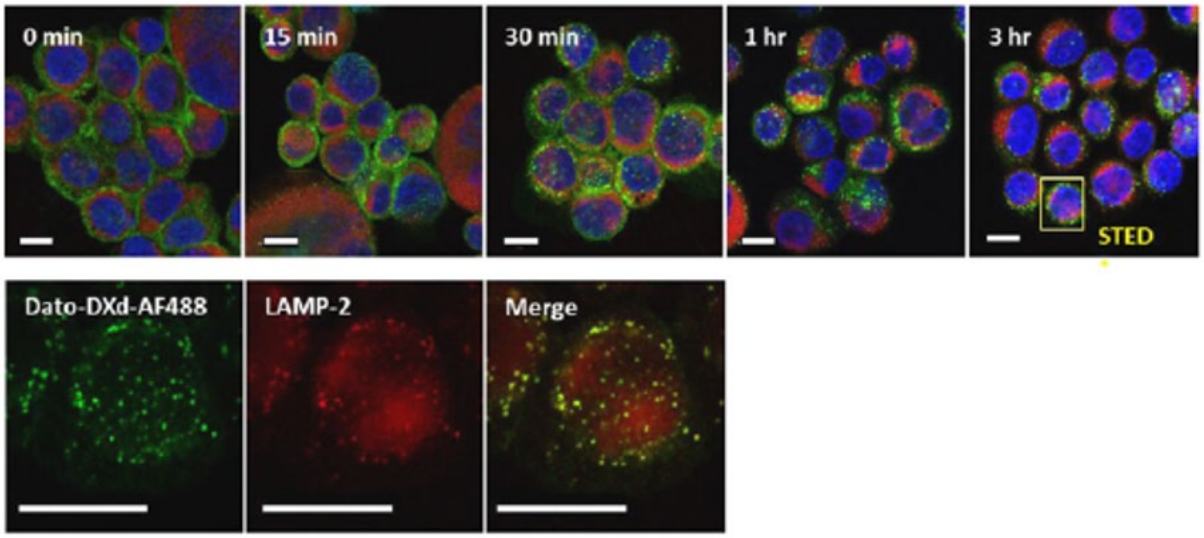
Target binding activity of datopotamab deruxtecan (Dato-DXd) to human TROP family proteins (EpCAM and TROP2) was evaluated by ELISA at doses of 1 µg/mL (CR16-H0009-R01). The study showed, that datopotamab deruxtecan (Dato-Dxd) binds specifically to the intended target TROP2 and not to EpCAM.

Species cross-reactivity and binding affinity were evaluated by ELISA in CHO-K1 cells overexpressing mouse, rat, cynomolgus monkey and human TROP2 (CR16-H0009-R02). Datopotamab deruxtecan (Dato-DXd) specifically bound to both human and cynomolgus TROP2 with EC_{50} (95% CLs) values of 110.42 ng/mL (80.32 to 151.79 ng/mL) and 97.65 ng/mL (77.70 to 122.72 ng/mL), respectively. No binding was seen to mouse or rat TROP2.

Internalisation and trafficking to lysosome (publication by Okajima et al. from 2021)

Datopotamab deruxtecan (Dato-DXd) internalisation and intracellular trafficking to the lysosomes were shown in BxPC3 cells by immunofluorescence imaging (see figure below). BxPC-3 cells treated with Alexa 488-labeled Dato-DXd (green) were co-stained with anti-LAMP2 antibody (red) and DAPI (blue), and analysed by confocal microscopy. Lysosomal transport of datopotamab deruxtecan (Dato-DXd) was illustrated by showing co-localisation of Alexa 488-labeled datopotamab deruxtecan (Dato-DXd) (green) with the lysosomal marker anti-LAMP2 antibody (red) in BxPC-3 cells.

Figure 4 Intracellular trafficking of datopotamab deruxtecan (Dato-DXd) to lysosome



Bars represent 10µm.

Inhibition of cell growth in human tumour cells by datopotamab deruxtecan (CR16-H0009-R03)

The effect of datopotamab deruxtecan (Dato-DXd or DS-1062a), datopotamab (Dato or MAAP-9001a) or the DXd payload (MAAA-1181a) on inhibition of cell growth in two human pancreas adenocarcinoma cell lines (CFPAC-1 and BxPC-3) and one human anaplastic carcinoma cell line (Calu-6) were demonstrated using CellTiter-Glo Luminescent Cell Viability Assay and results were correlated with TROP2 cell line expression determined by flow cytometry using a commercially available fluorescent antibody (Anti-Human Trop2 Alexa Fluor 488). An isotype control IgG-DXd was also included for control.

Datopotamab deruxtecan (Dato-DXd or DS-1062a) showed inhibitory activity in the two human pancreas adenocarcinoma cell lines, CFPAC-1 and BxPC-3, with IC_{50} values of 706 and 74.6 ng/mL. No inhibition was seen in the Calu-6 cell line. This corresponded with CFPAC-1 and BxPC-3 being TROP2 positive (TROP2 expression of 22.1 and 47.9 rMFI, respectively) and Calu-6 negative (1.1 rMFI). Additionally, high TROP2 expression levels appeared to be correlated with low IC_{50} values. All three cell lines (CFPAC-1, BxPC-3 and Calu-6) appeared to be sensitive to the DXd payload (MAAA-1181a) (please see table below).

Table 7 Cell growth inhibitory activity of datopotamab deruxtecan (Dato-DXd), datopotamab (Dato), isotype control IgG-DXd, and DXd, and TROP2 expression in human tumour cells.

Cell Line	IC_{50}				TROP2 Expression (rMFI)
	Dato-DXd (ng/mL)	Dato (ng/mL)	Isotype Control IgG-DXd (ng/mL)	DXd (nmol/L)	
CFPAC-1	706	≥20,000	≥20,000	2.82	22.1
BxPC-3	74.6	≥20,000	≥20,000	1.58	47.9
Calu-6	≥20,000	≥20,000	≥20,000	1.15	1.1

IC_{50} = 50% inhibitory concentration; rMFI = relative geometric mean of fluorescence intensity; TROP2 = trophoblast cell surface antigen 2

Human Topoisomerase 1 inhibitory activity of the DXd payload (CD13-H0072-R05)

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.

Inhibition of topoisomerase I causes cell death. Upon binding to TROP2 and internalisation in the tumour cells, the DXd moiety of deruxtecan (MAAA-1181a) is anticipated to be released from datopotamab deruxtecan (Dato-DXd) and induce cell death of the cell.

The human topoisomerase I inhibitory activity of DXd was evaluated by a topoisomerase I-mediated DNA relaxation assay using supercoiled DNA as a substrate. Recombinant human topoisomerase I was incubated with DXd (MAAA-1181a) at concentrations of 78.125 to 20000 nmol/L for 5 min. Supercoiled pBR322 DNA was then added and incubated at 37°C for 30 minutes. The mixture was electrophoresed on an agarose gel and the amount of the supercoiled DNA was measured.

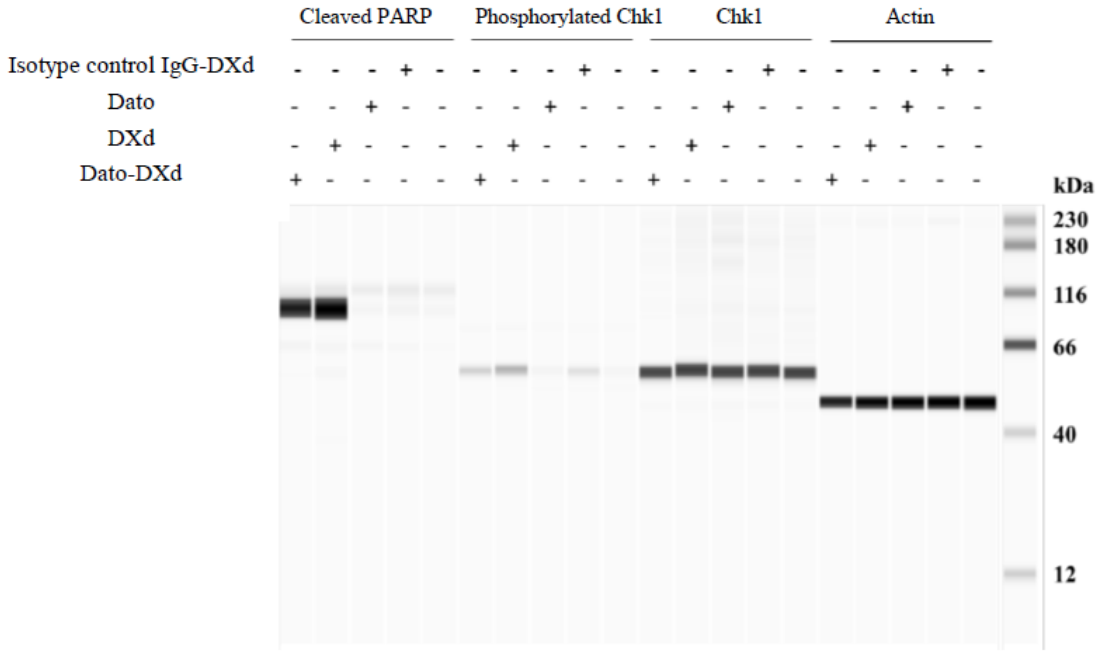
DXd (MAAA-1181a) inhibited the relaxation of supercoiled DNA caused by human topoisomerase I in a dose-dependent manner (IC_{50} value of 3581.19 nmol/L). This result indicated that DXd (MAAA-1181a) has inhibitory activity against human topoisomerase I.

This study has previously been assessed as a part of the marketing authorisation application for Enhertu® and the above study description is therefore harmonised with the EPAR of Enhertu®. Please note, that different terminology was used for the DXd payload, which are described in the study report as MAAA-1181c (CD13-H0072-R05) and in this dossier as MAAA-1181a. However, in the pharmacology written summary p. 9, it was stated that MAAA-1181c is representative of MAAA-1181a or DXd. MAAA-1181c appears to be an acetonitrile-methanol-water solvate of MAAA-1181a.

Induction of DNA damage and apoptosis by datopotamab deruxtecan (CR16-H0009-R04)

Topoisomerase I inhibitors can induce double-strand DNA-breaks leading to apoptosis. Hence, the ability of datopotamab deruxtecan (Dato-DXd), datopotamab (Dato) and the payload DXd to induce DNA damage and apoptosis was demonstrated in a human pancreas adenocarcinoma cell line (CFPAC-1) expressing TROP2 using phosphorylation of Chk1 and cleaved PARP as markers, respectively, in a Simple Western system. For cleaved PARP and phosphorylated Chk1, a strong signal was seen for datopotamab deruxtecan (Dato-DXd) and DXd. No signal was observed for datopotamab (Dato) alone for any of the markers but it should be noted that for phosphorylated Chk1 a positive response was seen for the isotype control antibody IgG-DXd, exhibiting a band intensity slightly weaker than for datopotamab deruxtecan (Dato-DXd) (please see figure below).

Figure 5 Changes in phosphorylated checkpoint kinase 1 (Chk1) and cleaved poly adenosine diphosphate-ribose polymerase (PARP) by treatment with datopotamab deruxtecan (Dato-DXd), isotype control IgG-DXd, datopotamab (Dato), or DXd.



ADC = antibody-drug conjugate; Chk1 = checkpoint kinase 1; DNA = deoxyribonucleic acid; PARP = poly adenosine diphosphate-ribose polymerase
After the CFPAC-1 cells were treated with Dato-DXd (10 μg/mL), DXd (10 nmol/L), Dato (10 μg/mL), or isotype control IgG-DXd (10 μg/mL) for 3 days, DNA damage and apoptosis were evaluated by the detection of phosphorylated Chk1 (56 kDa) and cleaved PARP (89 kDa) using the Simple Western system. The expression levels of total Chk1 (56 kDa) and Actin (45 kDa), which were used as internal controls, were also confirmed.

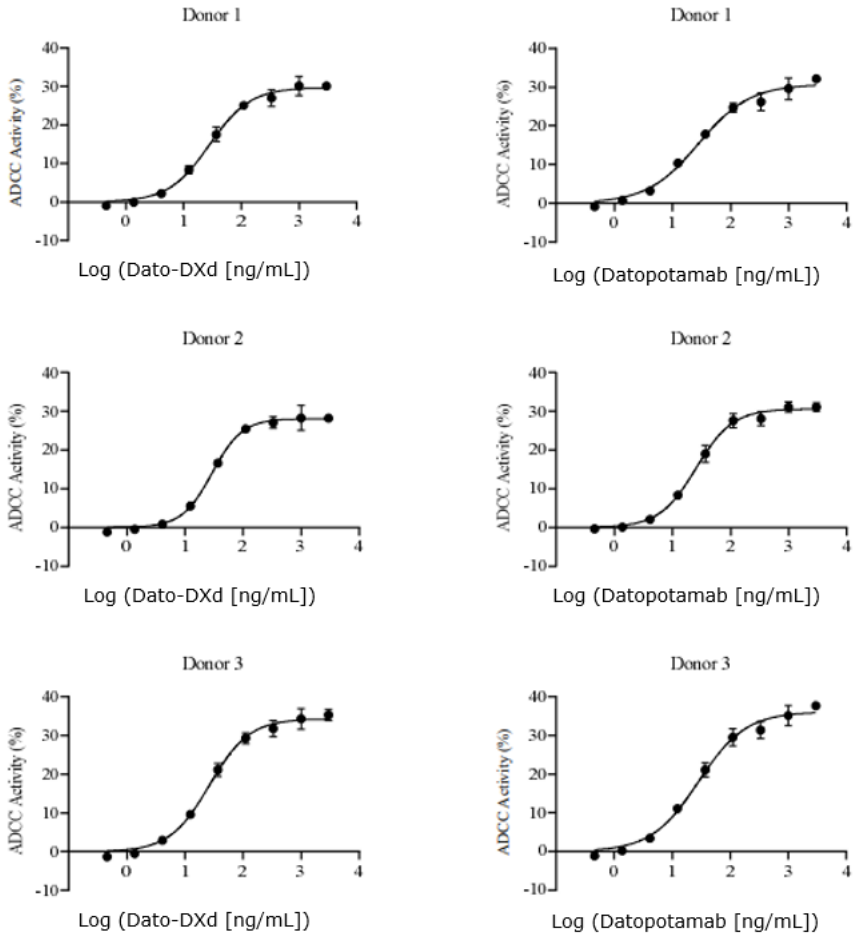
Antibody-dependent cellular cytotoxic activity of datopotamab deruxtecan

Datopotamab deruxtecan (Dato-DXd or DS-1062a) exhibited cytotoxic activity against human lung cancer NCL-H322 cells expressing TROP2 in the presence of human peripheral blood mononuclear cells (hPBMCs), with EC_{50} of 5.27 and 10.8 ng/mL.

Please note, that values from the donor of 206 ng/mL (95% CI: 9.09 to 4660 ng/mL) and 25.1%, was considered unreliable due to the large CI. The percentage of NK cell in the hPBMCs was 11-21.8% in the tree donors.

A new study was conducted showing that datopotamab (MAAP-9001a) and datopotamab deruxtecan (Dato-DXd) exhibited ADCC activity of similar magnitudes against TROP2-exprssing NCI-H322 cells in the presence of human PBMCs within a timeframe of 4 h (Study no. CY19-h0004-R04). The study was conducted following the same principles as the previously conducted study but now including both the conjugated and unconjugated antibody i.e. datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a). No negative control (IgG or IgG-DXd) was included in this new study but results from the previous study showed no cytotoxic effect of IgG-DXd within the 4 h timeframe.

Figure 6 ADCC activity of datopotamab deruxtecan (Dato-DXd) and datopotamab against TROP2-expressing NCI-H322 cells (study no. CY19-h0004-R04). Each point represents the mean and standard deviation of three wells.

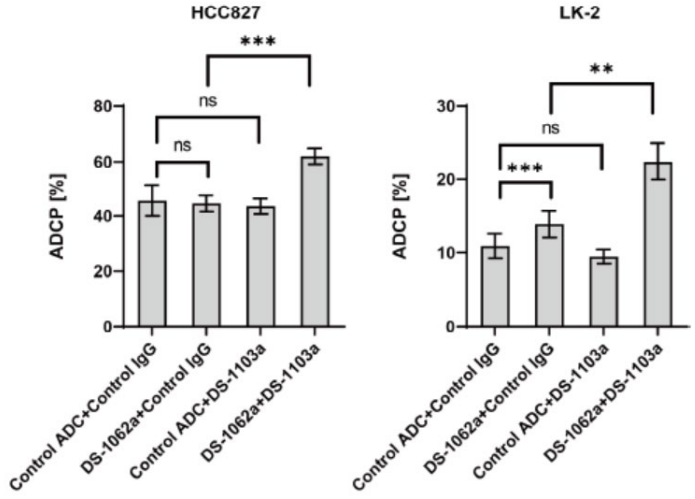


Antibody-dependent cellular phagocytotic activity of datopotamab deruxtecan (DS1062-237-R03)

The study (study no. DS1062-237-R03) was conducted to evaluate antibody-dependent cellular phagocytosis (ADCP) activity against human lung cancer cells treated with DS-1062a (datopotamab deruxtecan, Dato-DXd) in the presence or absence of DS-1103a using human monocyte-derived macrophages. DS-1103a is a humanized monoclonal antibody against human signal regulatory protein α (SIRPα) designed to block the interaction between SIRPα and CD47, which enhances antibody-dependent cellular phagocytosis (ADCP) against cancer cells in the presents of an Fc-active antitumor antibody.

Two TROP2-expressing human lung cell lines, HCC827 (high TROP2-expression) and LK-2 (low TROP2-expression), were included in the study. Datopotamab deruxtecan (dato-DXd or DS-1062a at 2000 ng/mL) alone failed to induce ADCP against HCC827 (TROP2-high), whereas addition of DS-1103a (10 µg/mL) significantly induced ADCP against HCC827 cells. However, in LK-2 (TROP2-low) cells datopotamab deruxtecan (Dato-DXd or DS-1062a at 2000 ng/mL) alone induced ADCP and addition of DS-1103a (10 µg/mL) further significantly enhanced ADCP against LK-2 cells (see figure below).

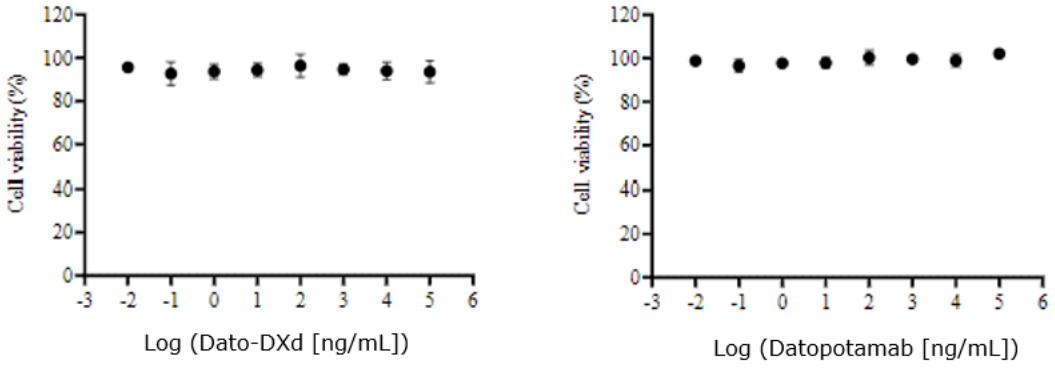
Figure 7 Datopotamab deruxtecan in combination with DS-1103a induced ADCP in human lung cancer cells. ADCP, antibody-dependent cellular phagocytosis; ADC, antibody-drug conjugate; Control ADC, isotype control ADC for DS-1062a (2000 ng/mL); Control IgG, isotype control for DS-1103a (10 µg/mL); DS-1062a, TROP2-targeted antibody-drug conjugate (2000 ng/mL); DS-1103a, anti-human SIRPα antibody (10 µg/mL)



Complement-dependent cytotoxic (CDC) activity of datopotamab deruxtecan (Dato-DXd) and datopotamab (CY19-H0004-R06)

The study evaluated complement-dependent cytotoxic (CDC) activity of datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a) in the presence of human complement using a bronchioalveolar carcinoma cell line NCI-H322 expressing human TROP2 on the cell surface. The IC_{50} values of datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a) against NCI-H322 cells in the presence of human complement were both >100000 ng/mL with a mean cell viability of 93.5 and 102.1%, respectively (please see figure below). Rituximab was used as positive control with a the IC_{50} value of 1209 ng/mL against Ramos cells in the presence of human complement. No known negative control was included. The study concluded, that neither datopotamab deruxtecan (Dato-DXd or DS-1062a) nor datopotamab (MAAP-9001a) showed CDC activity against NCI-H322 cells at concentrations up to 100,000 ng/mL.

Figure 8 Cell viability of NCI-H322 cells treated with datopotamab deruxtecan (Dato-DXd) and datopotamab (MAAP-9001a) with human complement



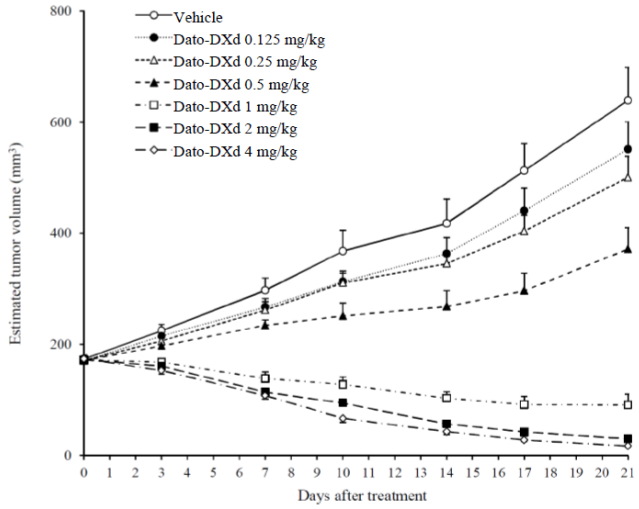
In vivo pharmacodynamic studies

Four in vivo studies were performed with datopotamab deruxtecan (Dato-DXd) administered intravenously to nude mouse xenograft models of human pancreatic cancer, non-small cell lung cancer (NSCLC) and breast cancer, with the two latter being in line with the sought indications. All xenograft

models were constructed using TROP2 expressing tumour cell lines. It was noted that all in vivo studies were conducted in only female mice (n = 6/group). This is considered acceptable, as no gender difference in exposure is expected (please see the Pharmacokinetic section).

In the mouse xenograft model of human pancreatic cancer (CFPAC-1), the primary focus was to determined dose-dependency of the anti-tumour activity by testing several doses of datopotamab deruxtecan (Dato-DXd) from 0.125 to 4 mg/kg and using vehicle as control. A significant effect on tumour growth inhibition of 41.9, 85.7, 95.3 and 97.3% was noted at dose of 0.5, 1, 2 and 4 mg/kg, respectively (below figure). Hence, datopotamab deruxtecan (Dato-DXd) showed a dose-dependent antitumor activity with the most marked effect from doses ≥ 1 mg/kg. However, no exposure measurements were reported for the different doses.

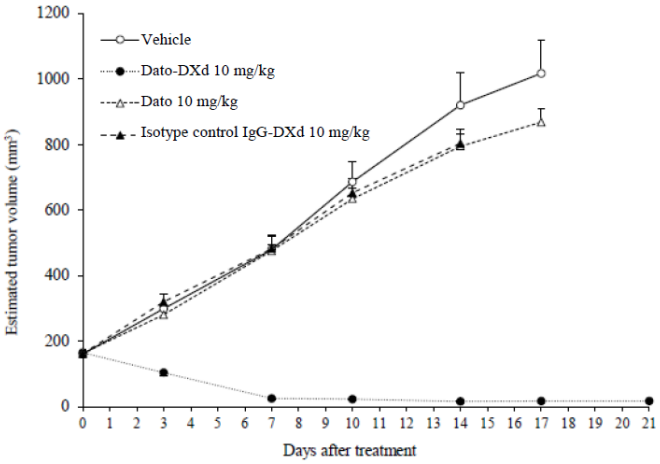
Figure 9 Antitumor activity of Dato-DXd against human pancreatic cancer cell line CFPAC-1 xenografted nude mice (dose-dependency study).



The mean estimated tumor volume and standard error (n = 6) are represented on the graph.

In two mouse xenograft models of non-small cell lung cancer (NSCLC) using the TROP2 expressing cell lines NCI-H292 and HCC827 without and with actionable genomic alterations (AGAs), respectively, datopotamab deruxtecan (Dato-DXd) at doses of 10 mg/kg significantly inhibited tumour growth compared to vehicle by 98.3% and 82.8%, respectively (see figure 9 below as a representative example). No significant inhibitory effect of datopotamab (Dato) or isotype control IgG-DXd were seen. Similar results, with a tumour growth inhibition of 96.1% were demonstrated in the breast cancer (BC) xenograft model of the TROP2 expressing HCC1806 cell line at doses of 10 mg/kg datopotamab deruxtecan (Dato-DXd).

Figure 10 Antitumor activity of Dato-DXd against human Non-Small Cell Lung Cancer cell line NCI-H292 xenografted nude mice.



The mean estimated tumor volume and standard error (n = 6) are represented on the graph.

2.5.2.2. Secondary pharmacodynamic studies

In a secondary pharmacodynamic study, testing DXd against an off-target panel of 86 receptors, channels, transporters or enzymes, no significant response (≥ 50% inhibition) was demonstrated at concentrations of 10 µmol/L (approximately 5000 ng/mL). The tested concentration provided > 1500-fold to the reported highest human C_{max} of 3.13 ng/mL (cycle 1). This study was conducted for the DXd payload alone and not for the full antibody drug conjugate (ADC). The study has previously been submitted and assessed as part of the market authorisation application for Enhertu (EMA/CHMP/636117/2022). In the screening report, the test substance is referred to as MAAA-1181d, whereas the active drug is named MAAA-1181a. MAAA-1181d is the monohydrate of MAAA-1181a.

2.5.2.3. Safety pharmacology programme

Two dedicated safety pharmacology studies were performed. A hERG study (study no. SBL315-029) and an in vivo study (study no. IP16220) with telemetered male cynomolgus monkeys assessing cardiovascular, respiratory and CNS endpoints. Both studies were GLP-compliant in accordance with ICH S7A.

The cardiovascular safety of the DXd payload was evaluated in an in vitro hERG study in transfected CHO-cells at concentrations of 1, 3 and 10 µmol/L (SBL315-029), showing no effect of DXd on hERG current at any of the tested concentrations. The tested maximum concentration provided > 1500-fold to the clinically relevant exposure of DXd, concluding that no effect of DXd on hERG K+ channels were expected at clinically relevant doses of datopotamab deruxtecan (Dato-DXd).

In the hERG study report (SBL315-029), the test substance is referred to as MAAA-1181d, whereas the active drug is named MAAA-1181a. MAAA-1181d is the monohydrate of MAAA-1181a. Furthermore, it should be noted that the hERG study has previously been submitted and assessed as part of the market authorisation application for Enhertu (EMA/CHMP/636117/2022).

Cardiovascular, respiratory and CNS endpoints were evaluated in a dedicated safety pharmacology study in telemetered male cynomolgus monkeys (n= 5) after intravenous administration of a single dose of 10 or 80 mg/kg datopotamab deruxtecan (Dato-DXd) (IP16220). Heart rate, blood pressure (systolic, diastolic, and mean), ECG parameters (PR interval, QRS duration, QT interval, and QTc interval), frequency of arrhythmia, physical condition, respiratory rate, blood gas parameters (partial

pressure of oxygen and carbon dioxide, pH, and oxygen saturation), body temperature, functional observational battery (FOB) method parameters, body weight and food consumption were monitored and no changes were seen at either dose level. Hence, concluding that datopotamab deruxtecan (Dato-DXd had no effect on the cardiovascular, respiratory and central nervous systems at single doses up to 80 mg/kg.

It was noted that only male monkeys were used in the safety pharmacology study but this was sufficiently justified due to the availability of better background data in male animals. More importantly, no significant gender differences were noted in exposure or target organs of toxicity as confirmed in the pharmacokinetic and toxicology sections.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted.

The omission of pharmacodynamic drug interaction studies is accepted, as no drugs with a likely pharmacodynamic interaction are anticipated to be co-administered with datopotamab deruxtecan (Dato-DXd).

2.5.3. Pharmacokinetics

The Dato-DXd and total anti-TROP2 antibody concentrations in rat and cynomolgus monkey plasma were determined with validated LBA methods. ADA in rat and monkey plasma were detected with validated ECL methods. The DXd concentrations in the samples were determined with validated LC-MS/MS methods. The below table outlines these validated analytical methods.

Table 8 Validation of Analytical Methods

Analyte	Assay Method	Matrix	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)
Dato-DXd[a] and total anti-TROP2 antibody[b]	LBA	Rat and monkey plasma	10.0 to 7500	10.0
Anti-Dato-DXd antibody	ECL	Rat and monkey plasma	NA	NA
DXd	LC-MS/MS	Human and mouse plasma, and buffer	0.100 to 20.0	0.100
	LC-MS/MS	Plasma supernatant (mouse, rat, monkey, human)	0.100 to 20.0	0.100
	LC-MS/MS	Rat plasma	0.100 to 20.0	0.100
	LC-MS/MS	Monkey plasma	0.100 to 20.0	0.100
	LC-MS/MS	Rat and monkey plasma	0.100 to 20.0	0.100

ECL = electro-chemiluminescence; LBA = ligand binding assay; LC-MS/MS = liquid chromatography-tandem mass spectrometry; LLOQ = lower limit of quantification; NA = not applicable
[a] Dato-DXd was referred to MAAP-9002a in the report.
[b] Total anti-TROP2 antibody was referred to total antibody in the report.

The validation of the analytical methods for determination of DXd in animal plasma using LC-MS/MS was already included as part of the Enhertu procedure (trastuzumab deruxtecan; publicly available EPAR: EMA/CHMP/636117 /2022). Validation data was also provided for the ligand binding assay, determining datopotamab deruxtecan (Dato-DXd) and total anti TROP2 antibody in rat and monkey plasma. Overall, the methods are considered robust and adequate for analysing plasma samples that

have been stored no more than 3 months (92 days) at -80℃ or after 5 freeze/thaw cycles. Incurred sample reanalysis was found to comply with guidelines in the assessed pivotal studies. The presence of ADAs against datopotamab deruxtecan in serum samples from rats and monkeys was furthermore determined using an electrochemiluminescent (ECL) assay.

2.5.3.1. Absorption

Following single IV dosing in male cynomolgus monkeys of doses between 0.2-6 mg/kg, datopotamab deruxtecan (Dato-DXd) exposure increased dose-dependently and a terminal elimination half-life (t½) of ~1.5-2 days was observed. The volume of distribution was low (38-43 ml/kg), as expected for an antibody and indicative of plasma only distribution. In addition, TK parameters of DXd (MAAA-1181a) dosing were evaluated upon weekly (QW) administration in a rat and monkey 4-week study. TK investigations showed that datopotamab deruxtecan exposure also increases dose-proportionally following repeat dosing of 20-200 mg/kg in rats and 10-80 mg/kg in monkeys, respectively. Linear PK has also been established in humans in the dosing range 4-10 mg/kg. DXd t½ was found to be much lower (0.6 – 4 hrs) after DXd dosing in animals than when dosing with Dato-DXd in humans. No significant sex differences were observed and datopotamab deruxtecan exposure did not accumulate over time. No significant differences in PK parameters were observed between datopotamab deruxtecan and the total anti-TROP2 antibody either following single or repeated dosing. The 3-months intermittent IV dosing study in monkeys confirmed that remaining levels of datopotamab deruxtecan, total anti-TROP2 antibody and DXd were almost completely eliminated at day 57 of the recovery period. Anti-DatoDXd antibodies (ADAs) were detected in several animals in both the rat and monkey multiple dose studies. ADA-positive animals showed declined levels (or BLQ) of Dato-DXd combined with increased (up to 60-fold) plasma DXd- levels at the 4th dosing period. ADA formation was observed in the low dose groups (10 mg/kg) in monkeys after the last dosing and significantly decreased the exposure values for datopotamab deruxtecan. In all other dose groups, ADA formation was however generally limited and it is considered to not affect the overall PK profile in monkeys. Only 1 incidence of ADA formation was observed in rats in treated animals (1 male at 20 mg/kg). However, 4 incidences of ADA-formation were observed in control- and treated groups prior to treatment with the compound, which may suggest an unspecific assay for detecting ADAs. When rats and monkeys were repeatedly dosed with DXd alone, exposure increased dose-proportionally and no sex differences or accumulation was observed.

2.5.3.2. Distribution

Studies on distribution to tissues and blood cells and plasma protein binding have been carried out for DXd. The tissue distribution studies are novel, but the dedicated studies on plasma protein binding and blood cell distribution have previously been assessed as a part of the marketing authorisation application for Enhertu. The study descriptions and results are harmonised with the publicly available EPAR of Enhertu (EMA/CHMP/636117/2022).

Tissue distribution was measured in vivo after single intravenous administration of 1 mg/kg ^{14}C-labeled DXd to non-fasted male Sprague Dawley rats and to non-fasted male cynomolgus monkeys (below tables). Radioactivity was quickly and widely distributed and cleared quickly as ^{14}C-DXd levels peaked in the majority of tissues within 0.25 or 1 h post-dose, except for the gastrointestinal and excretory organs. In the rat the radioactivity in brain, lens, and spinal cord were below limit of quantification (BLQ) at all time points, and in the monkey the anterior chamber, brain, cornea, lens, pituitary gland, spinal cord, and vitreous humor.

Table 9 Radioactivity Concentrations in Plasma and Tissues after Single Intravenous Administration of 14C-labeled DXd to Non-fasted Male Sprague Dawley Rats

Tissues/Organs	[14C]DXd (ng equiv/g) Hours post-dose						
	0.25	2	4	8	24	48	96
Plasma (LSC)	142	13.3	8.52	6.37	3.90	BQL	BQL
Blood (LSC)	94.8	8.82	5.41	4.21	2.53	BQL	BQL
Blood (cardiac)	114	BQL	BQL	BQL	BQL	BQL	BQL
Adrenal cortex	251	10.5	6.19	BQL	14.2	BQL	BQL
Adrenal gland	248	10.6	6.60	BQL	12.4	BQL	BQL
Adrenal medulla	250	10.4	6.98	BQL	6.18	BQL	BQL
Aorta	347	9.60	9.39	BQL	BQL	BQL	BQL
Bile (in duct)	43302	918	56.5	54.4	48.8	BQL	BQL
Bone (femur)	103	7.91	5.18	6.99	8.07	BQL	BQL
Bone marrow (femur)	216	23.1	6.09	BQL	BQL	BQL	BQL
Brown fat	182	8.88	5.75	BQL	BQL	BQL	BQL
Cecum contents	37.0	488	886	12728	933	77.9	7.66
Cecum mucosa	168	26.9	94.8	1100	45.5	5.17	BQL
Epididymis	139	BQL	BQL	BQL	BQL	BQL	BQL
Esophagus wall	215	15.8	BQL	BQL	BQL	BQL	BQL
Ex-orbital lachrymal gland	296	12.4	BQL	BQL	BQL	BQL	BQL
Eye	50.2	BQL	BQL	BQL	BQL	BQL	BQL
Harderian gland	402	79.3	35.5	BQL	BQL	BQL	BQL
Heart	176	6.01	6.07	BQL	BQL	BQL	BQL
Intra-orbital lachrymal gland	295	11.0	BQL	BQL	BQL	BQL	BQL
Kidney	737	32.3	21.0	11.3	13.7	8.60	10.1
Kidney cortex	538	32.5	29.5	13.1	16.9	11.3	11.3
Kidney medulla	915	31.4	8.52	9.39	9.25	BQL	7.43
Large intestine contents	335	51546	54887	57973	2464	77.2	BQL
Large intestine wall	127	4931	8490	20420	104	26.3	BQL
Liver	656	46.1	23.9	18.6	11.7	BQL	BQL
Lung	253	18.1	BQL	BQL	BQL	BQL	BQL
Lymph node (cervical)	270	29.0	BQL	BQL	BQL	BQL	BQL
Meninges	36.6	5.27	BQL	BQL	BQL	BQL	BQL
Muscle (femoral)	264	18.4	BQL	BQL	BQL	BQL	BQL
Nasal turbinates	42.8	BQL	BQL	BQL	BQL	BQL	BQL
Non-pigmented skin	206	99.7	104	87.8	72.6	5.72	5.22
Oral mucosa	157	6.08	5.73	BQL	BQL	BQL	BQL
Pancreas	361	32.6	14.0	8.62	6.65	BQL	BQL
Pituitary gland	413	17.1	BQL	BQL	BQL	BQL	BQL
Prostate	249	98.9	22.3	19.3	7.86	BQL	BQL
Salivary gland	178	15.0	8.93	BQL	BQL	BQL	BQL
Seminal vesicle	91.3	13.4	31.5	BQL	BQL	BQL	BQL
Small intestine contents	44946	9328	316	148	1097	BQL	BQL
Small intestine wall	14489	618	83.3	117	61.4	BQL	BQL
Spleen	207	21.7	45.6	BQL	BQL	BQL	BQL
Stomach contents	BQL	16.5	19.9	9.46	1935	BQL	BQL
Stomach wall (glandular)	164	29.0	13.2	7.61	24.4	BQL	BQL
Stomach wall (non-glandular)	85.1	12.7	BQL	11.1	7.19	5.45	BQL
Testis	28.8	BQL	BQL	BQL	BQL	BQL	BQL
Thymus	161	48.3	7.20	BQL	BQL	BQL	BQL
Thyroid gland	177	18.9	11.6	BQL	BQL	BQL	BQL
Trachea	60.5	BQL	BQL	BQL	BQL	BQL	BQL

Tissues/Organs	[14C]DXd (ng equiv/g) Hours post-dose						
	0.25	2	4	8	24	48	96
Urinary bladder contents	39983	832	58.2	75.8	8.56	BQL	BQL
Urinary bladder wall	3372	855	21.4	117	59.2	BQL	BQL
Uveal tract	67.5	BQL	BQL	BQL	BQL	BQL	BQL
White fat (inguinal)	77.3	5.90	BQL	BQL	BQL	BQL	BQL

BQL: below the quantifiable limit; NC: not calculated: LLC: liquid scintillation counting; LLOQ: lower limit of quantification. BQL = <LLOQ for QWBA = <5.11 ng equiv/g; BQL = <LLOQ for LSC = <1.31 ng equiv/g (plasma) or <2.31 ng equiv/g (blood).

N=7M; one animal per timepoint for QWBA; blood collected from all by cardiac puncture under anesthesia.

Table 10 Radioactivity Concentrations in Plasma and Tissues after Single Intravenous Administration of ^{14}C-labeled DXd to Non-fasted Male Cynomolgus Monkeys

Tissues/Organs	[14C]DXd (ng equiv/g) Hours post-dose				
	1	8	24	48	96
Plasma (LSC)	65.7	12.2	10.4	6.00	3.23
Blood (LSC)	39.6	7.30	5.23	4.01	3.14
Blood (cardiac)	74.8	11.7	BQL	BQL	BQL
Adrenal cortex	101	18.4	BQL	BQL	BQL
Adrenal gland	102	18.3	BQL	BQL	BQL
Adrenal medulla	98.7	18.0	BQL	BQL	BQL
Aorta	146	7.72	BQL	BQL	BQL
Bile (in gall bladder)	86485	22405	1138	545	BQL
Bone (femur)	15.3	BQL	BQL	BQL	BQL
Bone marrow (femur)	33.2	14.8	11.9	9.53	BQL
Brown fat	346	11.6	BQL	BQL	BQL
Cecum contents	59.4	91853	42171	684	46.2
Cecum mucosa	91.7	329	11441	763	BQL
Epididymis	98.1	112	9.37	BQL	BQL
Esophagus wall	85.2	42.0	28.4	18.4	7.85
Ex-orbital lachrymal gland	86.0	28.3	26.7	9.83	BQL
Eye - Choroid	130	BQL	BQL	BQL	BQL
Eye - Ciliary body	227	BQL	BQL	BQL	BQL
Eye - Iris	15.9	BQL	NS	BQL	NS
Eye - Retina	75.5	BQL	BQL	BQL	BQL
Eye - Sclera	179	BQL	BQL	BQL	BQL
Eye - Uveal tract	132	BQL	BQL	BQL	BQL
Eye - Whole	26.0	BQL	BQL	BQL	BQL
Gallbladder	4714	189	174	20.2	BQL
Heart	50.6	BQL	BQL	BQL	BQL
Intra-orbital lachrymal gland	16.7	BQL	BQL	BQL	BQL
Kidney	799	142	202	96.4	74.8
Kidney cortex	875	193	242	133	104
Kidney medulla	471	52.1	128	13.9	11.9
Large intestine wall	96.7	1682	42357	BQL	BQL
Liver	497	69.5	43.5	17.5	20.2
Lung	84.0	13.4	BQL	BQL	BQL
Lymph node (cervical)	57.1	BQL	BQL	BQL	BQL
Meninges	41.7	13.4	BQL	BQL	BQL
Muscle (femoral)	30.1	14.7	BQL	BQL	BQL
Nasal turbinates	71.0	11.4	BQL	BQL	BQL
Oral mucosa	91.3	93.8	25.6	17.1	BQL

Tissues/Organs	[14C]DXd (ng equiv/g) Hours post-dose				
	1	8	24	48	96
Orbital area	72.4	BQL	BQL	BQL	BQL
Pancreas	103	29.6	61.6	10.7	BQL
Pigmented skin	296	36.1	BQL	BQL	BQL
Prostate	73.2	24.4	BQL	BQL	BQL
Salivary gland	95.7	14.1	11.2	BQL	BQL
Seminal vesicle	80.3	201	BQL	BQL	BQL
Small intestine wall	31436	1418	46.2	14.4	10.4
Spleen	53.4	19.9	11.3	10.9	7.49
Stomach wall (glandular)	120	20.8	49.1	19.2	7.60
Stomach wall (non-glandular)	64.7	6.99	7.37	BQL	BQL
Testis	44.2	53.5	20.3	6.72	BQL
Thymus	64.9	14.1	BQL	BQL	BQL
Thyroid gland	41.8	23.9	BQL	BQL	BQL
Trachea	69.2	BQL	BQL	BQL	BQL
Urinary bladder wall	1247	1054	22.4	20.0	BQL
White fat (inguinal)	235	113	106	BQL	BQL

BQL: below the quantifiable limit; NC: not calculated: LLC: liquid scintillation counting; LLOQ: lower limit of quantification. BQL = <LLOQ for QWBA = <6.64 ng equiv/g; BQL = <LLOQ for LSC = <1.26 ng equiv/g (plasma) or <0.577 ng equiv/g (blood).
N=5; one animal per timepoint for QWBA; blood collected from all animals just prior to euthanasia.

The radioactivity was located mainly to the large and small intestine walls, the cecum mucosa, gallbladder, kidney, urinary bladder wall and liver in both species. By the end of sampling, the radioactivity in most tissues had declined in proportion to that in blood, or the count rate had decreased by half between sampling intervals, indicating that there was no obvious retention in these tissues. One notable exception was the renal retention observed in rats between sample intervals 24h-48h-96h with no change in measured radioactivity. Similar observation was made in monkeys between 48h and 96h. There was no noteworthy distribution to pigmented tissue and thus no indications of relevant melanin binding. Limited amounts of radioactivity were distributed to male reproductive organs, which was cleared over time. As the study was only conducted in male rats, no data has been generated to investigate distribution to female reproductive organs. In general, limited correlation was observed between tissue site of distribution and the identified target organs for toxicities. Rather, data indicates that organ toxicities correlate with pharmacological inhibition of TROP family proteins, specifically targeting mucosal tissue and excretory organs such as gastrointestinal tract, liver, eye, skin and oesophagus, kidneys, reproductive organs and bone marrow.

The in vitro plasma protein binding of DXd was determined in mice, rats, monkeys, and humans. DXd exhibited high plasma protein binding in the mouse (90.3 - 92.5%), rat (94.2 - 96.7%), monkey (86.5 - 89.1%) and human (96.8 - 98.0%). Unbound DXd plasma concentration appeared app. 2- and 5-fold lower in human plasma as compared to plasma in animals. The plasma protein binding ratios of DXd tended to decrease with the increasing concentration over the tested concentration range in all species tested, but plasma binding remained high.

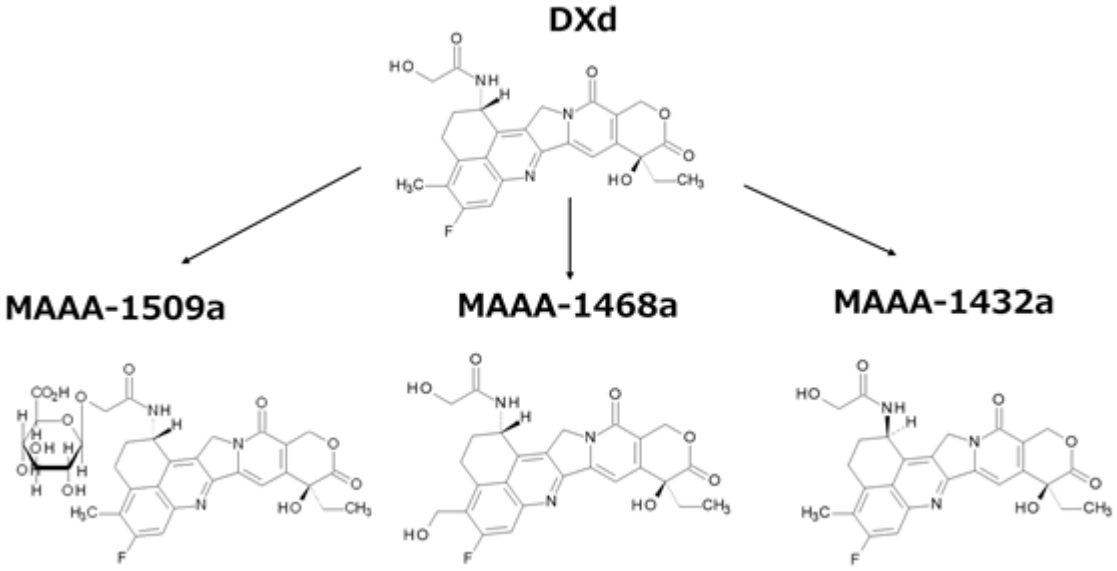
The in vitro distribution to blood cells and the blood/plasma (B/P) ratios of DXd was examined in mouse, rat, monkey, and human blood. Distribution to blood cells ranged from 13.0% and 17.7% in humans and was about 2-fold lower as compared to animals. B/P ratios were below 1 and indicated that DXd primarily was found in the plasma fraction. In summary, data in humans and animals showed limited distribution to blood cells.

No dedicated tissue distribution studies in pregnant animals were conducted and the extend of placental transfer of DXd into foetal tissues is unknown.

2.5.3.3. Metabolism

Release rates of DXd from datopotamab deruxtecan (Dato-DXd) appear to be stable, though a gradual increase in release rate was observed through the 21-days incubation period in mouse, rat, monkey, and human plasma, where release was highest in human and monkey plasma. In vitro tests demonstrate that DXd is stable against UGT enzymes in rat, monkey, and human liver microsomes. Using human CYP-expressing microsomes and human liver microsomes, it was demonstrated CYP3A4 is the primary CYP isoform involved in the metabolism of DXd, while CYP2C8 may play a minor role. DXd was the major radioactive component in urine, feces, and bile in rats and monkeys following single IV administration. Only a minor unidentified metabolite (1.1 %) was observed in feces in rats while nothing was observed in urine or bile. In monkeys, 3 minor metabolites were identified, primarily in feces (1.1% MAAA-1432a, an epimer of DXd) or bile (1.8% MAAA-1468a, a monoxide of DXd and 1.1% MAAA-1509a, a glucuronide of DXd). The proposed metabolic pathway of DXd is shown in the figure below. Of note, the metabolism profile in animals was only investigated in excreta over the course of either 6 or 24 hours and has not been determined in plasma from animals nor humans.

Figure 11 Proposed metabolic pathway of DXd



2.5.3.4. Excretion

Excretion of ^{14}C-DXd was determined in four mass balance studies in non-fasted male Sprague Dawley rats and male Cynomolgus monkeys both non-cannulated and cannulated using 1 mg/kg. The rat studies have previously been assessed as a part of the marketing authorisation application for Enhertu. The study descriptions and results related to the rat studies are harmonised with the publicly available EPAR of Enhertu (EMA/CHMP/636117/2022).

Following a single intravenous administration of 1 mg/kg ^{14}C-DXd in rats, more than 90% of the administered radioactivity was excreted from the body within 48 h. The results indicate that the major excretion route is through the faeces, accounting for 70% of the observed excreted radioactivity. Upon further assessment in cannulated rats, the majority of ^{14}C-DXd (72%) was found excreted through the bile and supports the presence of enterohepatic recycling. Up to 27% was excreted in urine while negligible amounts were recovered in the expired air, gastro-intestinal contents and carcass. Biliary excretion of DXd in rats was fast, reaching maximal levels within the 0 – 4 h collection interval.

In monkeys, a single intravenous administration (1 mg/kg) of ^{14}C-DXd confirmed faeces as the major excretion route, accounting for 62% of the observed excreted radioactivity. The presence of

enterohepatic recycling of ^{14}C-DXd seen in rats was also supported in cannulated monkeys, and biliary excretion was found to be similarly fast to that in rats, reaching maximal levels of 71% within the 0 – 6 h collection interval. Minor amounts of radioactivity were recovered in urine and through cage remains, amounting to 12% or less.

Table 11 Excretion data of ^{14}C-DXd: Cumulative excretion of radioactivity (% of dose)

Species	Study/Anal.	N/ sex	Dose (mg/ kg)	Rou te	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Other sources (% dose)	Recovery (% dose)	Time (h)
Rat	^{14}C-MAAA-1181a	3M	1	*IV*	27.2 ±2.7	**70.4** ±3.1		0.1[a]	**97.7** ±0.5	168
Rat BDC	^{14}C-MAAA-1181a	3M	1	*IV*	21.9 ±3.1	2.7 ±0.7	**71.6** ±3.4	0.4[b]	**96.6** ±1.0	48
Monkey	^{14}C-MAAA-1181a	3M	1	*IV*	5.41 ±5.62	**61.8** ±3.8		10.0[c, e]	**77.2** ±9.4	96
Monkey BDC	^{14}C-MAAA-1181a	4M	1	*IV*	4.78 ±3.41	0.1 ±0.1	**70.7** ±8.1	6.9[d, e]	**82.5** ±9.3	72-96

[a]expired air: 0.1 ±0.0; carcass: 0.0, [b]gastro-intestinal contents (0.2 ± 0.2); carcass (0.2 ± 0.3), [c]cage rinse: 5.51 (4.74); cage debris: 4.32 (0.56); cage wash: 0.18 (0.10), [d]cage rinse: 6.43 (1.19); cage wipe: 0.46 (0.14); bile wipe: 0.01 (-); [e] results from other sources in monkeys were considered part of the urine results. BDC=Bile duct-cannulated. Data is expressed as the mean ± standard deviation.

Unchanged DXd was the predominant radioactive component excreted, accounting for more than 80% in the analysis samples collected from excreta up to 6 h and 24 h post-dose. Possible gender related differences in biliary excretion were not assessed, as only male animals were included in the mass balance studies. However, no differences in pharmacokinetics nor in systemic exposures were noted between sexes in relevant studies. Overall the excretion profile in rats and monkeys is considered translatable to humans. Excretion into milk in lactating animals was not assessed.

2.5.3.5. Other pharmacokinetic studies

A rat PK study was conducted to support the transition from the early drug development batch, DS Process-1 used in non-clinical and early clinical studies, to DS Process-2 which has been used in Phase 2/3 studies. The PK of Dato-DXd, total antibody, and DXd was investigated after single IV administration of two drug substances of Dato-DXd (DS Process-1 [TC105] or DS Process-2 [TC202]) at 10 mg/kg to male rats (n = 5/group). The plasma Dato-DXd, total antibody, and DXd concentrations as well as ADA were measured predose and at designated postdose time points (0.25 and 7 hours, and 1, 3, 7, 14, and 21 days postdose). The value for AUC of DS Process-2 was similar to that of DS Process-1. The plasma concentrations of DXd were all below the lower limit of quantification. Anti-drug antibodies for both drug substances were not detected through 21 days after administration in any of the animals. No apparent differences in PK parameters were observed between batches.

2.5.4. Toxicology

A comprehensive toxicology programme for datopotamab deruxtecan was conducted in line with ICH guidelines S9, S6(R1) and other relevant ICH guidelines, and in member countries of the OECD Mutual Acceptance Data program in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice.

For safety assessment of datopotamab deruxtecan, cynomolgus monkeys were chosen as the cross-reactive species, and rats were chosen to evaluate the target-independent effects. To assess the general toxicity profile, 3-month intermittent intravenous dose toxicity studies (every 3 weeks (Q3W), five times in total) in rats and monkeys were conducted. The reversibility of toxic changes was also evaluated following a 2-month recovery period in the intermittent dose toxicity studies.

In vitro genotoxicity studies of DXd included a bacterial reverse mutation study and a chromosome aberration study with mammalian cultured cells. For the in vivo assessment, a micronucleus study of DXd was performed in rats.

Tissue cross-reactivity studies were conducted to determine the potential cross-reactivity of datopotamab deruxtecan in normal human and cynomolgus monkey tissues. The general toxicity profile of DXd was assessed in 4-week intermittent intravenous dose toxicity studies (every week (QW), 5 times in total) with a 4-week recovery period in rats and cynomolgus monkeys. For DXd, the potential phototoxicity was evaluated in an in vitro 3T3 neutral red uptake phototoxicity study and an in vivo rat phototoxicity study.

To assess the potential for datopotamab deruxtecan to induce cytokine release and immune cell activation, in vitro CRA of datopotamab deruxtecan and datopotamab were performed in a plate-bound format using human peripheral blood mononuclear cells and in a soluble format using human whole blood. The toxicity profile of MAAP-9002b (an antibody-drug conjugate comprised of same antibody, linker, and drug as those of datopotamab deruxtecan; the average drug-to-antibody ratio was approximately seven) was evaluated in a 2-week intermittent intravenous dose toxicity study (QW, two times in total) in cynomolgus monkeys.

Table 12 Summary of Toxicology Program for Datopotamab deruxtecan

Report No	Study Type	Test article	Route	Species/Strain	Regulatory compliance
Repeat–Dose Toxicity					
AN15-H0083-R01	3 months	Datopotamab deruxtecan	I.v.	Rats/Crl:CD(SD)	GLP
AN17-H0001-R01	6 weeks	Datopotamab deruxtecan	I.v.	Cynomolgus monkeys	Non-GLP
SBL315-405	3 months	Datopotamab deruxtecan	I.v.	Cynomolgus monkeys	GLP
SBL315-026	4 weeks	DXd monohydrate	I.v.	Rats/Crl:CD(SD)	GLP
SBL315-032	4 weeks	DXd monohydrate	I.v.	Cynomolgus monkeys	GLP
SBL314-884	2 weeks	MAAP-9002b[c]	I.v.	Cynomolgus monkeys	Non-GLP
Genotoxicity					
SBL315-617	Bacterial reverse mutation	DXd monohydrate[a]	In vitro	*Salmonella typhimurium, Escherichia coli*	GLP
SBL315-618	Chromosomal aberration	DXd monohydrate	In vitro	Chinese hamster lung cells	GLP
SBL315-756	Bone marrow micronucleus (single)	DXd monohydrate	I.v.	Rats/Crl:CD(SD)	GLP
Other toxicity					
20095172	Tissue cross reactivity	Datopotamab deruxtecan	In vitro	Human tissues	GLP
20095173	Tissue cross-reactivity	Datopotamab deruxtecan	In vitro	Cynomolgus monkey tissues	GLP
SBL315-101	Phototoxicity	DXd monohydrate	In vitro	Balb/c mouse 3T3 fibroblasts	GLP
SBL315-450	Phototoxicity	DXd monohydrate[a]	I.v.	Rats/Iar:Long-Evans	GLP
0730-177-R03	In vitro CRA	Datopotamab deruxtecan, Dato[b]	In vitro	Human PBMCs	Non-GLP
0730-177-R04	In vitro CRA	Datopotamab deruxtecan, Dato[b]	In vitro	Human whole blood	Non-GLP

CRA = cytokine release assays; PBMCs = peripheral blood mononuclear cells.

[a] DXd monohydrate was referred to MAAA-1181d in the reports.
[b] Dato was referred to MAAP-9001a in the reports.
[c] MAAP-9002b was an ADC comprised the same antibody, linker, and drug as those of Dato-DXd. The average DAR of MAAP-9002b was approximately 7 and different from that of Datopotamab deruxtecan.

2.5.4.1. Single dose toxicity

No single-dose studies with datopotamab deruxtecan were conducted. Acute toxicity information was available at the first dosing in the intermittent pivotal 3-month i.v. dose toxicity studies in rats and cynomolgus monkeys. Neither deaths nor moribundity were noted up to 200 mg/kg in rats (study No AN15-H0083-R01) or 80 mg/kg in monkeys (study No SBL315-405) in the 1st cycle following datopotamab deruxtecan dosing. Loss of fur was observed in rats at 200 mg/kg from eight days after the 1st dosing and abnormal skin colour was observed in monkeys given ≥30 mg/kg from approximately fourteen days after the 1st dosing. Decreases in body weight were also noted in rats given 200 mg/kg and monkeys given 30 and 80 mg/kg, respectively, after the 1st dosing.

2.5.4.2. Repeat dose toxicity

The general toxicity profile of datopotamab deruxtecan and DXd were assessed in repeat-dose studies in rats and cynomolgus monkeys.

Datopotamab deruxtecan

Table 13 Pivotal repeat-dose toxicity studies with datopotamab deruxtecan

Study details	No:Group	Dose (mg/kg)	Exposure		Major findings & NOAEL
			C0 µg/mL	AUC µg×d/mL	
Sprague-Dawley rats 12 + 8 w Q3W for 3 months i.v. GLP (AN15-H0083-R01)	Main: 10M+10F Recovery: 5M+5F (group 0 and 200 mg/kg)	0	-	-	**20 mg/kg** *Histopathology*: M: Thymus (increased number of tingible body macrophage). **60 mg/kg** *Clinical observations*: M+F: Overgrown teeth. M: Crushing and whitening of teeth. F: ↓*BW.* F: ↓*Food consumption*. *Macroscopic examination*: M+F: Incisor (crushing of teeth, whitening and overgrowth of teeth). *Histopathology*: M: Kidney (hyaline cast and regeneration of tubular epithelium), M+F: Thymus (increased number of tingible body macrophage). rectum (single cell necrosis in crypt), incisor (necrosis of ameloblast), M: Duodenum (single cell necrosis in crypt), incisor (gingivitis), F: Jejunum (single cell necrosis in crypt). **200 mg/kg** *Clinical observations*: M+F: Loss of fur, overgrown teeth, whitening of teeth. F: Crushing of teeth. F: ↓*BW.* M+F: ↓*Food consumption*. *Haematology*: M+F: ↓RBC and WBC. *Clinical chemistry*: M: ↓ALB and A/G. M+F: ↑UN. *Urinalysis*: M+F: ↑Protein. *Organ weight*: M: ↓Epididymides (absolute and relative). *Macroscopic examination*: M+F: Incisor (crushing, whitening, and overgrowth of teeth), skin (alopecia), thymus (small size), M: Lung (coloured focus) and F: Caecum (black contents).
		20	658	2580	
		60	2270	8740	
		200	6170	25100	

					Histopathology: M+F: Kidney (degeneration of podocyte, hyaline cast, regeneration of tubular epithelium), lung (haemorrhage, infiltration of neutrophil in alveolus, regeneration of alveolar epithelium and infiltration of foamy alveolar macrophage), duodenum, jejunum, ileum, caecum (single cell necrosis in crypt), bone marrow (decreased erythropoiesis and decreased granulopoiesis), thymus (increased number of tingible body macrophage, atrophy of cortex), incisor (abnormal dentin formation and single cell necrosis in enamel organ), F: Spleen (atrophy of PALS), skin (single cell necrosis in hair follicle), ovary (increased number of atretic follicle), vagina (single cell necrosis of mucosal epithelium), M: Skin (necrosis of epidermis), mammary gland (atrophy of gland epithelium), testis (degeneration of germinal epithelium, atrophy of seminiferous tubule), epididymis (cell debris in duct, decreased number of spermatozoa in duct, single cell necrosis of ductal epithelium), incisor (haemorrhage in root and necrosis in root). Recovery **200 mg/kg** *Clinical observations*: M+F: Whitening and overgrown of teeth and F: crushing of teeth. F: ↓*BW.* *Urinalysis*: M+F: ↑Protein. *Organ weight*: M: ↓Testes and epididymides (absolute and relative). *Macroscopic examination*: M+F: Incisor (crushing of teeth, whitening and overgrowth of teeth), M: Testis (small size). *Histopathology*: M+F: Incisor (gingivitis), M: Kidney (hyaline cast and regeneration of tubular epithelium), lung (haemorrhage and regeneration of alveolar epithelium), mammary gland (increased lipid droplet in glandular epithelium), testis (degeneration of germinal epithelium and atrophy of seminiferous tubule), epididymis (cell debris in duct, decreased number of spermatozoa in duct), F: Incisor (necrosis of ameloblast). **NOAEL: Not determined.**
Cynomolgus monkey 12 + 8 w Q3W for 3 months i.v. GLP (SBL315-405)	Main: 3M+3F Recovery: 2M+2F (group 30 and 80 mg/kg	0 10 30 80	- 125 645 1710	- 217 2520 8610	**10 mg/kg** M: ↓*BW.* *Haematology*: M: ↑Neutro and Mono. M+F: ↓Plat. *Histopathology*: M+F: Small intestine (single cell necrosis in the crypt epithelium). **30 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black; nose, cervix, shoulder, forelegs, chest, lower abdomen, and/or hindlegs). M+F: ↓*BW.* *Ophthalmoscopy*: F: Corneal pigmentation. *Haematology:* M+F: ↑Mono, F: ↑Neutro and Fibrin. M: ↑Luc. *Urinalysis*: M: ↓pH. *Organ weight*: M: ↑Lung weight (absolute and relative). *Macroscopic examination*: M: Red and brown focus in the lung. F: Black discoloration of the skin. *Histopathology*: M+F: Small intestine (single cell necrosis in the crypt epithelium), F: Skin (brown pigmentation in the epidermis), F: Eyeball (brown pigmentation and single cell necrosis in the corneal epithelium), M: Lung (oedema and haemorrhage in the alveolus, aggregation of foamy alveolar macrophage, mononuclear cell infiltration and fibrosis in the interstitium, inflammatory cell

					infiltration in the alveolus and interstitium and karyomegaly/cytomegaly in the alveolar and bronchiolar epithelium), M+F: Thymus (atrophy), M: Liver (single cell necrosis). **80 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black and red; cervix, forelegs, chest, axilla, lower abdomen, knee, inguinal, and/or hindlegs). F: Incomplete eyelid opening, abnormal gait and excoriation and erosion. M+F: ↓*BW.* *Ophthalmoscopy*: M+F: Corneal pigmentation. *Haematology*: F: ↓RBC, Hb, Ht and ↑Ret, M+F: ↑ Neutro. F: ↑ Fibrin. *Clinical chemistry:* M+F: ↑T-Bil, D-Bil and GLB. ↓ALB and A/G ratio. *Urinalysis*: M+F: ↓pH. *Macroscopic examination*: M+F: Skin (black discoloration), M: Lung (brown focus). F: Skin (red discoloration), hip joint (thickening of articular capsule) and lymph node (enlargement of the right axillary lymph node). *Histopathology*: M+F: Small intestine (single cell necrosis in the crypt epithelium), M+F: Skin (brown pigmentation in the epidermis, F: inflammatory cell infiltration in the epidermis), M+F: Eyeball (single cell necrosis and brown pigmentation and atrophy in and of the corneal epithelium and M: vacuolation in the corneal epithelium), M: Lung (oedema in alveolus, aggregation of foamy alveolar macrophage, mononuclear cell infiltration and fibrosis in the interstitium and karyomegaly/cytomegaly in the alveolar and bronchiolar epithelium), M: Thymus (atrophy), M: Kidney (karyomegaly in the proximal tubules) and F: Hip joint (fibrocartilage formation in the articular surface, erosion in the articular cartilage, hyperplasia of the synovial cell and fibrous thickening of articular capsule in the right hip joint). Recovery **30 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black; nose, cervix, shoulder, forelegs, chest, lower abdomen, and/or hindlegs). F: ↓*BW.* *Ophthalmoscopy*: M+F: Corneal pigmentation. *Macroscopic examination*: M+F: Black discoloration of the skin. *Histopathology*: M+F: Skin (brown pigmentation in the epidermis). **80 mg/kg** *Clinical observations*: M+F: Abnormal skin color (black; nose, cervix, shoulder, forelegs, chest, lower abdomen, hindlegs). F: ↓*BW* *Ophthalmoscopy*: M+F: Corneal pigmentation. *Macroscopic examination*: M+F: Skin (black discoloration). *Histopathology*: M+F: Skin (brown pigmentation in the epidermis), M+F: Eyeball (brown pigmentation in the corneal epithelium), M: Lung (aggregation of foamy alveolar macrophage, fibrosis in the interstitium, haemorrhage in the alveolus, inflammatory cell infiltration in the alveolus and interstitium, and karyomegaly/cytomegaly in the alveolar epithelium) and M: Liver (diffuse vacuolation).

					NOAEL: Not determined.

In a 3-month GLP repeat-dose study with a 2-month week recovery period datopotamab deruxtecan was administered i.v. at doses of 20, 60 or 200 mg/kg every three weeks on five occasions to rats. The major toxicities were observed in the thymus at ≥20 mg/kg; in the kidney, intestines, and incisor teeth at ≥60 mg/kg; and in the lung, skin, reproductive tract, and lymphatic or haematopoietic organs at 200 mg/kg. All of these changes observed were non-severe and showed recovery or a tendency towards recovery after the 2-month recovery period, except for the male reproductive toxicity. Anti-drug antibodies (ADA) were detected in one male given 20 mg/kg but mainly in pre-dose and control samples (study No AN15-H0083-R01).

In a preliminary 6-week non-GLP study, datopotamab deruxtecan was administered i.v. at doses of 10 and 30 mg/kg every three weeks on three occasions to cynomolgus monkeys. Neither death nor moribundity was observed during the dosing period. The major toxicities were limited to the lung (aggregation of foamy alveolar macrophage and cell infiltration in the interstitium), thymus (increased number of tingible body macrophage) and duodenum (single cell necrosis in crypt) at 30 mg/kg. Total antibody and free DXd were generally increased with dose. Anti-drug antibody formation was not determined in this study (study No AN17-H0001-R01).

Datopotamab deruxtecan was administered i.v. to cynomolgus monkeys at doses of 10, 30 or 80 mg/kg every three weeks on five occasions in a GLP-compliant 3-month toxicity study with a 2-month recovery period, no deaths or moribundity were noted up to 80 mg/kg. Severe lung toxicity was noted in one monkey at each 30 mg/kg and 80 mg/kg, respectively. The other major toxicities were observed in the intestine at ≥10 mg/kg; in the cornea, skin, thymus, and liver at ≥30 mg/kg; and kidney and hip joint cartilage accompanied by abnormal gait at 80 mg/kg. Almost all findings tended to recover, except for some findings in the lung as well as pigmentation in the cornea and skin. Decreased exposure levels of datopotamab deruxtecan were noted at 10 mg/kg in 5/6 monkeys after the 4th dose compared to the 1st dose. After the 4th and 5th the animals exhibited thrombocytopenia and showed lower datopotamab deruxtecan and higher DXd exposures after repeated dosingAlthough ADAs were formed exposure was sufficiently maintained during the treatment period in this group (study No SBL315-405).

DXd

A GLP-compliant repeat-dose study in rats with once weekly i.v. injection of 3, 10 and 30 mg/kg DXd monohydrate for 4 weeks with a 4-week recovery period led to toxicity findings in the lymphatic/haematopoietic system, the intestinal tract, and the cornea of the eye observed at ≥3 mg/kg. The changes observed during the dosing period showed reversibility by the end of the recovery period (study No SBL315-026).

In a GLP-compliant 4-week repeat-dose study in cynomolgus monkeys with a 4-week recovery period administration of DXd monohydrate i.v. once weekly on five occasions at doses of 1, 3, and 12 mg/kg resulted in findings similar to those in rats (i.e. toxicity in the lymphatic/haematopoietic system, the intestinal tract, and the cornea) already at dose levels of ≥1 mg/kg. In addition, one female monkey died and one male monkey became moribund in the high dose group at 12 mg/kg. Cardio- and hepatotoxicity were found in the moribund male monkey. Both monkeys exhibited deteriorated physical conditions associated with sustained decreases in food consumption, bone marrow toxicity and intestinal toxicity. The test article-related changes noted during the dosing period showed recovery by the end of the recovery period (study Nos SBL315-026 and SBL315-032).

MAAP-9002b

In a preliminary 2-week toxicity study, a former trophoblast cell surface antigen 2 antibody-drug conjugate, MAAP-9002b (with a drug-to-antibody ratio of approximately seven) was given i.v. at doses

of 10, 30, and 80 mg/kg once weekly on two occasions to monkeys. At 80 mg/kg one male monkey died and one female monkey was euthanized due to moribundity. The major findings of toxicity were observed in the skin, oesophagus, vagina and mammary glands at ≥10 mg/kg, in the cornea and prostate at ≥30 mg/kg and in the liver, intestine, bone marrow, heart, kidney and ovary at 80 mg/kg (study No SBL314-884).

The exposure levels (based on C_0 and AUC_{21d}) of datopotamab deruxtecan in rats were higher than those in humans at the clinically relevant dose of 6 mg/kg. In monkeys, the exposure level at the severely toxic dose of ≥30 mg/kg was 3-fold higher than those in humans at 6 mg/kg.

2.5.4.3. Genotoxicity

Table 14 Overview of genotoxicity studies of DXd

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 typhimurium (TA100, TA1535, TA98, TA1537) and Escherichia coli (WP2uvrA) Negative control: DMSO Positive controls: 4 nitroquinoline 1-oxide, sodium azide, 9 aminoacridine hydrochloride monohydrate, or 2 aminoanthracene.	313, 625, 1250, 2500, and 5000 µg/plate +/- S9 Solvent: DXd monohydrate in DMSO	**Negative**
Chromosome aberrations in mammalian cells/SBL315-618/GLP	CHL/IU cell line from the lungs of newborn female Chinese hamsters, sensitive to chemicals that induce chromosome aberrations Negative control: DMSO Positive controls: mitomycin C and cyclophosphamide monohydrate	0.05, 0.1, 0.2, and 0.4 µg/mL (short term treatment, - S9) 0.05, 0.1, 0.2, 0.4, and 1 µg/mL (short term treatment, + S9) 0.0125, 0.025, 0.05, 0.1, and 0.2 µg/mL (continuous treatment, - S9) Solvent: DXd monohydrate in DMSO	**Positive**: DXd increased the number of cells with structural chromosome aberrations in a dose-dependent manner in all treatment conditions. **Negative**: DXd did not cause a statistically significant increase in the number of cells with numerical chromosome aberrations in any treatment condition.
Chromosomal aberrations in-vivo/SBL315-756/GLP	Rats, micronuclei in bone marrow (n = 5 male Sprague-Dawley rats, 8 w old/group) Negative control: physiological saline i.v. Positive control: preserved positive control specimens	0.025, 0.05, 0.1, and 0.2 mg/kg (single dose, i.v.) Solvent: DXd monohydrate in physiological saline	**Positive**: A statistically significant increase in the number of micronucleated immature RBCs was observed at ≥0.05 mg/kg when compared with the negative control group. **Negative**: No statistically signi-ficant change in the proportion of immature RBCs observed when compared with the negative control group.

Genotoxicity studies evaluated the topoisomerase I inhibitor drug component, DXd, of the antibody-drug conjugate datopotamab deruxtecan. DXd was in the form of DXd monohydrate. The genotoxic potential was studied in a standard test battery comprising of GLP-compliant in vitro bacterial and mammalian cell assays (study Nos SBL315-617 and SBL315-618) and an in vivo rat bone marrow micronucleus assay (study No SBL315-756). These studies have previously been assessed as a part of the marketing authorisation application for Enhertu (EMA/CHMP/636117/2022).

DXd showed no potential to induce gene mutation in five standard strains of Salmonella and E. coli in the in vitro bacterial reverse mutation assay (no DXd-related increase in the number of revertant bacterial colonies in any group was observed). However, DXd was positive for the potential to cause chromosomal aberrations when assessed in the in vitro chromosome aberration study and at ≥0.05 mg/kg in the in vivo rat bone marrow micronucleus study. DXd induced structural chromosome aberrations in vitro and increased the number of micronucleated immature red blood cells in vivo, respectively. No statistically significant change in the proportion of immature red blood cells was observed in the in vivo study indicating that bone marrow cell proliferation was not inhibited. The positive findings in the in vitro chromosome aberration study in mammalian cells and in the in vivo rat bone marrow micronucleus study are considered to be clinically relevant.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been performed.

2.5.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

Fertility and early embryonic development studies were not conducted. However, male or female reproductive toxicity of datopotamab deruxtecan (study Nos AN15-H0083-R01, AN17-H0001-R01 and SBL315-405) and DXd (study Nos SBL315-026 and SBL315-032) were evaluated in rat and monkey repeat-dose studies.

Embryo-foetal development

No dedicated embryo-foetal studies were conducted.

Prenatal and postnatal development, including maternal function

Prenatal and postnatal development studies were not conducted.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile studies were submitted.

2.5.4.6. Interspecies comparison and exposure margins to clinical exposure

Interspecies comparison data after the 1st and 4th dosing of datopotamab deruxtecan were presented as a comparison of exposures (C_0/C_{max} and AUC_{21d}) of datopotamab deruxtecan and DXd from the pivotal 3-month repeat-dose rat (study No AN15-H0083-R01) and cynomolgus monkey (study No SBL315-405) studies with predicted adult human exposure (single and multiple doses) at the clinical dose of 6.0 mg/kg administered once every three weeks (clinical study No Study TP01).

The exposure levels (based on C_0 and AUC_{21d}) of datopotamab deruxtecan in rats were higher than those in human at 6 mg/kg. Those of DXd (based on C_{max} and AUC_{21d}) in rats ranged between 0.51 to 1.4 compared to the predicted adult human exposure following single and multiple dosing with datopotamab deruxtecan. In monkeys, the exposure level (based on C_0 and AUC_{21d}) of datopotamab deruxtecan at the severely toxic dose of ≥30 mg/kg was 3-fold higher than those in human at 6 mg/kg. In the low dose group (10 mg/kg) margins of exposure ratios between monkey and human ranged from 0.25- to 1.5-fold that in humans. The margin of exposure of DXd (based on C_{max} and AUC_{21d}) at all dose levels in monkeys were comparable with or lower than those in human at 6 mg/kg after the repeated doses and ranged from 0.05 to 2.1.

In addition, a presentation of margin of exposure (based on AUC) of datopotamab deruxtecan at the no observed adverse effect level (NOAEL) of each target organ of toxicity in rats and monkeys compared with the optimal dose of 6 mg/kg (multiple doses) in subjects with non-small cell lung cancer was included. In monkeys, slight intestinal toxicity was observed at ≥10 mg/kg, and no exposure margin was determined (margin of exposure <0.25). The NOAEL for pulmonary, corneal, dermal, hepatic and lymphoid (thymic) toxicity was concluded to be 10 mg/kg corresponding to a margin of exposure of 0.25. Exposure margin of haematopoietic and renal toxicity (30 mg/kg) was determined to 2.9, whereas reproductive toxicity (up to 80 mg/kg) was 10.

2.5.4.7. Toxicokinetic data

Toxicokinetics of datopotamab deruxtecan and DXd are presented above in section 2.5.3.1. Absorption.

2.5.4.8. Local Tolerance

Microscopic evaluation of the injection sites as part of the repeat-dose toxicology studies in both rats (study Nos AN15-H0083-R01 and SBL315-026) and monkeys (study Nos AN17-H0001-R01 and SBL315-405 and SBL315-032) identified no datopotamab deruxtecan or DXd-related effects.

2.5.4.9. Other toxicity studies

2.5.4.9.1. Antigenicity

No stand-alone antigenicity study of datopotamab deruxtecan was conducted. The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. Nevertheless, formation of anti-drug antibodies (ADA) against datopotamab deruxtecan and its impact on toxicokinetics was assessed based on data from i.v. 3-month repeat-dose toxicity studies in rats (study No AN15-H0083-R01) and cynomolgus monkeys (study No SBL315-405) in accordance with the ICH guideline S6(R1).

In rats, ADA formation was primarily seen in pre-dose and control samples (0 mg/kg: 2/20 animals; 20 mg/kg: 2/20 animals and 200 mg/kg: 1/20 animals) and in 1/8 animals on Day 85 dosed at 20 mg/kg. In 5/6 monkeys given 10 mg/kg ADA formation was observed at the end of the 3-month dosing period and there was a reduction in datopotamab deruxtecan exposure after the 4th dose compared to the 1st dose. After the 4th and 5th repeated dose the animals exhibited thrombocytopenia and showed lower datopotamab deruxtecan and higher DXd exposures after repeated dosing. Although ADAs were formed, exposure was still sufficiently maintained during the treatment period in this group. On recovery Day 57, 4/4 monkeys in the 30 mg/kg group had developed ADAs.

2.5.4.9.2. Immunotoxicity

Immunotoxicity evaluations were integrated in the repeat-dose toxicity studies. Datopotamab deruxtecan-related lymphatic organ toxicity was noted in rats and monkeys and included an increased number of tingiblebody macrophage in the thymus and thymic atrophy, respectively.

2.5.4.9.3. Phototoxicity studies

Table 15 Phototoxicity studies

Study ID	Test system	Concentrations/concentration range of DXd	UVA exposure/source	Major findings
SBL315-101/GLP	Balb/c mouse 3T3 fibroblasts	0.195 to 25 µg/mL	5 J/cm^2 (single exposure)	- IC50 cell viability = 2.356 µg/mL in the

	Positive control: Chlorpromazine hydrochloride		Sunlamps (1.70 mW/cm^2 for 50 min.)	presence of UV-A irradiation - MPE = 0.432 →phototoxic
SBL315-450/GLP	Rat (Iar:Long-Evans, 5 animals per dose group) Positive control: 8-methoxyp-soralen (orally)	Single i.v. dose 1 or 3 mg/kg	10 J/cm^2 (single exposure)	None

The conducted phototoxicity studies evaluated the topoisomerase I inhibitor drug component, DXd, of the antibody-drug conjugate datopotamab deruxtecan. DXd was in the form of DXd monohydrate.

The phototoxic potential was sufficiently studied in a standard test battery comprising of GLP-compliant studies; an in vitro 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU-PT) (study No SBL315-101) and an in vivo i.v. single dose phototoxicity study in male Iar:Long-Evans pigmented rats (study No SBL315-450). These studies have previously been assessed as a part of the marketing authorisation application for Enhertu® (EMA/CHMP/636117/2022).

DXd showed phototoxic potential in vitro however, no concern was identified in a follow-up in vivo i.v. single dose phototoxicity study in male pigmented rats. The negative result in the in vivo phototoxicity study supersedes the positive in vitro result and no further phototoxicity testing is warranted. Based on the non-clinical data, no direct phototoxicity is anticipated in humans following administration of datopotamab deruxtecan.

2.5.4.9.4. Other (toxicity) studies (including mechanistic studies)

In two GLP-compliant studies datopotamab deruxtecan tissue cross-reactivity was further assessed in a panel of cynomolgus monkey (study No 20095173) and human tissues (study No 20095172). Plasma membranous staining in the epithelium of the urinary bladder, eye (conjunctiva), fallopian tube, oesophagus, stomach, liver, lung, pancreas, salivary gland, skin, thyroid, tonsil, ureter, and uterus was commonly observed in monkeys and humans. Test article membrane stained tissue elements that were seen in the cynomolgus monkey but not in the human tissues included the small intestine and testis. In addition, membranous staining in the eye (cornea), breast, kidney, thymus and placenta was noted in humans.

The potential risk of datopotamab deruxtecan and datopotamab to induce infusion-related reactions (IRRs) via drug-induced cytokine release and immune cell activation was evaluated in two non-GLP in vitro cytokine release assays in Human Peripheral Blood Mononuclear Cells (hPBMC) (Plate-Bound Format) (study No 0730-177-R03) and Human Whole Blood (Soluble Format) (study No 0730-177-R04), respectively. Datopotamab deruxtecan and datopotamab were analysed at four concentrations (0.15-150 µg/mL) in each assay. Incubation with Datopotamab deruxtecan and Datopotamab increased the levels of multiple cytokines compared to vehicle in the hPBMC assay. However, these changes were either lower or comparable to what was seen for bevacizumab (IRR incidence in clinic: <3%). No signal of cytokine release activity was found in the human whole blood assay. These findings suggest that the risk of IRRs associated with datopotamab deruxtecan is comparable to that of other monoclonal antibodies, and likely falls within the lower range of risk.

2.5.5. Ecotoxicity/environmental risk assessment

The concerned moiety in terms of ERA of datopotamab deruxtecan is deruxtecan (DXd), a topoisomerase I inhibitor. DXd is released from the mAb and linker portion upon binding to the target cell. Therefore, the environmental risk assessment considers this molecule in isolation. The rest of the molecule is of protein nature, which is susceptible to rapid degradation in the environment, and, in accordance with the guideline (CHMP EMEA/CHMP/SWP/4447/00), ERA studies are not required. The maximum daily dose of DXd for a European adult with an average weight of 70.8 kg (Walpole et al. 2012) is estimated to be 5.5 mg per inhabitant per day. The calculation assumes the maximum daily dose is taken every day by all patients.

Partition coefficient

The partition coefficient of DXd in n-octanol/water was determined using the shake flask method (OECD 107) at the test facility Scymaris Ltd., Brixham, UK. The test was performed according to the protocol of OECD 107 and in compliance with GLP. The results of log Dow of 1.280, 1.799 and 1.924 at pH 9, 7 and 5, respectively, are below the trigger limit of 4.5.

Fpen refinement and PECsw calculation for breast cancer:

The Globocan database was accessed in 2023, where data from 2020 was used estimating Belgium to be the European Member State with the highest prevalence of breast cancer; 1-year prevalence is 191.3 per 100 000 females. The prevalence data is related to the female population and is considered equivalent to 95.7 per 100 000 total population. The worst-case *Fpen* used for dose calculation was therefore refined based only on overall breast cancer prevalence to 0.000957, resulting in a PECsw of 0.00263 µg/L, which is below the trigger value for phase II.

Table 16 Summary of main study results

Substance (INN/Invented Name): Deruxtecan/DXd/MAAA-1181d (drug part of datopotamab deruxtecan)			
CAS-number (if available): 1599440-13-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}/D_{ow}	OECD107	1.924 @ pH 5 1.799 @ pH 7 1.280 @ pH 9	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}/D_{ow}	1.924 @ pH 5 1.799 @ pH 7 1.280 @ pH 9	not B
PBT-statement:	Deruxtecan is considered to be not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined (based on 1-year prevalence)	0.00263	µg/L	≥ 0.01 threshold: N

2.5.6. Discussion on non-clinical aspects

Primary pharmacodynamics

Datopotamab deruxtecan, as a TROP2 targeting antibody-drug-conjugate, was demonstrated by specific binding to TROP2. No target cross-reactivity were observed in other species (i.e. mouse or

rat), confirming the cynomolgus monkey as the appropriate species for the non-clinical pharmacokinetic and toxicology program.

Lysosomal transport of datopotamab deruxtecan (Dato-DXd) was demonstrated. However, differences in internalisation depending on cell types and/or TROP2 expression were noted.

A TROP2-mediated effect of datopotamab deruxtecan on growth inhibition in human TROP2-positive pancreas adenocarcinoma cell lines was seen and a correlation between high TROP2-expression levels and low IC50 values were observed.

The mechanisms of cytotoxicity were further examined in vitro by showing dose-dependent topoisomerase I inhibitory activity of the payload DXd.

Bystander cytotoxicity was confirmed by the DXd payload exhibiting cytotoxic effect against cancer cells most likely as a result of deconjugated DXd penetrating into adjacent cells regardless of TROP2 expression.

An ADCC study, (study no. CY19-h0004-R04) including both the conjugated and unconjugated antibody i.e. datopotamab deruxtecan (Dato-DXd or DS-1062a) and datopotamab (MAAP-9001a), showed that datopotamab (MAAP-9001a) and datopotamab deruxtecan (Dato-DXd) exhibited ADCC activity of similar magnitudes against TROP2-expressing NCI-H322 cells in the presence of human PBMCs within a timeframe of 4 h, confirming that the antibody Fc part of datopotamab deruxtecan (Dato-DXd and datopotamab has ADCC activity.

Despite inconsistent results with respect to TROP2-expression level in the different target cells, a potential for antibody-dependent cellular phagocytosis (ADCP) activation was seen in study no. DS1062-237-R03 and this was reflected in the SmPC section 5.1.

Neither datopotamab deruxtecan nor datopotamab showed complement-dependent cytotoxic (CDC) activity at concentrations up to 100,000 ng/mL in study no. CY19-H0004-R06.

Hence, indirect cytotoxicity caused by bystander cytotoxicity, ADCC and ADCP were included as part of the mechanism of action in the SmPC section 5.1.

In vivo studies

Four in vivo pharmacology studies in xenograft mouse models confirmed the activity of datopotamab deruxtecan (Dato-DXd at doses of 10 mg/kg on tumour growth inhibition of 82.8 to 96.1% and revealed a tendency towards a dose-dependent effect (from doses ≥ 1 mg/kg).

Secondary pharmacodynamics

In a secondary pharmacodynamic study testing DXd against an off-target panel of 86 receptors, channels, transporters or enzymes, no significant response (≥ 50% inhibition) was demonstrated.

Safety pharmacology

DXd had no effect on hERG current at concentrations of 1, 3 and 10 µmol/L in hERG transfected CHO-cells. The maximum concentration tested provided a sufficient margin of exposure to the human clinically relevant C_{max} (> 1500-fold). Additionally, no cardiovascular, respiratory or central nervous effects were noted at single doses up to 80 mg/kg of datopotamab deruxtecan in male cynomolgus monkeys. Only male monkeys were used in the safety pharmacology study; however, this was sufficiently justified and supported by a lack of significant gender differences in exposure or target organs of toxicity.

In the repeat-dose toxicity studies, marked pulmonary toxicity identified the lungs as a target organ of toxicity and events of interstitial lung disease/pneumonitis have been observed in the clinical studies. This is further addressed in the toxicology and clinical parts of the assessment.

The primary target organs identified with datopotamab deruxtecan in cynomolgus monkeys and rats were the lung, skin, gastrointestinal tract, kidneys, cornea, liver, lymphatic/haematopoietic system and male and female reproductive tract.

Pharmacokinetics

The analytical methods in support of the pivotal toxicology studies were GLP-compliant, fully validated, and appear robust and adequate for the purpose of the studies.

Single and repeated dosing resulted in dose-proportional increases in exposure of datopotamab deruxtecan (Dato-DXd), total anti-TROP2 antibody and DXd in both rats and monkeys. No sex differences or accumulation over time was noted. Positive ADA-responses were observed, although the extent of responses was likely underestimated as a consequence of low sensitivity of the ADA assay (high risk of false negative readouts for ADA). Nonetheless, sufficient exposure was still maintained during the treatment period and ADA formation was not found to affect the pharmacokinetic/ pharmacodynamic parameters or the incidence/severity of adverse events, which is considered acceptable. Overall, the PK profile in rats and monkeys appears generally to be well described, and the rat and monkey as relevant non-clinical species for testing toxicity are supported by human PK data.

The major excretion pathway in rat and monkey was the faeces via the biliary route, accounting for ~71% of total excretion. Excretion into milk in lactating animals was not studied which is considered acceptable given the sought indication. The SmPC section 4.6 states that it is not known whether datopotamab deruxtecan is excreted in human milk. Human IgG is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed children, women should discontinue breast-feeding prior to initiating treatment. Women may begin breast-feeding 1 month after concluding treatment.

Toxicology

In accordance with the ICH guideline M3(R2) no single-dose studies with datopotamab deruxtecan were conducted. Acute toxicity information was available at the first dosing in the intermittent pivotal 3-month i.v. dose toxicity studies in rats and cynomolgus monkeys which is acceptable. The most significant change related to datopotamab deruxtecan was severe lung toxicity in monkeys at ≥30 mg/kg characterised as interstitial pneumonitis without reversibility after the recovery period. Trophoblast cell surface antigen 2 expression in the human lungs has been reported but the comprehensive mechanisms of pulmonary toxicity related to datopotamab deruxtecan still remain unclear. Events of interstital lung disease/pneumonitis have been observed in clinical studies and is considered to be an important identified risk (see RMP).

According to ICH guideline S9, embryo-foetal toxicity studies were not considered essential for anticancer pharmaceuticals that are genotoxic and target rapidly dividing cells in general toxicity studies or belong to a class that has been well characterized as causing developmental toxicity.

Dedicated fertility studies have not been conducted with datopotamab deruxtecan. Based on the results from an animal toxicity study in rats, datopotamab deruxtecan at 200 mg/kg (approximately 29 times the human recommended dose of 6 mg/kg based on AUC) may impair male and female reproductive function and fertility at exposure levels of the topoisomerase I inhibitor below clinical plasma exposure. Toxicity to male reproductive tract included testis (degeneration of germinal epithelium and atrophy of seminiferous tubule) and epididymis (single cell necrosis of ductal epithelium, cell debris in duct and decreased number of spermatozoa in duct), which did not reverse

after 8 weeks of treatment cessation except for single cell necrosis of ductal epithelium. The effects on female fertility, including an increase in the number of atretic follicles in the ovaries and single cell necrosis of mucosal epithelium in the vagina, may be reversible (see SmPC section 5.3).

Reproductive and developmental toxicity studies have not been conducted with datopotamab deruxtecan. Based on results from general animal toxicity studies, datopotamab deruxtecan and DXd were toxic to rapidly dividing cells (testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity (see SmPC section 5.3).

In addition, relevant warnings were included in section 4.4 of the SmPC to highlight that DXd can cause embryo-foetal harm when administered to a pregnant woman, and that pregnancy status of females of childbearing potential should be verified prior to the initiation of treatment, that patients should be informed of the potential risks to the foetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose (see SmPC 4.4). The impact on reproductive function and fertility was also reflected in SmPC 4.6, to highlight that treatment with datopotamab deruxtecan may impair male and female reproductive function and fertility, and that it is not known whether datopotamab deruxtecan or its metabolites are found in seminal fluid. Both men and women should seek advice on fertility preservation before treatment. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose. Females must not donate, or retrieve for their own use, ova throughout the treatment period and for at least 7 months after the final dose (see also Genotoxicity below). Embryo-foetal toxicity was also included as an Important Potential Risk in the RMP.

DXd was clastogenic in both an in vivo rat bone marrow micronucleus assay and an in vitro Chinese hamster lung chromosome aberration assay (see SmPC 5.3). The positive findings in the in vitro chromosome aberration study in mammalian cells and in the in vivo rat bone marrow micronucleus study are considered to be clinically relevant.

Regarding the potential genotoxicity of the linker molecule, which consists of a maleimide tetrapeptide. The peptide moiety is a naturally occurring structure and is not considered a genotoxic risk. In datopotamab deruxtecan, maleimide binds to the antibody in the succinimide state. The maleimide part (SuMH) and linker (MFAH) were deemed negative in the Ames test. Hence, no genotoxic risk of the linker is expected.

The lack of carcinogenicity studies was acceptable based on the proposed indication being in scope of ICH guideline S9.

In accordance with ICH guideline S9 no prenatal and postnatal development, including maternal function studies were conducted.

No juvenile studies were submitted which is accepted, as the proposed marketing authorisation application of datopotamab deruxtecan is for treatment of adult patients.

Considering the sought indication low margins of exposure are acceptable and within the scope of the ICH guideline S9.

Overall, the metabolism of datopotamab deruxtecan was sufficiently explored.

Based on the non-clinical data, no direct phototoxicity is anticipated in humans following administration of datopotamab deruxtecan.

Intravenous administration of monoclonal antibodies is commonly associated with infusion-related reactions (IRR), and in vitro cytokine release assays suggested that the risk of IRRs associated with

datopotamab deruxtecan is comparable to that of other monoclonal antibodies, and likely falls within the lower range of risk.

Datopotamab deruxtecan PEC $_{surfacewater}$ value is below the action limit of 0.01 μg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, datopotamab deruxtecan is not expected to pose a risk to the environment. The Applicant provided 1-year prevalence data from the IARC (Globocan) website to refine the market penetration factor (Fpen), which was deemed acceptable. Of note, the evaluation of the 1-year prevalence data provided by the IARC gave rise to the consideration of being insufficient since it does not illustrate the total number of patients, that may be eligible for treatment of breast cancer with datopotamab deruxtecan. Estimates provided by the IARC database were not considered to be good estimates for the maximum number of patients that may potentially be treated with datopotamab deruxtecan at a given point in time as the data do not take into account the patient population already having the disease before this 1-year period. If there are patients alive that were diagnosed in the period before this 1-year, they could be included to arrive at the potentially maximum, but realistic number of patients. The 5-year prevalence does include this proportion of patients and could therefore be considered a more appropriate estimate. Using other than 1-year prevalence data (e.g. multiple year prevalence) is permitted according to The *Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'*. Nevertheless, the usage of 1-year prevalence data was deemed acceptable, since it is in agreement with the guideline, and estimates from the IARC database were considered to contain incidence-to-prevalence refinement. In addition, the 1-year prevalence data comprised all patients with breast cancer, ignoring the HR+ and HER2-ve biomarkers, disease stage, previous treatments and treatment regimen, and is thus considered a conservative measure.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that datopotamab deruxtecan showed anti-tumour activity against TROP2 positive cancer models in vitro and in vivo. The suggested mechanism of action for direct cytotoxicity was verified and a potential for bystander cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis indentified. The primary target organs identified with datopotamab deruxtecan in cynomolgus monkeys and rats were the lung, skin, gastrointestinal tract, kidneys, cornea, liver, lymphatic/haematopoietic system and male and female reproductive tract. Datopotamab deruxtecan is considered approvable from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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.

Table 17 Tabular overview of clinical studies

Study Number DCO	Study Title (N = Number of subjects enrolled)	Objectives of the Study	Dosage and Regimen[a]	Pharmacokinetic Assessments Immunogenicity
TB01 (TROPION-Breast01; D9268C00001) DCO 17 July 2023	Phase III, Open-label, Randomized Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants With Inoperable or Metastatic Hormone Receptor Positive, HER2-negative BC Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy (N = 732)	**Primary** - To demonstrate the superiority of Dato-DXd compared to ICC through assessment of PFS by BICR and OS **Secondary** To demonstrate the superiority of Dato-DXd compared to ICC by assessment of: ORR, DoR, PFS by investigator assessment, DCR, TFST, TSST, PFS2, TTD in pain, TTD in physical functioning and TTD in Global health status/quality of life (GHS/QoL) To assess plasma concentrations of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a. To investigate the immunogenicity of Dato-DXd. **Safety** To assess the safety and tolerability profile of Dato-DXd compared to ICC. **Exploratory** To assess patient-reported symptomatic AEs and treatment tolerability as measured by selected items from the PRO-CTCAE and EORTC Item Library (IL; ie, EORTC IL117). To assess patient-reported global impression of the severity of overall cancer symptoms as measured by PGIS. To assess patient-reported global impression of change in health status as measured by PGIS.	Dato-DXd 6 mg/kg IV on Day 1 of each 21-day cycle Capecitabine 1000 or 1250 mg/m^2 oral bd on Days 1 to 14 of a 21-day cycle Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of a 21 day cycle Eribulin mesylate 1.4 mg/m^2 IV on Days 1 and 8 of a 21-day cycle Vinorelbine 25 mg/m^2 IV on Day 1 and 8 of a 21-day cycle	PK: Plasma concentration Immunogenicity: ADA

		To assess patient-reported symptoms, functioning and health-related QoL as measured by EORTC-QLQ-C30. To assess breast and arm symptoms in patient treated with Dato-DXd compared to ICC as measured by EORTC QLQ- BR45/IL116. To assess patient-reported health status as measured by EQ-5D-5L.. Association of TROP2 or other tumor derived biomarkers with response and tolerability to Dato-DXd and ICC. Association of exploratory biomarkers in tumor, plasma, whole blood, or serum collected before, during treatment or at disease progression with disease status and/or response and tolerability to Dato-DXd. Assessment of ctDNA mutational profile and dynamic changes as an indicator for early response and/or relapse on Dato-DXd, and assessment of molecular and genomic determinants of response to Dato-DXd in tumor and blood. To explore the impact of treatment and disease on health care resource use.		
TL01 (TROPION-Lung01; DS1062-A-U301) (DCO 29 Mar 2023)	Phase III randomized study of DS-1062a vs docetaxel in previously treated advanced or metastatic NSCLC with or without actionable genomic alterations (N = 604)	**Primary** To compare the efficacy of Dato-DXd with that of docetaxel, as measured by PFS and OS, for subjects with NSCLC with or without actionable genomic alterations **Secondary** To further evaluate the efficacy of Dato-DXd compared with docetaxel To further evaluate the safety of Dato-DXd compared with docetaxel	Dato-DXd: 6.0 mg/kg IV on Day 1 of each 21-day cycle Docetaxel: 75 mg/m^2 IV on Day 1 of each 21-day cycle	PK: Plasma concentration and PK parameters for Dato-DXd, total anti-TROP2 antibody, and DXd Immunogenicity: ADA

		To assess the PK of Dato-DXd To assess the immunogenicity of Dato-DXd **Exploratory** To evaluate PFS2 for Dato-DXd compared with that of docetaxel To evaluate biomarkers that may associate with the clinical benefit from Dato-DXd used to treat NSCLC To explore how changes in biomarkers may relate to exposure and clinical outcomes To evaluate exposure-response relationships for efficacy and safety endpoints To evaluate PRO endpoints for DS-1062a compared with that of docetaxel		
TL05 (TROPION-Lung05 (DS1062-A-U202) (DCO 14 Dec 2022)	Phase II, single-arm, open-label study of DS-1062a in advanced or metastatic NSCLC with actionable genomic alterations and progressed on or after applicable targeted therapy and platinum-based chemotherapy (N = 137)	**Primary** To assess the efficacy of Dato-DXd, as measured by the ORR, as a treatment for subjects with NSCLC with actionable genomic alterations that has progressed on or after 1 platinum-containing therapy and 1 or more lines of targeted therapy to the applicable genomic alterations in the study **Secondary** To further evaluate the efficacy of Dato-DXd To further evaluate the safety of Dato-DXd To assess the PK of Dato-DXd To assess the immunogenicity of Dato-DXd **Exploratory** To evaluate biomarkers that may associate with the clinical benefit from Dato-DXd used to treat NSCLC To explore how changes in biomarkers may relate to exposure and clinical outcomes	Dato-DXd: 6.0 mg/kg IV on Day 1 of each 21-day cycle	PK: Plasma concentration and PK parameters for Dato-DXd, total anti-TROP2 antibody, and DXd Immunogenicity: ADA

		To evaluate pre-treatment tumor biopsy samples and archival tumor samples for key biomarkers that correlate with the clinical benefit from Dato-DXd To evaluate exposure response relationships for efficacy and safety endpoints		
TP01 (TROPION-PanTumor01 (DS1062-A-J101) NSCLC: (DCO 30 Jul 2021) BC: (DCO 22 Jul 2022)	Phase I, two-part, multicenter, open-label, multiple dose, first-in-human study of DS-1062a in subjects with advanced solid tumors (N = 210 in NSCLC and N = 85 in BC)	**Primary** *Dose Escalation* To investigate the safety and tolerability and to determine the MTD and the RDE of Dato-DXd *Dose Expansion* To investigate the safety and tolerability of Dato-DXd **Secondary** *Dose Escalation*: To characterise the PK properties of Dato-DXd, total anti-TROP2 antibody, and DXd To investigate the antitumor activity of Dato-DXd To assess the incidence of ADAs against Dato-DXd *Dose Expansion*: To investigate the antitumor activity of Dato-DXd To characterise the PK properties of Dato-DXd total anti-TROP2 antibody, and DXd To assess the incidence of ADAs against Dato-DXd **Exploratory** *Dose Escalation* and *Dose Expansion*: To explore biomarkers which correlate with response to DatoDXd	Dose Escalation: Dose levels from Dato-DXd 0.27 to 10 mg/kg IV on Day 1 of each 21-day cycle Dose Expansion: Dato-DXd 4.0 mg/kg IV 6.0 mg/kg IV 8.0 mg/kg IV On Day 1 of each 21-day cycle	PK: Plasma concentrations and PK parameters for Dato-DXd, total anti-TROP2 antibody, and DXd Immunogenicity: ADA
DS8201-A-A104 (Enhertu DDI study) (DCO 26 Sep 2018) ()	Phase I, multicenter, open-label, single sequence crossover study to evaluate the drug-drug interaction potential of	**Primary** Cohort 1: To evaluate the effect of ritonavir (dual inhibitor of CYP3A [strong] and OATP1B) on	DS-8201a: 5.4 mg/kg infusion	PK: Serum concentrations and PK parameters of
	(OATP1B/CYP3A inhibitor) on the PK of DS-8201a in subjects with HER2-expressing advanced solid malignant tumors. (N=40)	DS-8201a and MAAA-1181a PK in subjects with HER2-expressing advanced solid malignant tumors. Cohort 2: To evaluate the effect of itraconazole (strong CYP3A inhibitor) on DS-8201a and MAAA-1181a PK in subjects with HER2-expressing advanced solid malignant tumors. **Secondary** To assess the safety of DS-8201a with/without ritonavir or itraconazole. To evaluate the efficacy of DS-8201a To assess the incidence of ADA against DS-8201a. **Exploratory** To assess the effect of genetic polymorphism (OATP1B1 and BCRP) on the exposure of MAAA-1181a.	Cycle 1 to Cycle 4: administered every 3 weeks After Cycle 5: administered every 3 weeks ±2 days Ritonavir: 200mg bd On Day 17 of Cycle 2 until Day 21 of Cycle 3 Itraconazole: 200mg bd on Day 17 followed by 200mg once daily until Day 21 of Cycle 3.	Ds-8201a and MAAA-1181a Immunogenicity: ADA

[a] Formulation used in Study TL05 was clinical Lyo-DP; in Study TL01 and TB01, it was clinical Lyo-DP and to be-marketed Lyo-DP; in Study TP01, it was FL-DP (see Summary of Biopharmaceutics Studies and Associated Analytical Methods Module 2.7.1).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical methods

In the conducted clinical studies three moiety were quantified by PPD in plasma: Dato-DXd, total anti-TROP2 antibody and the DXd. Dato-DXd was quantified in plasma with two validated ligand binding assay based on the Gyrolab platform using fluorescent detection. A mouse monoclonal antibody, anti-XAFG-5737/1A3, that specifically binds to conjugated DXd was utilized in the method. The two assays, one for each drug product, Fl-DP and Lyo-DP, were cross-validated and able to quantify Dato-Dxd in the nominal concentration range of 20 to 5000 ng/ml and 100 to 5000 ng/ml, respectively. The total anti-TROP2 antibody was also quantified in plasma with two validated ligand binding assay based on the Gyrolab platform using fluorescent detection. A mouse monoclonal antibody that specifically binds to the MAb of Dato-DXd was utilized in the method. The two assays, one for each drug product, Fl-DP and Lyo-DP, were cross-validated and able to quantify Dato-Dxd in the nominal concentration range of 20 to 5000 ng/ml and 100 to 5000 ng/ml, respectively. Xd in plasma was quantified with a validated LC-MS/MS method using a stable labelled internal standard. Samples were analyzed over the nominal concentration range of 10 to 2000 pg/mL. The bioanalytical methods for the three analytes were also transferred to LabCorp in China, for analysing clinical samples collected from China subjects. The China methods were cross-validated with the original methods.

PD biomarker method

The TROP2 immunohistochemistry was performed on Formalin-Fixed Paraffin-Embedded (FFPE) tissue samples collected in the TB01 study. The validated biomarker method, was based on an antibody against TROP2, the rabbit monoclonal EPR20043, that recognises an epitope in the intracellular domain of TROP2 protein, and utilized the OptiView detection kit on a Benchmark ULTRA staining platform.

Immunogenicity methods

Immunogenicity was evaluated in a tiered fashion: Plasma samples were first evaluated using a Anti Dato-DXd antibody method (ADA assay) and of the ADA confirmed positives, the ADA titter was determined and NAbs against Dato-DXd was determined (NAb assay). Anti Dato-DXd antibody in plasma was measured at PPD using a Meso Scale Discovery platform-based LBA with electrochemi-luminescent detection. Two assays were validated for each of the two drug products, FL-DP and Lyo-DP. The drug tolerance to Dato-DXd in the FL-DP ADA assay was determined to 75 µg/mL of Dato-DXd in the presence of a 100 ng/mL positive control antibody. The drug tolerance to Dato-DXd in the Lyo-DP ADA assay was determined to 25 µg/mL of Dato-DXd for a 250 ng/mL PC antibody and estimated to 10 µg/mL in the presence of 130 to 144 ng/mL PC antibody. Nab against Dato-DXd was measured using a validated cell-based neutralizing antibody (NAb) bioassay. Drug tolerance toward Dato-DXd in the assay was determined: 0.978 µg/mL neutralizing antibodies can be detected in the presence of up to 2.50 µg/mL excess Dato-DXd. The ADA and Nab assay were also transferred to LabCorp in China, for analysing clinical samples collected from China subjects. The LabCorp methods were cross validated with the PPD methods.

Evaluation and qualification of models

PopPK modelling

Data from Studies TP01, TL05, TL01 and TB01 were included in Pop PK population. Studies included 1081 patients, of which 644 subjects had lung cancer and 437 subjects had breast cancer, resulting in 12911 Dato-DXd observations and 12873 DXd observations. DatoDXd PK was described by a 2-compartment model while DXd PK was described by a 1-compartment model. Dato-DXd clearance, which was the DXd input, consisted of a linear part and a non-linear part described by Michaelis-Menten kinetics. IIV was included on disposition parameters, Vmax and RUV. Furthermore, time dependent changes in the payload:intact ratio across a cycle and between cycles were also

implemented. DatoDXd parameters appear to be estimated with reasonable precision. The GOF plots and pcVPC plots indicate no clear structural deviations. DXd parameters appear to be estimated with reasonable precision. The GOF plots are acceptable. However, the pcVPC plot at cycle 1 shows a slight underprediction at the beginning (~day 2-7) of the concentration-time curve and a overprediction at the end (~day 9-21) of the curve. The pcVPC plots after multiple dosing are not very clear due to the clouds of observed data in the plots. But overall, a slight trend of overprediction is observed during the first 3 cycles wherein PK sampling was rich (until day 63). The model seems to predict better for the periods of sparse sampling during steady state after cycle 3. Therefore, the model is fit for purpose.

c-QT modelling

The C-QTc analysis used data from study DS1062-A-J101 with a cutoff date of 30 Jul 2021. Dose levels in the escalation part ranged from 0.27 mg/kg to 10 mg/kg Q3W.

Static linear mixed effects exposure-response models including effects of covariates tested on the intercept term was used to describe the exposure-QTc relation. Correction of the baseline QTc for heart-rate using a population approach gave a better alignment than the Fridericia method, therefore both correction methods were used. The parameters of the final models were estimated with good precision except for Slope. The random effects were large on all parameters as well as the residual error. All 95% CI on Slope contained the null except in the model of Dato-DXd and ΔQTcP where the p-value for Slope was 0.031.

Exposure-response modelling

The data for exploration of exposure-response relations originated from studies TP01, TL05, TL01 and TB01 in NSCLC and BC patients. Exposure metrics were generated by the PopPK model. Efficacy end-points were evaluated in the breast cancer population while the safety analyses also contained data from subjects with NSCLC. Cox Proportional Hazards models were used to assess OS and PFS, while logistic regression models were used to assess ORR and safety events.

Univariate analyses were conducted for safety events related to exposure by body weight categories using median exposures of each body weight category (below 60kg [<60 kg], 81-100kg [≥81 and ≤100 kg], above 100 kg [>100 kg], and using 60-81kg [≥60 and ≤81] as the reference). Forest plots of safety events showed that patients with baseline body weight above 100 kg had an odds ratio of 1.46 to 2.26 based on median Dato-DXd and DXd exposure, and that all patients with body-weights >81 kg had odds ratios >1. Therefore, a maximum of 540 mg for patients ⩾90 kg was agreed to reduce the risk for serious safety events while maintaining efficacy for subjects of high body weight.

PBPK modelling

Previous PBPK models for T-DXd developed in Simcyp V18 were updated in Simcyp V21 to describe the pharmacokinetics of T-DXd and Dato-DXd which share the same payload molecule DXd. For both ADCs two different modelling approaches were used: the small molecule simulator or a mechanistic minimal ADC PBPK model. PK of the payload DXd was described by a bottom-up PBPK model which was subsequently linked to the final models for Dato-DXd and T-DXd as a metabolite in the small molecule simulator and as a payload in the ADC simulator to give the final models.

The final PBPK models for T-DXd and Dato-DXd were evaluated against clinical data that was part of model development and verified with clinical data not used in model development. The minimal ADC model for Dato-DXd could fit the observed data of Dato-DXd and DXd in all data set and seems suitable for description of DXd PK.

The impact of concomitant ritonavir or itraconazole was simulated using the minimal PBPK model for DXd and the results were in line with the observations from DDI Study DS8201-A-A104 with trastuzumab deruxtecan (T-DXd) which contains the same DXd payload. No clinical DDI studies has been performed with Dato-DXd. The DDI recommendations in the SmPC are based on the clinical DDI study with T-DXd.

Absorption

An *in vitro* study using Caco-2 cells was conducted investigating the permeability of DXd (1 µM). DXd is a moderate permeable compound.

Dato-DXd was administered by IV infusion in the conducted clinical studies. Therefore, bioavailability studies and food-effect studies were not conducted. The PK parameters of DXd following a dose of 6 mg/kg are summarised in Table 18.

Table 18 Summary of PK Parameters on Cycle 1 at 6 mg/kg Dato-DXd

PK Parameter	Statistic	Dato-DXd	Total Anti-TROP2 Antibody	DXd
Cmax[a] (µg/mL)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	197 155 (91.0, 262) 157 (31.8) 154 (20.3)	197 155 (96.4, 254) 157 (32.2) 153 (20.5)	198 2.61 (0.953, 66.0) 3.53 (5.05) 2.82 (58.1)
Tmax (h)	N Median (min, max)	197 2.02 (1.50, 192.45)	197 2.00 (1.50, 192.45)	198 21.29 (2.78, 192.82)
Ctrough (µg/mL)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	184 4.43 (0, 17.7) 4.89 (2.99) NC (NC)	184 5.94 (0, 21.4) 6.13 (3.66) NC (NC)	185 0.16 (0, 0.698) 0.179 (0.0974) NC (NC)
AUCtau (µg·d/mL)[b]	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	193 694 (241, 2210) 702 (222) 671 (31.4)	195 730 (230, 2190) 737 (229) 703 (32.1)	183 17.9 (7.50, 131) 20.5 (13.4) 18.5 (42.6)
AUCinf (µg d/mL)[b]	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	189 729 (239, 1480) 733 (215) 701 (31.4)	188 785 (242, 1620) 781 (227) 747 (31.7)	178 19.4 (8.25, 136) 22.2 (14.0) 20.0 (42.3)
t1/2 (d)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	192 4.82 (1.04, 8.23) 4.86 (1.07) 4.72 (26.1)	194 5.23 (1.05, 10.91) 5.25 (1.29) 5.07 (28.5)	179 5.50 (3.16, 8.75) 5.57 (1.04) 5.48 (19.0)
CL (mL/d/kg)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	189 8.25 (4.06, 25.1) 9 (3.09) 8.57 (31.5)	NR	NR
Vss (mL/kg)	N Median (min, max) Mean (standard deviation) GeoMean (CV%)	189 53.5 (29.3, 93.7) 54.6 (12.5) 53.3 (22.9)	NR	NR

[a] ng/mL for DXd.
[b] ng·d/mL for DXd.
Notes: Means are arithmetic means.

Bioequivalence – comparability of drug products

Different Dato-DXd drug products (DP) have been administered to patients in the conducted clinical studies: FL-DP in the Phase I TPO study, clinical Lyo-DP in the phase II study TL05 and in the phase III studies TL01 and TB01, in which also the to-be-marketed (tbm) Lyo-DP was administered. A comparison of the PK for the FL-DP and the clinical Lyo-DP at 6.0 mg/kg using non compartmental analysis of observed Cycle 1 full PK data from studies TP01 (FL-DP, n = 133) and TL05 (clinical Lyo-DP, n = 45). The geometric mean ratios (GMR) of the Cmax, AUCtau and AUCinf for all three analytes, of the clinical Lyo-DP and the FL-DP were determined. The GMRs were found to be within the range of 0.8 to 1.25, indicating the similarity of the two drug products.

A PK comparison of the clinical Lyo-DP and the to-be-marketed Lyo-DP at 6.0 mg/kg using non-compartmental analysis of observed Cycle 1 full PK data from studies TL05 (Clinical Lyo-DP, n = 45) and TL01 (to-be-marketed Lyo-DP, n = 20) was made.The geometric mean ratios (GMR) of the Cmax, AUCtau and AUCinf for all three analytes were found to be within the range of 0.8 to 1.25, indicating the similarity of the two drug products.

The tmax) of Dato-DXd and total anti-TROP2 antibody were around 2 hours for both drug products, which largely reflected the sampling time at the end of the infusion. The median tmax of the payload DXd was higher for FL-DP compared to the other 2 formulations (22.4 h for FL-DP, 7.0 h for clinical Lyo-PD and 5.9 h for tbm Lyo-DP).

The influence of formulation (FL-DP, clinical Lyo-DP, and the to be marketed Lyo-DP) on the PK of Dato-DXd and DXd was also evaluated in the PopPK analysis using a combined dataset across all studies. Among 1081 subjects included in Population PK analysis, 295 received FL-DP, 446 received clinical Lyo-DP, 145 received to-be-marketed Lyo-DP, 194 received both clinical Lyo-DP and to-be-marketed Lyo-DP. The relative change in Dato-DXd Cycle 3 AUC and Cmax for FL-DP to the clinical Lyo-DP was estimated in the Pop-Pk model to be +18.2% and +6.47% respectively. For the to-be-marketed Lyo-DP the relative change in Dato-DXd Cycle 3 AUC and Cmax to subjects who received clinical Lyo-DP were +0.79% and +1.12%, respectively. The relative change in exposure among formulations were within the criteria (80%-125%) for what is considered as not clinical meaningful.

Distribution

The mean human plasma protein binding of DXd was determined using ultracentifugation to 96.8% and 98.0% across the concentration range of 10 to 100 ng/ml. The blood-to-plasma ratio of the was 0.59 to 0.62 across the concentration range of 10 to 100 ng/ml.

For a typical subject with a body weight of 66 kg, the geometric mean (geoCV%) of Vss is calculated to be 3.52 L (22.9%) for Dpd-DXd. Based on Population PK analysis, the central volume of distribution of Dato-DXd (VcDato-DXd) was estimated to be 3.02 L.

Metabolism

Dato-DXd is metabolised to its monoclonal antibody, linker and DXd. The MAb is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. It is unknown how the linker is further metabolised and eliminated.

Dato-DXd stability and relase of DXd was investigated *in vitro* using human plasma. Dato-DXd was found to be stable in human plasma. The metabolism of DXd in humans has only been investigated with *in vitro* methods. In vitro studies of DXd with CYP-expressing microsomes showed that CYP1A2, CYP2D6, CYP3A4, and CYP3A5 were involved in the metabolism of DXd. Additional experiments in human liver microsomes with specific inhibitors of CYP enzymes indicated that CYP3A4 is the primary

CYP isoform involved in the metabolism of DXd. In additional *in vitro* studies it was shown that DXd is not metabolized by UGT enzymes.

Transporters

DXd is a substrate of P-glycoprotein, BCRP, OATP1B1, OATP1B3, MATE2-K, and MRP1, but not of OAT1, OAT3, OCT1, OCT2, MATE1, BSEP, MRP2 and MRP3. MRP1 is a transporter expressed in tumour cells. Thus higher expression in some tumour types could decrease the concentration to deruxtecan in these tumour cell which may affect the efficacy.

Elimination

The routes of excretion were not investigated in humans for the relevant payload part DXd of Dato-DXd. In the integrated PK analysis for a dose of 6 mg/kg, the geometric mean (geoCV%) clearance of Dato-DXd in Cycle 1 was 565.6 mL/day (31.5%), approximately 0.024 L/h for a typical subject with a body weight of 66 kg. The median elimination half-life (t½) was 4.82 days for Dato DXd, 5.23 days for total anti–TROP2 antibody, and 5.50 days for DXd.

Dose proportionality and time dependencies

Dose proportionality

The Cmax of Dato-DXd increases dose proportional in the dose range of 0.27 mg/kg to 10 mg/kg. In the dose range from 0.27 mg/kg to 2 mg/kg the AUC of datopotamab deruxtecan increases more than dose-proportional. From 4 mg/kg to 10 mg/kg the AUC increases dose-proportional. The more than dose-proportional increase in exposure of datopotamab deruxtecan at the lower dose range is probably caused by the target-mediated drug disposition that is not saturated. After saturation of the target-mediated drug disposition (e.g. doses >2-4 mg/kg) the more linear elimination process of catabolism dominates. The pharmacokinetics of deruxtecan is approximately dose-proportional for Cmax and AUC in the dose range of 0.27 to 10 mg/kg.

Time dependency

Steady state appears to be reached by Cycle 3, Day 1 (day 42). From Cycle 1 and Cycle 3 PK data the accumulation ratio of AUC and Cmax was estimated to 1.29 and 1.07, respectively.

Impact of ADA's on the PK of Dato-DXd and DXd in pivotal study TB01

The impact of anti-Dato-DXd antibodies on PK was assessed in BC patients in the confirmatory study TB01. The geometric mean plasma concentrations of Dato-DXd were numerically lower in treatment-emergent ADA-positive patients at some timepoints (Cycle 2 Day 1 and Cycle 4 Day 1) while higher at others (Cycle 6 Day 1 and Cycle 8 Day 1). These data indicate that there were no apparent effect of ADA or nAb on the PK of Dato-DXd.

Table 19 Plasma Dato-DXd Concentration (µg/mL) by Visit and ADA Category (Pharmacokinetic Analysis Set)

Visit/ Statistic	Dato-DXd concentration (µg/mL) (N = 221)			
	Treatment-emergent ADA-positive [a]	Non-treatment-emergent ADA-positive [b]	nAb-positive	ADA-negative [c]
Cycle 1, Day 1, pre-dose				
n (n < LLOQ)	0 (37)	0 (10)	0 (6)	1 (169)
Geometric mean	NQ	NQ	NQ	NC
Geometric CV (%)	NC	NC	NC	NC
Cycle 1, Day 1, post-dose				
n (n < LLOQ)	30 (1)	9 (0)	5 (0)	143 (2)
Geometric mean	102.1	149.7	153.8	127.1
Geometric CV (%)	228.4	14.19	26.28	107.9
Cycle 2, Day 1, pre-dose				
n (n < LLOQ)	37 (0)	10 (0)	6 (0)	164 (2)
Geometric mean	2.010	2.215	1.356	2.599
Geometric CV (%)	136.9	74.69	131.8	126.9
Cycle 2, Day 1, post-dose				
n (n < LLOQ)	33 (0)	9 (0)	147 (0)	4 (0)
Geometric mean	129.6	127.9	125.9	132.4

Geometric CV (%)	78.31	19.48	38.92	53.28
Cycle 4, Day 1, pre-dose				
n (n < LLOQ)	27 (0)	8 (0)	5 (0)	129 (0)
Geometric mean	4.477	5.005	2.883	4.558
Geometric CV (%)	131.9	65.22	188.2	101.0
Cycle 4, Day 1, post-dose				
n (n < LLOQ)	25 (0)	8 (0)	4 (0)	116 (0)
Geometric mean	101.0	153.0	163.3	140.1
Geometric CV (%)	251.7	13.40	18.29	37.42
Cycle 6, Day 1, pre-dose				
n (n < LLOQ)	20 (1)	6 (0)	5 (0)	100 (0)
Geometric mean	6.562	6.406	4.674	5.436
Geometric CV (%)	207.8	377.8	113.2	145.4
Cycle 6, Day 1, post-dose				
n (n < LLOQ)	20 (0)	4 (0)	4 (0)	89 (0)
Geometric mean	123.7	167.3	171.8	146.5
Geometric CV (%)	170.8	17.38	24.79	21.60
Cycle 8, Day 1, pre-dose				
n (n < LLOQ)	12 (0)	3 (0)	2 (0)	58 (0)
Geometric mean	8.041	4.587	6.056	5.413
Geometric CV (%)	77.04	23.53	NC	98.55
Cycle 8, Day 1, post-dose				
n (n < LLOQ)	10 (0)	3 (0)	1 (0)	52 (0)
Geometric mean	114.2	45.24	146.1	140.8
Geometric CV (%)	109.1	631.7	NC	21.52

[a] TE-ADA positive is defined as treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive) or treatment-boosted ADA positive (ADA positive at baseline and boosted the pre-existing titre 4-fold or higher following drug administration).

[b] Non-TE ADA positive is defined as having at least one ADA positive assessment and not fulfilling the conditions of TE-ADA positive.

[c] ADA negative at all assessments.

Intra- and inter-individual variability

The inter-individual variability of Dato-DXd exposure (geometric CV%) after a single dose of 6 mg/kg Dato-DXd,was determined to 20.4% for Cmax, 35.4% for AUCtau, and 27.4% for AUCinf . At steady-state, after 3 doses of 6 mg/kg Dato-DXd in participants, the inter-individual variability of Dato-DXd exposure (geometric CV%) was 25.3% for Cmax and 31.2% for AUCtau. Intra-individual variability has not been estimated. For deruxtecan, the inter-individual variability ranges from 31.5% to 141% for the Cmax and from 28.8% to 116% for the AUC.

Pharmacokinetic in target population

The observed data suggest that breast cancer patients have a 11-21% higher dato-DXd Cmax and 19-39% higher AUC after single dose compared to non-small cell lung cancer patients. After multiple doses, breast cancer patients have 12% higher Cmax and 14% higher AUC. DXd Cmax levels are comparable between breast cancer and non-small cell lung cancer patients. The AUC is 11-34% higher for breast cancer patients. However, these differences were not evident from the PopPK analysis. The exposure parameters in breast cancer and non-small cell lung cancer patients in similar and not

considered clinically relevant. The observed differences are most likely due to the gender and weight differences in the different patient groups.

Therapeutic window

A lower boundary of the therapeutic window cannot be defined since there was no relationship between Dato-DXd PK and PFS or ORR in the pivotal TB01 study. In a pooled exposure-safety analysis, including safety data from NSCLC patients, a Dato-DXd dose of 8 mg/kg Q3W was identified as the MTD.

Special populations

Impaired renal function

No dedicated renal impairment (RI) study was conducted for Dato-DXd. The impact of renal impairment was evaluated in the PopPK model, in which creatinine clearance, CRCL (ml/min), determined by the Cockroft-Gault formula, was incorporated as a covariate and a measure of renal function. The PopPK dataset included 439 patients with mild RI, 176 with moderate RI, 2 patients with severe RI and 464 patients with normal renal function. Mild and moderate RI did not influence the steady state exposure. The impact of severe renal impairment has not been fully evaluated due to the limited number of patients.

Impaired hepatic function

No dedicated hepatic impairment (HI) study was conducted for Dato-DXd. The impact of HI on Dato-DXd and DXd PK was evaluated in the PopPK analysis, in which HI status was determined using the NCI-ODWG criteria from total bilirubin and alanine aminotransferase (AST) baseline values. The PopPK dataset included 295 patients with mild HI (total bilirubin ≤ ULN and any AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST), 6 subjects with moderate HI (total bilirubin >1.5 to 3 times ULN and any AST), one subject with severe HI (total bilirubin >3 times ULN and any AST) and 779 patients with normal function. No clinically meaningful differences in the steady-state exposure, AUCss, of Dato-DXd and DXd in patients with mild HI compared to patients with normal liver function, were observed. Patients with moderate and severe HI had greater than 140% relative increase in DXd AUCss and Cmax,ss. The analysis of moderate and severe HI was limited by the few patients in the data-set.

Gender

The effect of gender on the PK of Dato-DXd and DXd was evaluated in the PopPK model. Gender had no clinically relevant effect on the Cmax and AUC of Dato-DXd and DXd.

Ethnic factors

The impact of ethnic factors on the PK of Dato-DXd and DXd was evaluated in the PopPK analysis. The PopPK dataset of 1081 patients included: 510 (47.2%) white, 432 (40.0%) Asian, 19 (1.75%) black or african American and 79 multiple or other race. Ethnic factors did not have a clinically relevant effect on the PK of Dato-DXd and DXd. The Cmax and AUC differed <15% between the different ethnic groups.

Bodyweight

The effect of baseline body weight was evaluated in the PopPK analysis. Body weight was identified as a statistically significant covariate affecting both the clearance and the volume of distribution for Dato-DXd and DXd. The model estimated an increase of clearance and volume of distribution with increasing body weight. The 5th and 95th percentile of body weight (46 and 97 kg respectively) had a 21% lower and 25% higher predicted Dato-DXd AUCss compared to the reference patient(body weight of 64.2 kg). The impact on Cmax,ss for the same patients was similar with a 18% lower and 27% higher Cmax,ss compared to reference patient.

Elderly

The effect of age on the PK of Dato-DXd and DXd was assessed across the range of 26 to 86 years in the PopPK analysis (below table). Age was identified as a significant covariate on Dato-DXd linear clearance, with decrease in clearance with increasing age. Age did not show a clinically meaningful effect on Dato-DXd or DXd exposure. The increase of Dato-DXd AUCss at the 5th percentile (39 years) and 95th percentile of age (76 years) was estimated to be - 11.6% to 7% compared to the AUCss at the median age (60 years).

Table 20 Number of Patients by Age Categories in Individual Studies

PK study	Age 65 to 74 years (Older patients number /total number)	Age 75 to 84 years (Older patients number /total number)	Age 85+ years (Older patients number /total number)
TP01	77/295	26/295	0/295
TL05	32/137	14/137	0/137
TL01	114/297	21/297	0/297
TB01	72/360	18/360	1/360

Pharmacokinetic interaction studies

DDI of the antibody part of Dato-DXd is not expected, whereas DDI of the released payload DXd, as a small molecule, is a possibility. The potential of drug-drug interactions DXd was investigated in vitro and by leveraging clinical DDI data of the already approved DXd ADC trastuzumab deuruxtecan, Enhertu. The in vitro and in vivo DDI studies of DXd have previously been submitted and assessed as part of trastuzumab deuruxtecan (EMA/2446/2021).

As victim

In vitro data indicate that DXd is mainly metabolised by CYP3A, with involvement if CYP1A2 and 2D6 to a lesser extent. DXd is a substrate of P-glycoprotein, BCRP, OATP1B1, OATP1B3, MATE2-K, and MRP1. No clinical DDI studies were conducted with Dato-DXd to investigate the effect of inhibitors of CYP3A, P-glycoprotein, BCRP, OATP1B1, OATP1B3, MATE2-K, and MRP1 on the PK of DXd. However, for trastuzumab deuruxtecan a clinical DDI study was conducted with ritonavir (inhibitor of CYP3A4 and OATP1B1 and 1B3) and itraconazole (inhibitor of CYP3A4). The Cmax of DXd was not affected by ritonavir or itraconazole. The AUC of DXd was increased 1.2-fold by both inhibitors which was not considered clinically relevant. Therefore, inhibitors of CYP3A4, OATP1B1 and OATP1B3 will most likely

not have a clinically relevant effect on the PK of DXd released fromat Dato-DXd. Since, Dato-DXd is administered IV, inhibitors of P-glycoprotein and BCRP will not affect the exposure and will most likely affect the elimination to a limited extent (most of the DXd is metabolised). Inhibitors of MATE1 will most likely affect the elimination of DXd to a limited extent, since most of DXd is directly eliminated into feces via bile. Therefore no additional DDI studies are warranted.

As perpetrator

In vitro studies indicate that DXd is not an inhibitor of CYPs or transporters at clinically relevant systemic concentrations. Therefore, no clinical studies with DXd as perpetrator are warranted.

2.6.2.1. Pharmacodynamics

Mechanism of action

Datopotamab deruxtecan (Dato-DXd, DS-1062a) is an antibody-drug conjugate (ADC). Dato-DXd is a TROP2-targeted antibody and DNA topoisomerase I inhibitor conjugate. The anti-TROP2 component is a humanised IgG1κ monoclonal antibody. The total anti-TROP2 antibody is the sum of all DXd-conjugated and unconjugated mAb. The payload, DXd, is a DNA topoisomerase I inhibitor derivative of exatecan. The mAb is covalently conjugated to a drug-linker, MAAA-1162a, which is composed of a cleavable maleimide tetrapeptide linker and the payload (DXd. The tetrapeptide linker is designed to be stable in plasma to reduce systemic exposure of the payload. Dato-DXd binds to TROP2, and, after cell internalisation, the payload is released from the drug-linker through enzymatic processing. The released drug inhibits topoisomerase I, which leads to the inhibition of cell replication and promotes apoptosis of the target tumour cells. The released drug is cell membrane-permeable, giving it the ability to penetrate and act in surrounding cancer cells. The average drug-to-antibody ratio of Dato-DXd is 4.

Primary and Secondary pharmacology

No specific PD endpoints or biomarkers were defined and reported.

QTc prolonging effect

The relationship between concentration of Dato-DXd or DXd and change from baseline in QT (ΔQTc) was evaluated in Study TP01 using linear mixed effect modelling. The final models were used to predict means and 90% Cis for ΔQT at the highest observed geometric mean Cmax values across Cycles 1 and 3, for all subjects with valid data at the 6 mg/kg and 8 mg/kg doses. Some subjects were excluded from the Cmax calculation due to dose changes and other reasons, leaving 50 subjects at 6 mg/kg for both Dato-DXd and DXd, and at 8 mg/kg, 74 subjects for Dato-DXd and 76 subjects for DXd.

The dataset contained 2205 ECG assessments with timematched Dato-DXd concentrations (2203 assessments with DXd) from 195 subjects with NSCLC in Dato-DXd dose levels ranging from 0.27 to 10.0 mg/kg. The slopes of ΔQTc (ΔQTc with Fridericia correction as primary analysis [ΔQTcF]; QTc with Population-derived correction [ΔQTcP] as secondary analysis) vs concentration (of Dato-DXd or DXd) were estimated to be near zero at the α = 0.01 (below table).

Table 21 Predictions of Mean (90% CI) Δ QTc at the Geometric Means of Cmax observed at 6.0 to 8.0 mg/kg

Model (Analyte, Endpoint)	Cmax at 6.0 mg/kg	Predicted Δ QTc (msec)		Cmax at 8.0 mg/kg	Predicted Δ QTc (msec)	
		Mean	90% CI		Mean	90% CI
Dato-DXd, Δ QTcF	153 µg/mL	0.639	(-0.469, 1.75)	201 µg/mL	0.858	(-0.468, 2.18)
DXd, Δ QTcF	2.93 ng/mL	-0.130	(-1.37, 1.11)	3.51 ng/mL	-0.293	(-1.71, 1.12)
Dato-DXd, Δ QTcP	153 µg/mL	0.896	(-0.199, 1.99)	201 µg/mL	1.28	(-0.0300, 2.59)
DXd, Δ QTcP	2.93 ng/mL	0.720	(-0.538, 1.98)	3.51 ng/mL	0.854	(-0.588, 2.30)

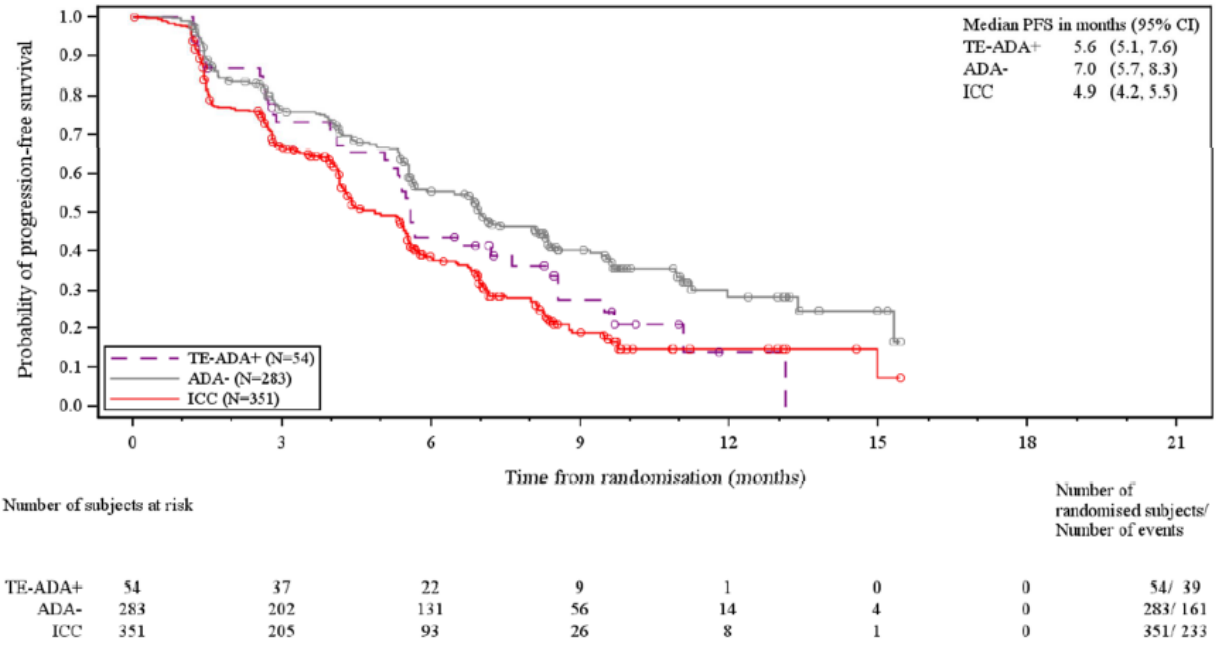
CI, confidence interval; Cmax, maximum observed plasma concentration; QTcF, corrected QT interval by Fridericia's formula; QTcP, population-derived QT interval correction.

Immunogenicity

Impact on efficacy

The potential impact of ADA on efficacy was assessed in TB01 study. Figure 12 Kaplan-Meier PFS (BICR) Curve for Dato-DXd Stratified by ADA Status (ADA evaluable Set, TB01) shows the Kaplan-Meier PFS curves for the Dato-DXd arm stratified by TE-ADA+ (those who were TE-ADA+ vs those who were ADA-).

Figure 12 Kaplan-Meier PFS (BICR) Curve for Dato-DXd Stratified by ADA Status (ADA evaluable Set, TB01)



Impact on safety

The assessment of Dato-DXd immunogenicity and the potential effect of ADA on safety was based on Study TB01 data and on the pooled dataset (BC pool) consisting of patients from BC Study TB01 and BC patients from Study TP01, who received the target dose of 6.0 mg/kg.

A summary of TEAEs and AESIs by ADA category is presented below.

Table 22 Summary of TEAEs by ADA Category (ADA Analysis Set) – TB01 and BC pool

AE category	Number (%) of patients [a]							
	TB01 (6 mg/kg) (N = 352)				BC pool (6 mg/kg) (N = 435)			
	TE-ADA+ (n = 54)	Non-TE-ADA+ (n = 15)	ADA- (n = 283)	nAb+ (n = 8)	TE-ADA+ (n = 60)	Non-TE-ADA+ (n = 17)	ADA- (n = 358)	nAb+ (n = 10)
Any TEAE, n (%)	54 (100)	15 (100)	273 (96.5)	8 (100)	60 (100)	17 (100)	348 (97.2)	10 (100)
CTCAE Grade ≥ 3	18 (33.3)	5 (33.3)	93 (32.9)	1 (12.5)	21 (35.0)	6 (35.3)	127 (35.5)	1 (10.0)
CTCAE Grade 5	0	0	0	0	0	0	1 (0.3)	0
Any TEAE associated with dose reduction	12 (22.2)	3 (20.0)	68 (24.0)	1 (12.5)	14 (23.3)	3 (17.6)	77 (21.5)	1 (10.0)
Any TEAE associated with infusion interruption	0	0	0	0	0	0	0	0
Any TEAE associated with dose delay	0	0	0	0	0	0	0	0
Any TEAE associated with drug interrupted	9 (16.7)	0	68 (24.0)	0	12 (20.0)	1 (5.9)	90 (25.1)	1 (10.0)
Any TEAE associated with drug withdrawn	1 (1.9)	2 (13.3)	8 (2.8)	0	1 (1.7)	2 (11.8)	14 (3.9)	0
Any TEAE associated with death	0	0	0	0	0	0	1 (0.3)	0
Any treatment-related TEAE, n (%)	54 (100)	14 (93.3)	261 (92.2)	8 (100)	60 (100)	16 (94.1)	335 (93.6)	10 (100)
CTCAE Grade ≥ 3	12 (22.2)	3 (20.0)	60 (21.2)	1 (12.5)	15 (25.0)	4 (23.5)	76 (21.2)	1 (10.0)
CTCAE Grade 5	0	0	0	0	0	0	0	0
Any serious TEAE, n (%)	10 (18.5)	2 (13.3)	41 (14.5)	1 (12.5)	10 (16.7)	2 (11.8)	54 (15.1)	1 (10.0)
CTCAE Grade ≥ 3	9 (16.7)	2 (13.3)	35 (12.4)	1 (12.5)	9 (15.0)	2 (11.8)	48 (13.4)	1 (10.0)
CTCAE Grade 5	0	0	0	0	0	0	1 (0.3)	0
Any treatment-related serious TEAE, n (%)	4 (7.4)	1 (6.7)	16 (5.7)	1 (12.5)	4 (6.7)	1 (5.9)	19 (5.3)	1 (10.0)
CTCAE Grade ≥ 3	4 (7.4)	1 (6.7)	12 (4.2)	1 (12.5)	4 (6.7)	1 (5.9)	15 (4.2)	1 (10.0)
CTCAE Grade 5	0	0	0	0	0	0	0	0

TE-ADA+ were patients who were either treatment-boosted ADA+ or treatment-induced ADA+. Non-TE-ADA+ were patients who were ADA positive but not fulfilling the conditions for TE-ADA+. ADA- was defined as patients who were ADA- at all assessments, including baseline and post-baseline. nAb+ was defined as patients with positive nAb assessment at any visit.

Percentages were based on the number of subjects in the ADA Analysis Set. TEAEs were coded using MedDRA version 26.0 and graded using NCI CTCAE version 5.0 for TB01, TL01 and TL05, and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01.

A TEAE was defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TL01, TL05, TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy was not considered as a subsequent anticancer therapy in TB01. Dose delay and infusion interruption were only collected in TL01, and TL05.

If a patient had both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade was treated as the lowest severity grade.

Table 23 Summary of AESIs by ADA Status (ADA Analysis Set) – TB01 and BC pool

Category	Number (%) of patients							
	TB01 (N = 352)				BC pool (6 mg/kg) (N = 435)			
	TE-ADA+ (n = 54)	Non-TE-ADA+ (n = 15)	ADA- (n = 283)	nAb+ (n= 8)	TE-ADA+ (n = 60)	Non-TE-ADA+ (n = 17)	ADA- (n = 358)	nAb+ (n = 10)
Any adjudicated ILD	2 (3.7)	1 (6.7)	7 (2.5)	0	2 (3.3)	1 (5.9)	8 (2.2)	0
Any adjudicated ILD Grade ≥ 3	2 (3.7)	0	0	0	2 (3.3)	0	1 (0.3)	0
Any serious adjudicated ILD	2 (3.7)	0	1 (0.4)	0	2 (3.3)	0	2 (0.6)	0
Any treatment-related adjudicated ILD	2 (3.7)	0	7 (2.5)	0	2 (3.3)	0	8 (2.2)	0
Any adjudicated ILD associated with death	1 (1.9)	0	0	0	1 (1.7)	0	0	0
Any IRR	10 (18.5)	1 (6.7)	21 (7.4)	3 (37.5)	12 (20.0)	1 (5.9)	32 (8.9)	4 (40.0)
Any IRR Grade ≥ 3	0	0	1 (0.4)	0	0	0	1 (0.3)	0
Any treatment-related IRR	9 (16.7)	0	17 (6.0)	3 (37.5)	11 (18.3)	0	27 (7.5)	4 (40.0)
Any IRR associated with death	0	0	0	0	0	0	0	0
Any mucosal inflammation other than stomatitis/oral mucositis	2 (3.7)	0	3 (1.1)	0	2 (3.3)	0	3 (0.8)	0
Any mucosal inflammation other than stomatitis/oral mucositis Grade ≥ 3	0	0	0	0	0	0	0	0
Any treatment-related mucosal inflammation other than stomatitis/oral mucositis	2 (3.7)	0	3 (1.1)	0	2 (3.3)	0	3 (0.8)	0
Any mucosal inflammation other than stomatitis/oral mucositis associated with death	0	0	0	0	0	0	0	0
Any ocular surface toxicity	30 (55.6)	8 (53.3)	136 (48.1)	4 (50.0)	33 (55.0)	9 (52.9)	164 (45.8)	5 (50.0)
Any ocular surface toxicity Grade ≥ 3	0	1 (6.7)	2 (0.7)	0	0	1 (5.9)	3 (0.8)	0
Any treatment-related ocular surface toxicity	25 (46.3)	7 (46.7)	111 (39.2)	3 (37.5)	28 (46.7)	8 (47.1)	135 (37.7)	4 (40.0)

Any ocular surface toxicity associated with death	0	0	0	0	0	0	0	0
Any stomatitis/oral mucositis	31 (57.4)	9 (60.0)	169 (59.7)	3 (37.5)	37 (61.7)	10 (58.8)	233 (65.1)	5 (50.0)
Any stomatitis/oral mucositis Grade ≥ 3	3 (5.6)	0	22 (7.8)	0	6 (10.0)	1 (5.9)	27 (7.5)	0
Any treatment-related stomatitis/oral mucositis	30 (55.6)	9 (60.0)	160 (56.5)	3 (37.5)	35 (58.3)	10 (58.8)	221 (61.7)	4 (40.0)
Any stomatitis/oral mucositis associated with death	0	0	0	0	0	0	0	0

TE-ADA+ were patients who were either treatment-boosted ADA+ or treatment-induced ADA+. Non TE-ADA+ were patients who were ADA positive but not fulfilling the conditions for TE-ADA+. ADA- was defined as patients who were ADA- at all assessments, including baseline and post-baseline. nAb+ was defined as patients with positive nAb assessment at any visit.

Percentages are based on the number of subjects in the ADA Analysis Set. TEAEs were coded using MedDRA version 26.0 and graded using NCI CTCAE version 5.0 for TB01, TL01 and TL05, and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01.

If a patient had more than one event per AESI category (or preferred term) level, the patient was counted once at each level of summation.

If a patient had both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade was treated as the lowest severity grade.

Grades for adjudicated ILDs and adjudicated drug-related ILDs were from the adjudication committee. IRR terms were defined by the occurrence of the relevant preferred term up to 24 hours after dosing.

Where events occurred the day after an infusion and onset time is not provided, these patient are excluded from the table. Dose delay and infusion interruption were only collected in TL01, and TL05.

Source: see ISI Table 2.7.4.6.8, Module 5.3.5.3.

Relationship between plasma concentration and effect and safety

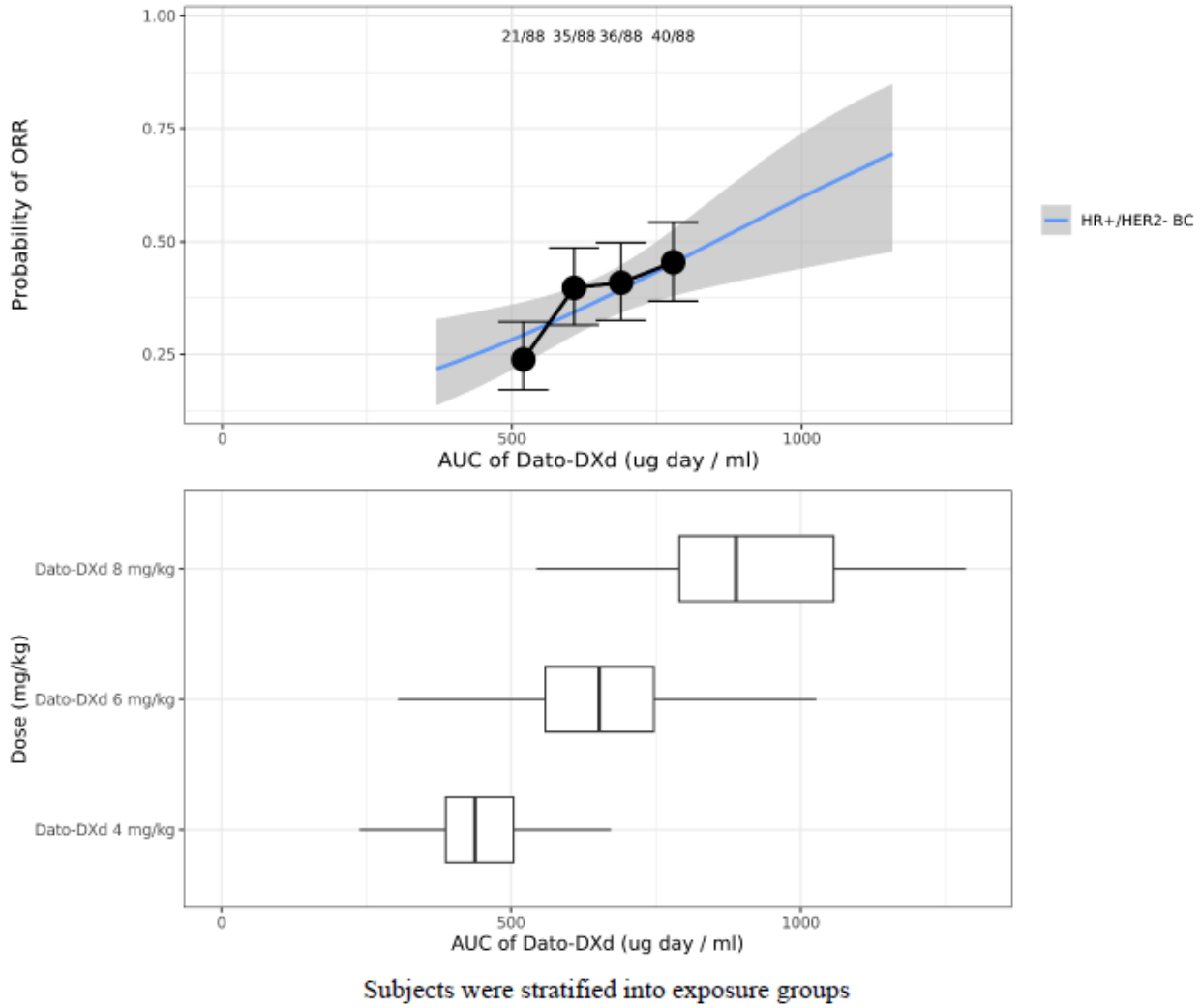
Exposure-efficacy analyses

The analysis of efficacy endpoints encompassed all of the HR-positive, HER2-negative BC patients (n= 352) from TB01. Individual post-hoc Dato-DXd exposure metrics were derived from the final Population PK model using simulated Dato-DXd and DXd time-course PK profiles.

Exposure-efficacy results for ORR

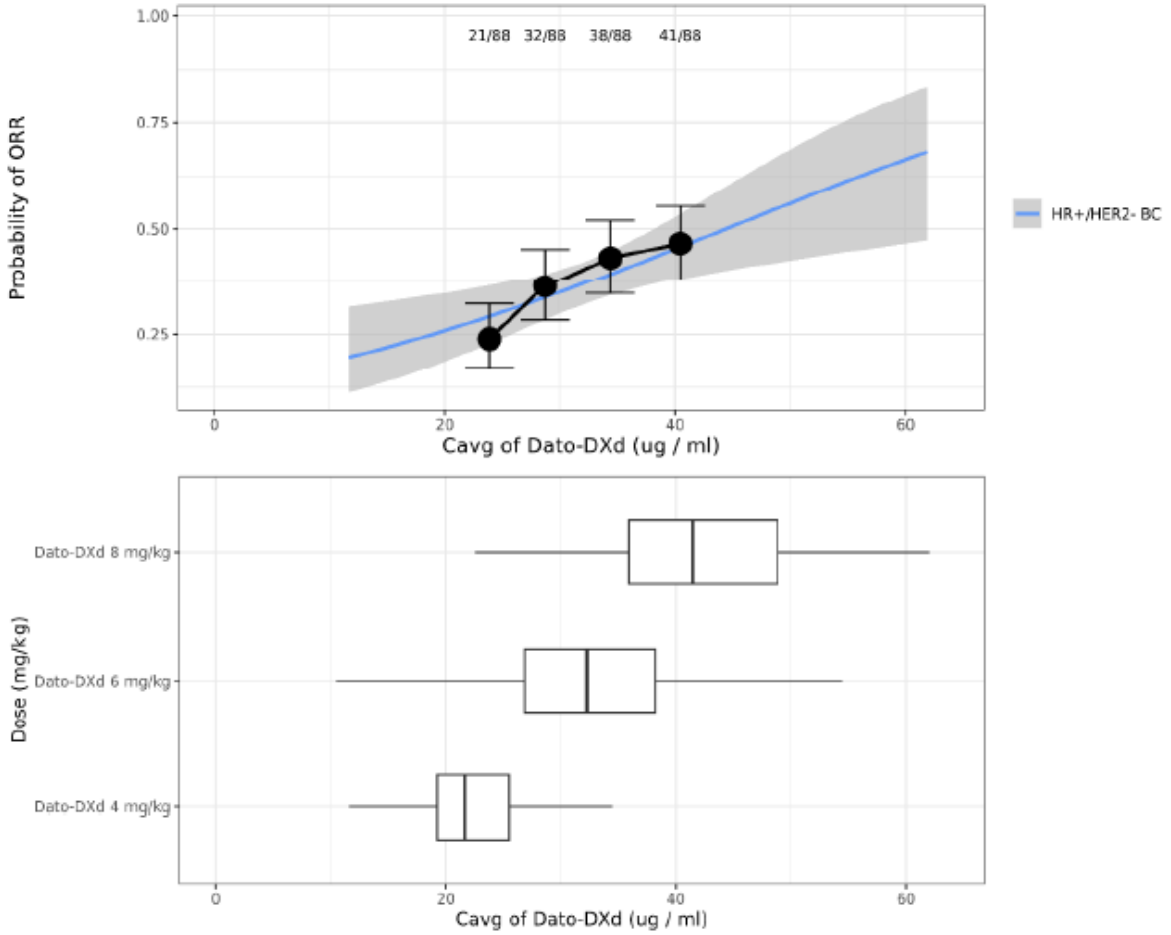
For the probability of being a responder in the four quartiles of Dato-DXd exposure metrics (AUC1), together with an exploratory figure from the logistic regression (below figures). The results of Cavg were similar.

Figure 13 Exposure Response Analysis of ORR with Respect to cycle 1 Dato-DXd AUC



Circles = observed proportions of event per exposure quartile; Fractions indicate the total number of events over the total number of patient within the exposure quantile; Horizontal boxplots show the exposure for 4, 6, and 8 mg/kg of Dato-DXd in all patients from pooled BC and NSCLC patients (the data from ORR logistic regression only consist of TB01 HR-positive/HER2-negative BC patients dosed at 6 mg/kg of Dato-DXd); Smoothed lines represent observed proportions of event fitted by generalized linear model (glm); Vertical error bars and the grey shaded region around the glm curve represent the 95% confidence interval of the observed data.

Figure 14 Exposure-response Analysis of ORR with Respect to Dato-DXd Cavg



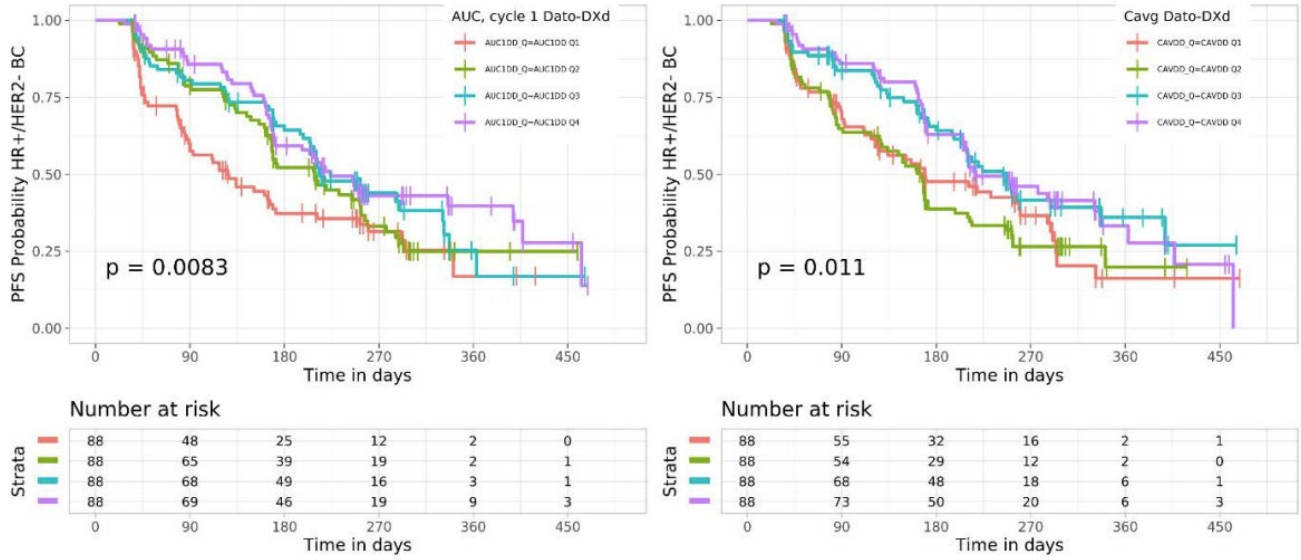
Subjects were stratified into exposure groups; Vertical error bars and the grey shaded region around the glm curve represent the 95% confidence interval of the observed data

Subjects were stratified into exposure groups; Vertical error bars and the grey shaded region around the glm curve represent the 95% CI of the observed data. Circles represent observed proportions of event per exposure quartile; Fractions indicate the total number of events over the total number of subjects within the exposure quartile; Horizontal boxplots show the exposure for 4, 6, and 8 mg/kg of Dato-DXd in all subjects from pooled BC and NSCLC subjects (the data from ORR logistic regression only consist TB01 HR-positive, HER2-negative BC of subjects dosed at 6 mg/kg of Dato-DXd); Smoothed lines represent observed proportions of event fitted by glm.

Exposure-efficacy results for PFS

Kaplan-Meier curves stratified by Dato-DXd exposure quartiles are presented in Figure 15**.** The Cox PH model analysis identified baseline tumor size as the significant ($p<0.001$) prognostic factor for the PFS hazard, while the exposure of Dato-DXd was not considered as a significant covariate for PFS ($p>0.001$).

Figure 15 Progression Free Survival as Assessed by BICR Stratified by Dato-DXd Exposure



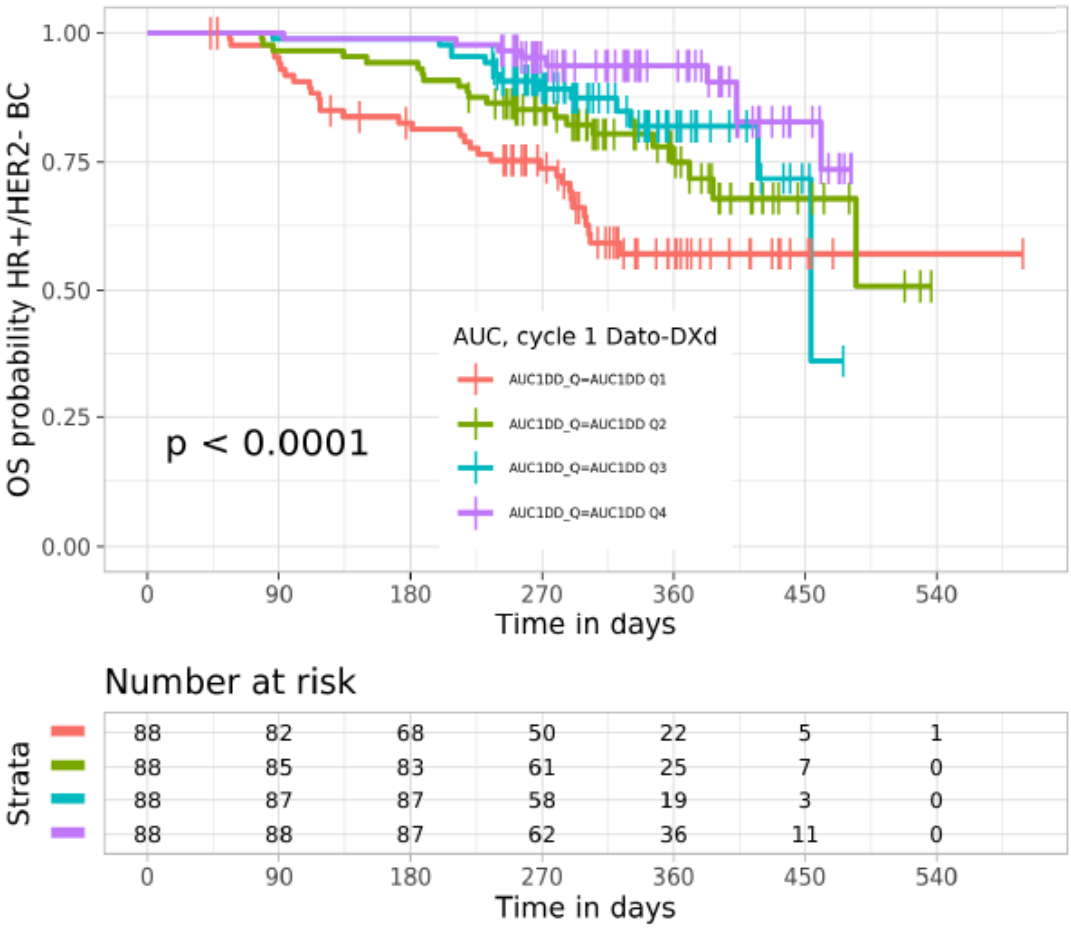
(left: Dato-DXd cycle 1 AUC and right: Dato-DXd Cavg)

The Red, green, blue and purple lines represent the exposure metric quartiles with Q1 being the lowest and Q4 the highest; The solid lines represent the % of subjects alive; Vertical bars indicate where one or multiple subjects have been censored in time.

Exposure-efficacy results for OS

Kaplan-Meier curves stratified by Dato-DXd exposure quartiles are presented in Figure 16. The Cox PH model analysis identified Dato-DXd exposure as a significant ($p<0.001$) covariate for the OS hazard. However, the OS data is considered immature as the median survival time cannot be determined for the above median Population.

Figure 16 Overall Survival Stratified by Dato-DXd Exposure



The Red, green, blue and purple lines represent the exposure metric quartiles with Q1 being the lowest and Q4 the highest; The solid lines represent the % of subjects alive; Vertical bars indicate where one or multiple subjects have been censored in time; The count indicates the number of patients.

Exposure-safety analyses

The ER analyses for safety were conducted using data from 644, 393, and 44 NSCLC, HR-positive, HER2-negative BC and TNBC patients, respectively, in Studies TB01, TL01, TL05, and TP01. Safety endpoints for the exposure-safety analyses are as follows:

· Grade ≥ 3 TEAEs

· Serious TEAEs

· TEAEs associated with dose interruption, dose reduction, or treatment discontinuation

· Oral mucositis/stomatitis (any grade and Grade ≥ 2)

· Adjudicated drug-related ILD

· Ocular surface toxicity (any grade and Grade ≥ 2)

Individual post-hoc Dato-DXd and DXd exposure metrics were derived from the final Population PK model using the actual individual dosing histories. The Dato-DXd and DXd exposure metrics included for all endpoints are AUC1, Cmax1, and Cavg. A logistic regression model was used to derive the exposure-safety relationship.

The following covariates of clinical interests were evaluated in the exposure-safety analyses: baseline demographics (race, age, sex, body weight, region), albumin, tumour size, number of prior lines of therapy, last prior line therapy being IO, history of CNS metastasis, history of liver metastasis, ECOG performance status, smoking status, tumour type and prior use of CDK4/6 inhibitor.

Among the 1081 evaluable patients in the exposure-safety analysis Population, 919 patients received 6.0 mg/kg. The remaining patients received a dose of < 4.0 mg/kg (n = 22), 4.0 mg/kg (n = 50), or ≥ 8.0 mg/kg (n = 90).

Results:

Exposure-safety relationships were observed between Dato-DXd or DXd exposure and 8 AE endpoints: Grade ≥ 3 TEAEs, serious TEAEs, TEAEs associated with dose interruption, TEAEs associated with dose reduction, oral mucositis/stomatitis (any grade), oral mucositis/stomatitis (Grade ≥ 2), ocular surface toxicity (any grade), and ocular surface toxicity (Grade ≥ 2) with dose range of 0.27 to 10 mg/kg.

No relevant ER relationship was observed between Dato-DXd or DXd exposure and the safety endpoints of adjudicated drug-related ILD and TEAEs associated with treatment discontinuation. The current conclusion for adjudicated drug-related ILD is based on limited number of events.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of Dato-DXd was evaluated by modelling and simulation studies, in vitro studies and clinical pharmacology studies. The relevant analytes for an ADC as Dato-DXd were quantified in the conducted clinical studies: conjugated drug (Dato-DXd), total AB (total anti-TROP2 antibody) and the payload (DXd). Overall, the bioanalytics performed in support of the Dato-DXd clinical program is found to be in accordance with regulatory requirements. The immunogenicity assays were validated according to regulatory guidelines. The proposed clinical dose of Dato-DXd is 6 mg/kg in patients on Day 1 of each 21-day cycle for patients with a body weight of <90 kg and a dose of 540 mg for patients ≥90 kg. The dose may be decreased to 4 mg/kg (up to a maximum of 360 mg for patients ≥90 kg) and even to 3 mg/kg (up to a maximum of 270 mg for patients ≥90 kg) in case of adverse events.

The comparability of the 3 Dato-DXd drug formulations administered to patients in the conducted clinical studies was evaluated. It was demonstrated that the different drug products with regards to pharmacokinetics can be considered comparable. However, clinical data after a single dose across studies TP01, TL01 and TL05 suggest that tmax of DXd is reached earlier for the to-be-marketed lyophilized powder formulation versus the frozen-liquid formulation at the therapeutic dose of 6 mg/kg. Upon request, the difference in mean tmax was explained as a result of PK-sampling scheme and the flat PK-profile of DXd.

A human mass-balance study was not conducted to determine the routes of excretion of DXd in line with recently approved ADCs. This is acceptable due to the high toxicity of the payload preventing that such studies be conducted in healthy volunteers. It is assumed that DXd is primarily eliminated hepatically by metabolism and biliary excretion in humans, where billiary excretion is presumely the most important pathway of elimination. The analysis of DXd elimination is reasonable in the lack of human mass-balance data and was as previously reported for T-DXd. The in vitro metabolism studies of DXd were previously submitted and reviewed as part of the trastuzumab deruxtecan dossier (see Enhertu EPAR EMA/2446/2021). The metabolism of DXd in humans has been investigated using in vitro methods. The lack of in vivo investigation is justified and acceptable.

The upper boundary of the therapeutic window was determined whereas the lower boundary in BC could not be defined.

The impact of renal (RI) and hepatic impairment (HI) on the PK of Dato-DXd and DXd has been adequately evaluated in the PopPK model. No dedicated RI or HI studies were conducted. This is considered acceptable due to the toxicity of Dato-DXd, in line with previously approved T-DXd. As DXd is primarily cleared by the liver, metabolism and biliary excretion, the systemic exposure of the toxic payload DXd could be increased in patients with moderate and severe HI, potentially resulting in an increased systemic toxicity in this population. A more than 140% increase in DXd exposure at steady state, AUCss was reported in the limited number of patients with moderate and severe HI. As metabolism and biliary excretion are the primary routes of elimination of DXd, Datroway should be administered with caution in patients with moderate and severe hepatic impairment (see sections 4.2, 4.4 and 5.2 of the SmPC). Gender, age and ethnic factors were demonstrated not to impact the PK of Dato-Dxd and DXd in a clinically relevant manner using PopPK modelling. Very limited data of Dato-DXd is available in patients above 85 years. The impact of body weight on the PK-parameters and exposure of Dato-DXd and DXd were investigated by PopPK modelling. It was demonstrated that the mean AUCss and Cmaxss of Dato-DXd and DXd in the 5th and 95th percentile was outside the 0.8-1.25 range. The impact of body weight is further discussed below under pharmacodynamics. Overall, the evaluation of the PK of Dato-DXd and DXd in special populations is acceptable and has been appropriately reflected in the SmPC.

The DDI potential of DXd has been assessed adequately. All in vitro DDI studies were previously submitted and reviewed as part of the approved deruxtecan ADC, T-DXd. No DDI potential was identified for DXd as perpetrator. The potential object DDI has not been evaluated in a dedicated clinical DDI study. In vitro studies indicated that DXd is mainly metabolised by CYP3A and is a substrate of P-glycoprotein, BCRP, OATP1B1, OATP1B3, MATE2-K, and MRP1. No clinical DDI studies were conducted with Dato-DXd. However, clinical drug-drug interaction studies were conducted with T-DXd. The C_{max} of DXd was not affected by ritonavir (inhibitor of CYP3A4 and OATP1B1 and 1B3) or itraconazole (inhibitor of CYP3A4). The AUC was increased 1.2-fold by both inhibitors which was not considered clinically relevant. Therefore, inhibitors of CYP3A4, OATP1B1 and OATP1B3 will most likely not have a clinically relevant effect on the PK of DXd released from Dato-DXd. Dato-DXd is administered IV inhibitors of P-glycoprotein and BCRP will not affect the exposure and will most likely affect the elimination to a limited extent (most of the deruxtecan is metabolised). Inhibitors of MATE1 will most likely affect the elimination of deruxtecan to a limited extent, since deruxtecan is mostly eliminated via metabolism. Therefore no additional DDI studies are warranted.

Pharmacodynamics

Dato-DXd is a TROP2-targeted antibody and DNA topoisomerase I inhibitor conjugate (antibody-drug conjugate). The mechanism of action has been sufficiently characterised and described.

No specific PD endpoints or biomarkers were defined and reported, and no biomarker claims are presented.

Data from study DS1062-A-J101 (cutoff date of 30 Jul 2021), was used for evaluation of a potential c-QTc relation. The parameters of the final models were estimated with good precision except for slope. A large number of ECG records with missing PK (about 20%) were excluded. In a c-QTc analysis, the highest observed geometric mean Cmax values across Cycles 1 and 3 were used to ensure maximum exposure. At the proposed 6 mg/kg dose, the upper bound of the 90% CIs for ΔQTc(F) at the geometric mean Cmax for DXd was 1.11 ms, indicating that no significant increase in QTc is expected with the proposed dose regimen.

No clinical drug interaction studies with datopotamab deruxtecan have been conducted; this is acceptable. No PD interactions are expected.

Based on the provided data, presence of ADAs (including Nabs) does not seem to negatively affect the efficacy or safety associated with the treatment with Dato-DXd.

Data for the E-R analyses came from studies A-J101 (TP01), A-U202 (TL05), A-U301 (TL01) and TB01. Exposure metrics were generated by the Pop PK model. Efficacy endpoints were evaluated in the breast cancer population while the safety analyses also contained data from subjects with NSCLC. Cox Proportional Hazards models were used assess OS and PFS, while logistic regression models were used to assess ORR and safety events. Body weight was not found to be a significant covariate of efficacy across the investigated body weight range. Forest plots of odds ratio of safety events related to exposure stratified by body-weight categories indicated that patients with body-weights >81 kg had odds ratios >1 based on their median Dato-DXd and DXd exposures. In the >100 kg group the odds ratio ranged from 1.46 to 2.26. A dose cap for patients above 90 kg body weight would be appropriate, as it would reduce the risk of serious adverse events. SmPC section 4.2 suggests that the recommended dose is up to a maximum of 540 mg for patients ≥90 kg.

Based on mature OS data (OS at interim analysis 2; (395/444 events)), a positive relationship between OS and exposure of Dato-DXd ($P<0.001$) is assumed.

As for exposure-safety, a relationship was observed between Dato-DXd or DXd exposure and 8 AE endpoints, including Grade ≥ 3 TEAEs, serious TEAEs, and TEAEs associated with dose interruption/reduction.

2.6.4. Conclusions on clinical pharmacology

A sufficient investigation of the clinical pharmacology of Dato-DXd has been conducted, both with regards to pharmacokinetics and pharmacodynamics, using in vitro studies, clinical pharmacology studies and by PopPK modelling. In conclusion, the provided clinical pharmacology package supports approval of Dato-Dxd in breast cancer.

2.6.5. Clinical efficacy

Table 24 Clinical studies

Study Status DCO	Study Design	Treatment Groups and Dose Regimen	Outcome measures	Number of patients
Studies supporting clinical efficacy and safety				
Pivotal Phase III study				

Study Status DCO	Study Design	Treatment Groups and Dose Regimen	Outcome measures	Number of patients
TROPION-Breast01 Ongoing (DCO: 17 July 2023 for Final PFS analysis; OS IA1)	Open-label, randomized study of Dato-DXd versus ICC (capecitabine, gemcitabine, eribulin mesylate, or vinorelbine) in subjects with inoperable or metastatic HR+/HER2- BC who have been treated with one or 2 prior lines of systemic chemotherapy in the inoperable/metastatic setting.	Dato-DXd 6 mg/kg IV on Day 1, Q3W Chemotherapy: - Capecitabine 1000 or 1250 mg/m^2 BID PO on Days 1 to 14, Q3W or - Gemcitabine 1000 mg/m^2 IV on Days 1 and 8, Q3W or - Eribulin mesylate 1.4 mg/m^2 IV on Days 1 and 8, Q3W or - Vinorelbine 25 mg/m^2 IV on Days 1 and 8, Q3W	Primary: *Efficacy*-Dual endpoints PFS (by BICR) and OS Secondary: *Efficacy* - PFS (by investigator); ORR, DoR, and DCR (by BICR/investigator); TFST, TSST, and PFS2 *Safety* - AEs, laboratory evaluations, ECOG PS, ECHO/MUGA, physical examinations, vital signs, ECG, and ophthalmologic assessments PK and immunogenicity PROs: secondary endpoints of TTD in pain, physical function, and GHS/QoL Exploratory: IncludesTROP2 IHC expression and exposure/efficacy relationship, additional PRO	732 (total randomised) 365 (Dato-DXd) 367 (ICC)

Study Status DCO	Study Design	Treatment Groups and Dose Regimen	Outcome measures	Number of patients
Supportive Phase I/II studies (also contributed data to the pooled safety analysis)				
TROPION-PanTumor01 Ongoing NSCLC: 30 Jul 2021 BC: 22 Jul 2022	Phase 1, 2-part, multicenter, open-label, multiple dose, FTIH study of DS-1062a in subjects with advanced solid tumors	Dose Escalation Dose levels from 0.27 to 10 mg/kg IV on Day 1, Q3W Dose Expansion 4, 6, and 8 mg/kg IV on Day 1, Q3W Note: All patients with HR positive, HER2 negative metastatic BC received 6 mg/kg IV on Day 1, Q3W	Primary: Safety (including AEs, DLTs) Secondary: PK Efficacy data from BC cohort only included as supportive evidence	**NSCLC:** 0.27 mg/kg (n=4) 0.5 mg/kg (n=5) 1 mg/kg (n=7) 2 mg/kg (n= 6) 4 mg/kg (n=50) 6 mg/kg (n=50) 8 mg/kg (n=80) 10 mg/kg (n=8) **TNBC:** 6 mg/kg (n=42) 8 mg/kg (n=2) HR-positive, HER2 negative BC: 6 mg/kg (n=41)

AE, adverse event; BC, breast cancer; BICR, blinded independent central review; BID, twice daily; CSR, clinical study report; CYP, Cytochrome P450; Dato-DXd, Datopotamab deruxtecan (formerly DS 1062a); DCO, data cut-off; DCR, disease control rate; DDI, drug-drug interaction; DLT, dose limiting toxicity; DoR, duration of response; ECG, electrocardiogram; GHS, Global health status; HER2-negative, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; IA1, interim analysis 1; ICC, Investigator's choice of chemotherapy; IV, intravenous; n/N, number of patients; NSCLC, non-small cell lung cancer; OATP, organic anion transporting polypeptide; OD, once daily; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic(s); PO, per oral; PRO, patient reported outcome; Q3W, once every 3 weeks; QoL, quality of life TTD; time to deterioration.

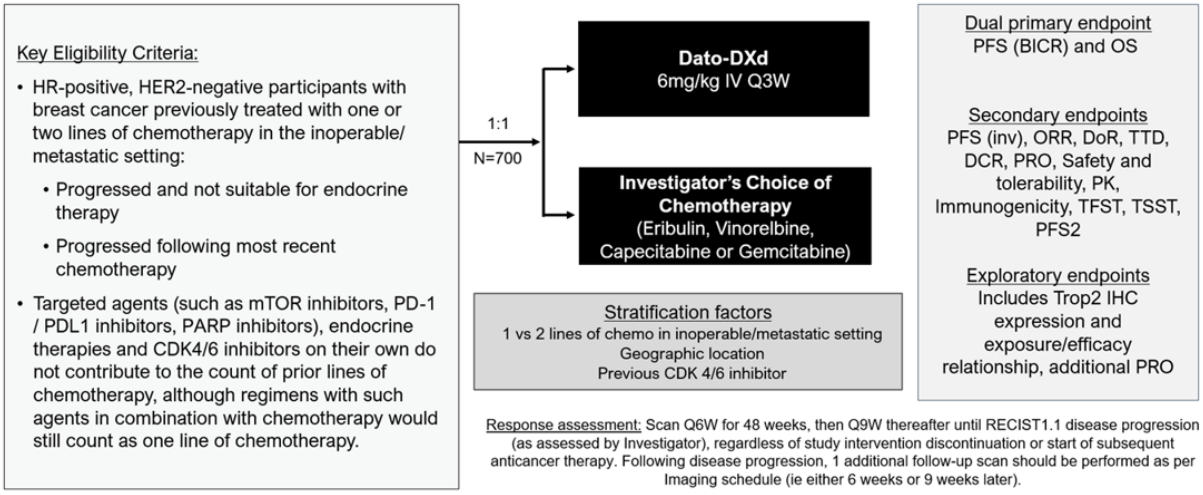
2.6.5.1. Dose response study(ies)

Please refer to the section on Clinical pharmacology and Supportive study TP01 for more details.

2.6.5.2. Main study

TROPION-Breast01 (TB01): a global, randomised, multicentre, open-label Phase III trial evaluating the efficacy and safety of datopotamab deruxtecan versus investigator's choice of single-agent chemotherapy in adult patients with unresectable or metastatic HR-positive, HER2-low or negative breast cancer who have progressed on and are not suitable for endocrine therapy and have received at least one additional systemic therapy for unresectable or metastatic disease.

Figure 17 TB01 Study Design



BICR, blinded independent central review; CDK4/6, cyclin-dependent kinases 4 and 6 inhibitors; DCR, disease control rate; DoR, duration of response; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PDL-1, programmed death-ligand 1; PFS, progression-free survival; PFS2, time from randomisation to second progression; PK, pharmacokinetic(s); PRO, patient reported outcome; Q3W, once every 3 weeks; Q6W, once every 6 weeks; Q9W, once every 9 weeks; RECIST 1.1, response evaluation criteria in solid tumours version 1.1; TFST, time from randomisation to the first subsequent progression; TSST, time from randomisation to the second subsequent progression; TTD, time to deterioration.

Methods

- **Study Participants**

All patients must have had inoperable or metastatic HR -positive-,, HER2 -negative BC [IHC 0, IHC1+ or IHC2+/ISH-] per ASCO/CAP guidelines, on local laboratory results) who progressed on and were not suitable for endocrine therapy per investigator assessment and must have been treated with one to 2 lines of prior standard of care chemotherapy in the inoperable/metastatic setting. HER2-negative includes HER2-low, which is defined as IHC 1+ or IHC 2+/ISH-.

The target population of interest in Study TB01 was required to have a formalin--fixed paraffin- embedded- tumour sample at the time of screening for the patient to be included in the study unless approval was given by the Sponsor.

Inclusion Criteria

1. Participant must be ≥ 18 years (≥ 20 years in Japan) at the time of screening.

2. Inoperable or metastatic HR-positive, HER2-negative breast cancer (per ASCO/CAP guidelines, on local laboratory results); ie, is documented as HR-positive (either ER and/or PgR positive [ER or PgR ≥ 1%]) and HER2-negative. If a participant had multiple results after metastatic disease, the most recent local test result will be used to confirm eligibility (Allison et al 2020, Wolff et al 2018).

3. Progressed on or not suitable for endocrine therapy per investigator assessment, and treated with 1 to 2 lines of prior chemotherapy in the inoperable/metastatic setting. Participant must have documented progression on their most recent line of chemotherapy. **Note:** If a chemotherapy drug is changed within 28 days of use to another drug in the same class (ie, antimetabolite to antimetabolite) for any reason, the first drug is not counted as a line (Flatiron 2019). Targeted agents (such as mTOR inhibitors, PD-1/PD-L1 inhibitors), endocrine therapies, and CDK4/6 inhibitors on their own do not contribute to the count of prior lines of chemotherapy; however, regimens with such agents in combination with metastatic chemotherapy should be classified as one line of chemotherapy. PARP inhibitor treatment should be classified as one line of therapy.

4. Eligible for one of the chemotherapy options listed as ICC (eribulin, capecitabine, vinorelbine, gemcitabine), per investigator assessment. **Note:** Participants who previously received any of these agents are eligible for enrolment to another ICC agent in this study.

5. ECOG PS of 0 or 1, with no deterioration over the previous 2 weeks prior to day of first dosing.

6. At least 1 measurable lesion not previously irradiated that qualifies as a RECIST 1.1 Target Lesion at baseline and can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT or MRI, which is suitable for accurate repeated measurements. **Note**: Participants with bone-only metastases are not permitted.

7. Participants with a history of previously treated neoplastic spinal cord compression, or clinically inactive brain metastases, who require no treatment with corticosteroids or anticonvulsants, may be included in the study, if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of radiotherapy and study enrolment.

8. Adequate organ and bone marrow function.

9. LVEF≥ 50% by either an echocardiogram or MUGA within 28 days of first dosing.

10. Has had an adequate treatment washout period before Cycle 1 Day 1.

11. All participants must have available a FFPE tumor sample (block preferred, or a minimum of 20 freshly cut slides), at the time of screening. This can be from either the primary disease setting (surgical resection or diagnostic sample), or from a metastatic lesion (excluding bone) for tissue-based analysis (including but not restricted/limited to IHC staining of potential predictive biomarkers as well as tumor mutational analysis).

12. Minimum life expectancy of 12 weeks at screening.

13. Male or female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies; however, oral estrogens are not permitted.

14. Negative pregnancy test (urine and/or serum) for women of childbearing potential

15. Female participants must be post-menopausal for at least 1 year, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly).

16. Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception.

Exclusion Criteria

1. As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, uncontrolled hypertension, history of allogeneic organ transplant, and active bleeding diseases, ongoing or active infection, or significant or cardiac or psychological conditions) which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardize compliance with the protocol.

2. History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 3 years before the first dose of study intervention and of low potential risk for recurrence. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy, adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated.

3. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; suspected infections (eg, prodromal symptoms); or inability to rule out infections.

4. Known active or uncontrolled hepatitis B or C infection; or positive for hepatitis B or C virus based on the evaluation of results of tests for hepatitis B (HBsAg, anti-HBs, anti-HBc, or HBV DNA) or hepatitis C (HCV antibody or HCV RNA) infection at screening. **Note**: Participants who have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis, and participants who have been curatively treated for hepatitis C infection (as demonstrated clinically and by viral serologies) are eligible.

5. Known HIV infection that is not well controlled.

6. Uncontrolled or significant cardiac disease, including myocardial infarction or uncontrolled/unstable angina within 6 months prior to C1D1, CHF (New York Heart Association Class II to IV), uncontrolled or significant cardiac arrhythmia, or uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg).

7. Investigator judgment of 1 or more of the following:

- Mean resting corrected QTcF interval > 470 ms, obtained from triplicate ECGs performed at screening.

- History of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and cause Torsades de Pointes.

- Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.

8. 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.

9. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within three months of first dosing, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc), or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, Rheumatoid arthritis, Sjogren's, sarcoidosis etc), or prior pneumonectomy.

10. Leptomeningeal carcinomatosis.

11. Clinically significant corneal disease.

12 Known active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).

13. Any of the following prior anticancer therapies:

- Any treatment (including ADC) containing a chemotherapeutic agent targeting topoisomerase I

- TROP2-targeted therapy

- Prior treatment with same ICC agent

- (**Note**: Participants are eligible for enrolment into this study if they able to receive treatment with another ICC agent not previously received; see the Inclusion Criteria)

14. Any concurrent anticancer treatment, with the exception of bisphosphonates, denosumab, for the treatment of bone metastases.

15. Concurrent use of hormonal therapy for non-cancer -related conditions (eg, hormone replacement therapy, except topical).

16. Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

17. Receipt of live, attenuated vaccine within 30 days prior to the first dose of study treatment.

18. Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing adverse events (inhaled steroids or intra articular steroid injections are permitted in this study). **Note**: Participants with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.

19. Previous treatment in the present study.

20. Known history of severe hypersensitivity reactions to other monoclonal antibodies.

- **Treatments**

Table 25 Investigational products

Arm name / Intervention name	Arm 1: Dato-DXd	Arm 2: Investigator's Choice of Chemotherapy			
		Capecitabine	Gemcitabine	Eribulin	Vinorelbine
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Lyophilized powder for concentrate for solution for infusion	Tablet	Injection	Solution for injection	Injection
Unit Dose Strength(s)	100 mg vials	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]	As sourced locally [a]
Dosage Level(s)	6 mg/kg on Day 1 of each 21-day cycle	1000 or 1250 mg/m^2 BID on Days 1 to 14 of a 21-day cycle [b]	1000 mg/m^2 on Days 1 and 8 of a 21-day cycle	1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle [c]	25 mg/m^2 on Day 1 and 8 of a 21-day cycle [d]
Route of Administration	IV infusion	Oral	IV infusion	IV infusion	IV infusion

- **Objectives**

Dual primary objectives

- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of OS in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting.

Secondary objectives

- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of ORR in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DoR in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting, per investigator assessment.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of DCR in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting, per BICR and per investigator assessment.
- To assess pain in patients treated with Dato-DXd compared to ICC.
- To assess physical functioning in patients treated with Dato-DXd compared to ICC.
- To assess global health status/quality of life (GHS/QoL) in patients treated with Dato-DXd compared to ICC.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TFST in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of TSST in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting.
- To demonstrate the superiority of Dato-DXd compared to ICC by assessment of PFS2 in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who have been treated with one or 2 lines of chemotherapy in the inoperable/metastatic setting.
- To assess the PK of Dato-DXd 6 mg/kg IV Q3W.

To investigate the immunogenicity of Dato-DXd 6 mg/kg IV Q3W.

- **Outcomes/endpoints**

Planned analyses

Table 26 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who sign the ICF.
ITT population	All participants who are randomized in the study. The ITT will be used for all the efficacy analyses (including PROs). Treatment groups will be compared on the basis of randomized study intervention, regardless of the intervention actually received. Participants who were randomized but did not subsequently receive study intervention are included in the analysis in the intervention group to which they were randomized.
SAS	Participants who have received at least 1 dose of study intervention. Safety data will not be formally analyzed but summarized using the SAS according to actual study intervention received.
PAS	All participants randomly assigned to study intervention who received at least 1 dose of study intervention for whom any post-dose PK data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the sponsor Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

Table 27 Pre-planned Statistical and Sensitivity Analyses to be Conducted for Primary Endpoints

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank test for: Dual primary analysis using BICR RECIST 1.1 assessments: • Dato-DXd versus ICC (ITT population) Secondary analysis using Investigator assessment: • Dato-DXd versus ICC (ITT population) Sensitivity analysis for the dual primary analysis (ITT population): • Evaluation-time bias • Attrition bias • Ascertainment bias
Overall survival	Stratified log-rank test for: Dual primary analysis: • Dato-DXd versus ICC (ITT population)

Primary endpoints

PFS

PFS is analysed using a stratified log-rank test adjusting for the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor.

The hazard ratio (HR) and its 95% confidence interval and the appropriate CI according to the significance level in the MTP and p-value are presented. The HR and CI are estimated from a stratified Cox Proportional Hazards model (with ties = Efron and stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor) and the CI calculated using a profile likelihood approach. A HR less than 1 favours Dato-DXd.

Estimates and 95% CI for PFS rates at 3 months intervals and median PFS for each treatment group are presented.

The treatment status at progression of participants at the time of analysis is summarised. This includes the number (%) of participants who were on treatment at the time of progression, the number (%) of

participants who discontinued IP prior to progression, the number (%) of participants who have not progressed and were on IP or discontinued IP.

Kaplan-Meier (KM) plots of PFS are presented by treatment group. Summaries of the number and percentage of participants experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided for each treatment. The number of participants censored may be summarised by treatment group together with baseline prognostic factors of the censored participants. This number and percentage of prematurely censored participants is summarised. A participant will be defined as prematurely censored if they did not progress (or die in the absence of progression) and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

Proportionality assumption

The assumption of proportionality will be assessed. Proportional hazards will be tested firstly by examining plots of log(-log(survival probability)) versus log (time) and, if these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-ln(time) interaction term) to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect can be described by presenting piecewise HR calculated over distinct time-periods for example 0- 6m, 6-12m etc. In such circumstances, the HR from the primary analysis can still be meaningfully interpreted as an average HR over the observed extent of follow-up unless there is extensive crossing of the survival curves. If lack of proportionality is found this may be a result of a treatment-by-covariate interaction, which will be investigated.

Sensitivity Analysis

1. Evaluation-time bias: A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analysed using a stratified log-rank test, as described for the primary analysis of PFS. Note that midpoint values resulting in non-integer values should be rounded down. For participants whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules.

To support this analysis, the mean of participant-level average inter-assessment times will be tabulated for each treatment. This approach will use the BICR RECIST assessments.

2. Attrition bias: Attrition bias is assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of participants who progressed or died in the absence of progression immediately following two, or more, missed tumour assessments are included. In addition, and within the same sensitivity analysis, participants who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death are censored at their last evaluable assessment prior to taking the subsequent therapy.

This analysis is supported by a KM plot of the time to censoring using the PFS data from the primary analysis and where the censoring indicator of the PFS analysis is reversed.

3. Ascertainment bias: Ascertainment bias is assessed by analysing the site investigator data which is a secondary efficacy endpoint. The stratified log rank test is repeated on PFS using the site investigator data based upon RECIST. The HR and CI are presented.

If there is an important discrepancy between the primary analysis using the BICR data and this sensitivity analysis using site investigator data a summary table is produced showing the number and

proportion of participants with site but no central confirmation of progression and with progression determined by central review but not at site. Such participants have the potential to induce bias in the central review due to informative censoring. An approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists. Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group.

4. Subsequent Anti-cancer Therapy: An additional sensitivity analysis is produced which is a repeat of the primary analysis for PFS, but the censoring rule is modified so that participants who take subsequent therapy prior to their last evaluable RECIST assessment or progression or death are censored at their last evaluable assessment prior to taking the subsequent anti-cancer therapy.

A forest plot illustrating the hazard ratio and 95% confidence interval will be provided to compare the primary and sensitivity analyses of progression free survival.

OS

Overall survival will be analysed using a stratified log-rank test, adjusting for the stratification factors at randomisation. The treatment effect of Dato-DXd against ICC will be estimated by the HR together with its 95% CI and the appropriate CI according to the significance level in the MTP. Estimates and 95% CI for OS rates at 6 monthly intervals are presented along with the median OS for each treatment group.

Kaplan-Meier (KM) plots of OS are presented by treatment group. Summaries of the number and percentage of participants who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided.

Secondary endpoints

ORR

The analysis will include all randomized participants as randomized, with measurable disease at baseline. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

The ORR will be compared between the treatment arms using a logistic regression model adjusting for the same stratification factors as the PFS as covariates in the model. The results of the analysis will be presented in terms of an adjusted odds ratio (OR) together with its associated 95% CI and p-value. If there are not enough responses for a meaningful analysis using logistic regression, then a CMH test is presented. The CMH test is stratified using the same stratification factors as PFS. The results of the analysis are presented in terms of an OR together with the 95% CI and p-value.

Comparisons between treatment groups will be made using both BICR RECIST 1.1 and investigator assessments. Summaries will be produced that present the number and percentage of participants with a tumor response (CR/PR).

<u>BOR</u>

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment. It is the best response a participant has had following randomization, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorization of BoR will be based on RECIST using the following response categories: CR, PR, SD, PD, and NE.

Best objective response will be determined programmatically based on RECIST from the overall visit response using all BICR data up until the first progression event. It will also be determined programmatically based on RECIST using all site investigator data up until the first progression event. The denominators for each case will be consistent with those used in the ORR analysis.

DOR

The analysis will include all randomized participants as randomized who have a confirmed response, regardless of whether the participant withdraws from therapy, receives another anti-cancer therapy or clinically progresses prior to RECIST 1.1 progression.

Duration of response will be analyzed by summary statistics and Kaplan-Meier plots. Comparisons will be presented for both BICR RECIST 1.1 and investigator assessments.

PFS by Investigator assessment

This secondary endpoint of PFS based Investigator assessment will be analyzed using the same methodology described for the primary endpoint PFS.

DCR at 12 weeks

The analysis will include all randomized participants as randomized. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to week 11 will not be considered to have disease control in the analysis.

Disease control rate will be analyzed using the same methodology specified for ORR.

TFST and TSST

The time to first subsequent therapy and the time to second subsequent therapy analysis will include all randomized participants as randomized, regardless of progression status.

These two endpoints will be analyzed using the same methodology as that used for the analysis of PFS. In addition, medians and a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be summarized.

PFS2

Time to second progression or death will be analyzed using identical methods as outlined for PFS.

TTD

The secondary PRO endpoints include:

-TTD in pain as measured by the pain scale from EORTC QLQ-C30

-TTD in physical functioning as measured by the physical functioning scale from EORTC QLQ-C30

-TTD in GHS/QoL as measured by the GHS/QoL scale from EORTC QLQ-C30.

Time to deterioration (TTD) is defined as time from the date of randomization to the date of deterioration. Deterioration is defined as change from baseline that reaches a clinically meaningful deterioration threshold. Anchor-based methods using the participant-based anchors PGIS and PGIC will be considered to define thresholds for clinically meaningful within-participant change used in the TTD endpoints. Other methods including distribution-based methods, cumulative distribution function, and probability density function curves, and methods using other anchors may also be considered.

Clinically meaningful thresholds will be estimated for the following patient-reported outcomes:

-EORTC QLQ-C30: Global health status/QoL, functioning, and select symptom subscales including pain and fatigue

-EORTC QLQ IL116: breast symptoms, arm symptoms.

The analysis to define clinically meaningful change thresholds in the TTD PRO endpoints will include all randomized participants using the pooled treatment arms data prior to database lock. These TTD PRO endpoints will be analyzed using the same time-to-event analysis methodology described for the primary endpoint PFS.

- **Sample size**

Approximately 1000 participants will be enrolled to achieve approximately 700 randomly assigned to study intervention. The study is sized for dual primary endpoints to characterise the PFS and OS benefit of Dato-DXd versus ICC in the participants with HR-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy in the inoperable/metastatic setting. The study will be considered positive (a success) if either the PFS analysis results and/or the OS analysis results are statistically significant.

For the primary analysis of PFS assuming the true PFS treatment effect under the alternative hypothesis is a hazard ratio of 0.55 for Dato-DXd versus ICC, and the median PFS times of 4.7 months and 8.5 months in ICC and Dato- DXd, 419 PFS events from the FAS Population (60% maturity) will provide greater than 99% power to demonstrate statistical significance at the 2-sided alpha level of 1.0%. This also assume the median PFS times in both groups are exponentially distributed. The smallest treatment difference that is statistically significant will be a hazard ratio of 0.775. Assuming a recruitment period of 19 months, this analysis is anticipated to be approximately 21 months after the first participant has been randomised.

The primary analysis of OS will be performed when approximately 444 OS events from the FAS have occurred across the Dato-DXd and ICC treatment groups (63% maturity). Assuming the true OS hazard ratio is 0.75 for Dato-DXd versus ICC, and the median OS in ICC is 19.0 months, the study will have 85% power to demonstrate statistical significance at the 5.0% level (using a 2-sided test). This assumes the PFS primary analysis crosses the efficacy threshold, and allowing 2 interim analyses to be conducted at information fractions of approximately 40% and 80% of the target events, respectively (per the O'Brien and Fleming approach). The smallest treatment difference that could be statistically significant at the primary OS analysis is a hazard ratio of 0.824.

If the PFS primary analysis does not cross the efficacy threshold, the OS analysis will have 83% power to demonstrate statistical significance at the 4.0% level (using a 2-sided test).

The smallest treatment difference that could be statistically significant at the primary analysis is a hazard ratio of 0.817. All OS calculations assume median OS times of 19.0 months and 25.3 months in ICC and Dato-DXd, respectively when the survival times are exponentially distributed.

With a recruitment period of approximately 19 months, it is anticipated that the primary OS analysis will occur approximately 44 months after the first participant has been randomised.

The study may continue monitoring participants for OS up to the scheduled primary analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

A nonuniform accrual of participants (with $k = 1.5$) is assumed when estimating the analysis times. The total proportion of participants randomised at time t [$t \leq 19$ months] following the start of the study is assumed to be $(t/19)k$.

- **Randomisation and Blinding (masking)**

This randomized, open-label, 2-arm study will investigate Dato-DXd monotherapy versus ICC (eribulin, vinorelbine, capecitabine, or gemcitabine).

Approximately 700 participants will be randomized in a 1:1 ratio to one of 2 intervention arms.

The blocked Randomization will be stratified by the following prognostic and/or predictive factors:

- Number of previous lines of chemotherapy (1 versus 2)
- Geographic region (Region 1 [US, Europe] versus Region 2 [Rest of World])
- Prior use of CDK4/6 inhibitor (Yes versus No)

- **Statistical methods**

Planned subgroup analyses

Subgroup analyses are conducted comparing PFS and OS between the treatments for the following subgroup of the FAS:

1. Stratification factors at randomisation:

- Number of previous lines of chemotherapy: 1, 2
- Geographic region: Region 1 [US, Canada, Europe], Region 2 [Rest of World]
- Prior use of CDK4/6 inhibitor: Yes, No

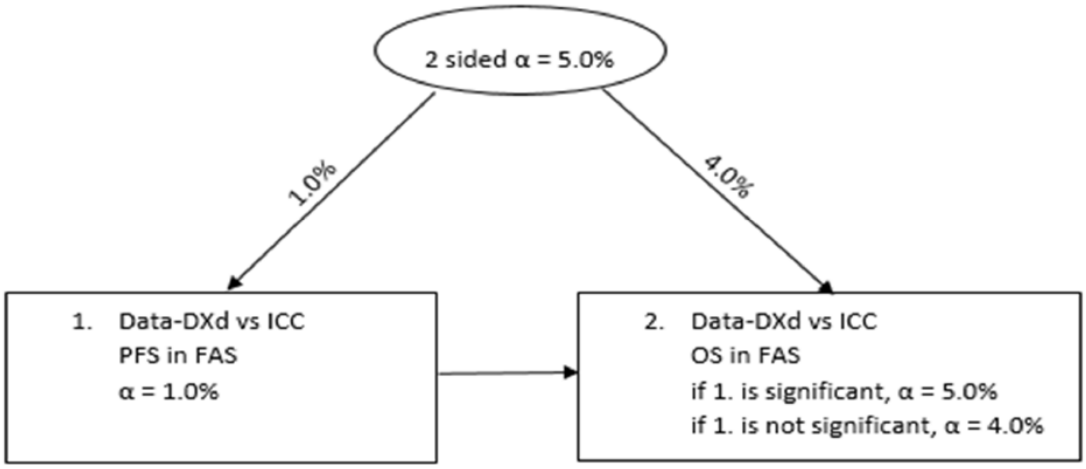
2. Exploratory factors

- Prior use of taxanes and/or anthracyclines: taxanes alone, anthracyclines alone,
- both taxanes and anthracyclines, neither taxanes nor anthracyclines
- Age at randomisation: <65, ≥65 years of age
- Race: Asian, non-Asian
- Pre-selected investigator's choice of chemotherapy: Capecitabine, Gemcitabine,
- Eribulin mesylate, Vinorelbine
- Brain metastases: Yes, No
- Sex: male, female

Multiplicity

To preserve the overall type 1 error (familywise error rate) at 5% in the strong sense, a multiple testing procedure (MTP) for the dual primary endpoints of PFS and OS is implemented at DCO2, DCO3 and DCO4. An overview of the MTP with an alpha-splitting and exhaustive recycling strategy is provided below.

Figure 18 Multiple Testing Procedure



An alpha level of 1.0% will be allocated to the PFS primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses. If the PFS primary analysis meets statistical significance, the 1.0% type 1 error allocated to PFS endpoint will be reallocated to the OS endpoint for a total 2-sided type 1 error of 5.0%. If the PFS primary analysis does not meet statistical significance, the OS endpoint will have a total 2-sided type 1 error of 4.0%. Alpha spending functions are applied for the OS endpoint in order to preserve the overall 2- sided type 1 error (familywise error rate) in the strong sense across the three planned analyses of OS.

The Lan DeMets approach that approximates the O'Brien and Fleming spending function will be used to account for multiplicity introduced by including 2 interim analyses for superiority of OS.

The significance level alpha for OS across the three analysis times is dependent on the OS information fraction (number of OS events at interim/number of OS events at primary). The significance levels are calculated at the time of the analyses based on the number of events observed.

No multiplicity adjustment is applied for other endpoints as other endpoints are considered supportive endpoints.

Interim analysis

Details of the planned timing of the two interim and final analyses are provided below. Note that the actual allocation of alpha across the three analysis times will be driven by the actual information fraction associated with the analysis.

The interim analyses will be performed by an IDMC. It is expected that recruitment will have completed prior to the results of the interim analyses being available. For the interim analyses, the IDMC will review unblinded interim data and inform the sponsor whether the interim boundaries specified in the table below are met.

Table 28 Summary of Planned Timings of the Interim and Final OS Analyses

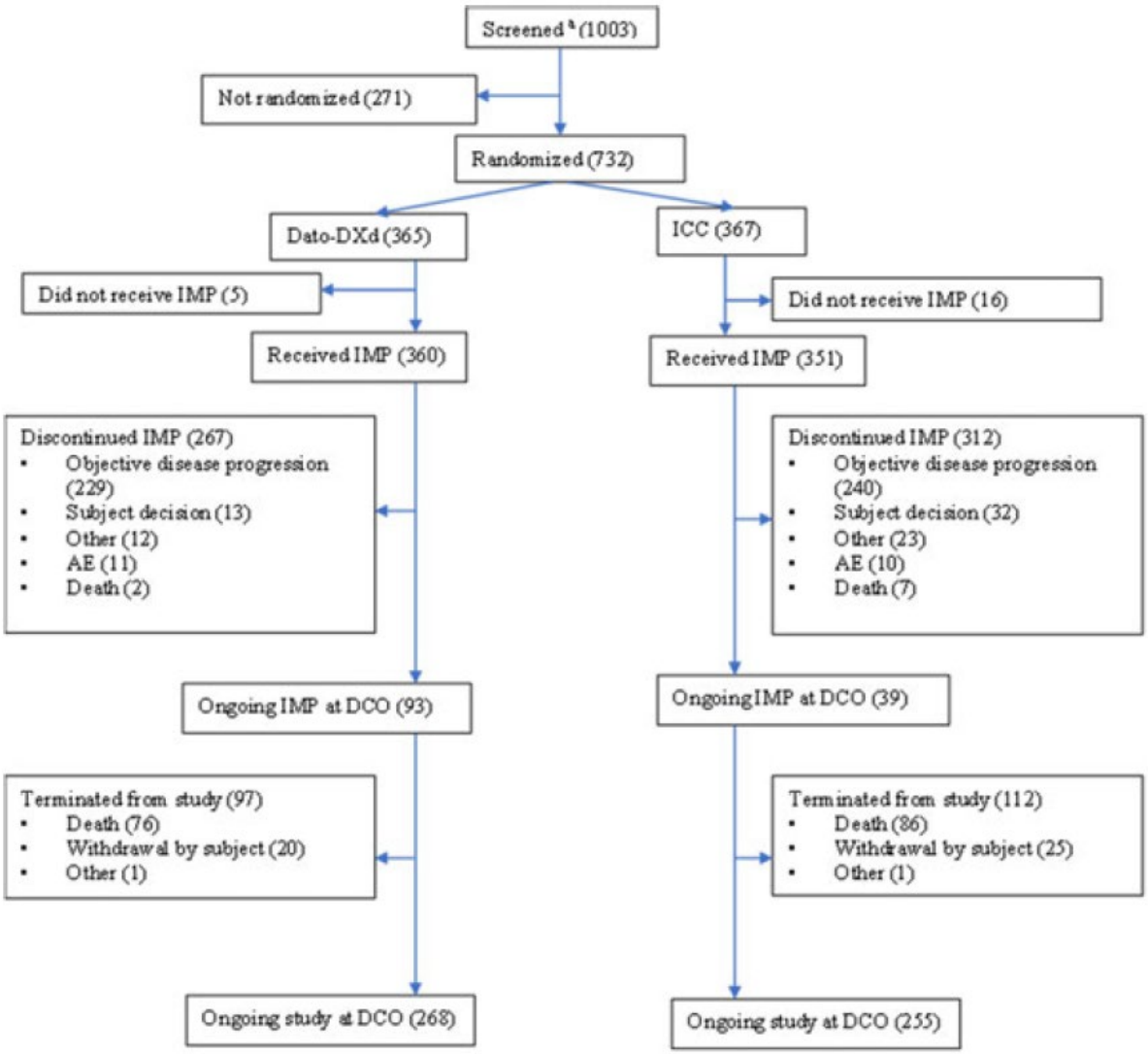
	Interim Analysis 1		Interim Analysis 2		Primary Analysis	
Projected Timing	21 Months [b]		34 Months		44 Months	
Number of Deaths [a]	178		355		444	
Information Fraction	40%		80%		100%	
Maturity	25%		51%		63%	
Recommendation	**Continue**	**Reject Null Hypothesis**	**Continue**	**Reject Null Hypothesis**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
At 4.0% 2-sided alpha [c]						
2-sided nominal p-value	≥ 0.0005	< 0.0005	≥ 0.0184	< 0.0184	≥ 0.0345	< 0.0345
Estimated hazard ratio	≥ 0.591	< 0.591	≥ 0.777	< 0.777	≥ 0.817	< 0.817
At 5.0% 2-sided alpha [c]						
2-sided nominal p-value	≥ 0.0008	< 0.0008	≥ 0.0241	< 0.0241	≥ 0.0427	< 0.0427
Estimated hazard ratio	≥ 0.604	< 0.604	≥ 0.786	< 0.786	≥ 0.824	< 0.824

[a] Estimates based on exponential survival where the median OS is 19.0 months for ICC and 25.3 months for Dato-DXd. The total proportion of participants randomized at time t [$t \leq 19$ months] following the start of the study is assumed to be $(t/19)^{1.5}$.
[b] Timing of first IA based on PFS. Number of deaths is an estimate.
[c] Alpha allocated to OS endpoint (4.0% or 5.0%) dependent on statistical significance of PFS.

The study may continue monitoring participants for OS up to the scheduled final analysis, beyond planned interim analyses, to provide more refined estimates of treatment effects for survival.

Results

Figure 19 Participant flow



[a] Screened subjects are those who signed informed consent.

Subjects are summarized in the arm to which they were randomized.

Source: Table 14.1.1.IA1

Table 29 Patient disposition at IA1 (Data cut-off: 17 July 2023)

	Dato-DXd n (%)	Total ICC n (%)	Capecitabine n (%)	Gemcitabine n (%)	Eribulin mesylate n (%)	Vinorelbine n(%)	Total n (%)
Subjects screened [a]							1003
Subjects not randomised							271
Screen failures							250
Death							3
Lost to follow-up							0
Study terminated by sponsor							0
Withdrawal by subject							16
Other							2
Subjects randomised [b]	365 (100)	367 (100)	76 (20.7)	33 (9.0)	220 (59.9)	38 (10.4)	732 (100)
Subjects randomised, not treated	5 (1.4)	16 (4.4)	1 (1.3)	2 (6.1)	13 (5.9)	0	21 (2.9)
Subjects started treatment	360 (98.6)	351 (95.6)	75 (98.7)	31 (93.9)	207 (94.1)	38 (100)	711 (97.1)
Subjects ongoing treatment at data cut-off date [c]	93 (25.8)	39 (11.1)	14 (18.7)	2 (6.5)	22 (10.6)	1 (2.6)	132 (18.6)
Subjects discontinued treatment [c]	267 (74.2)	312 (88.9)	61 (81.3)	29 (93.5)	185 (89.4)	37 (97.4)	579 (81.4)
Subject decision	13 (3.6)	32 (9.1)	9 (12.0)	3 (9.7)	15 (7.2)	5 (13.2)	45 (6.3)
Adverse event	11 (3.1)	10 (2.8)	2 (2.7)	0	8 (3.9)	0	21 (3.0)
Severe non-compliance to protocol	0	0	0	0	0	0	0
Objective disease progression	229 (63.6)	240 (68.4)	45 (60.0)	22 (71.0)	144 (69.6)	29 (76.3)	469 (66.0)
Subject lost to follow-up	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Death	2 (0.6)	7 (2.0)	1 (1.3)	0	6 (2.9)	0	9 (1.3)
Other	12 (3.3)	23 (6.6)	4 (5.3)	4 (12.9)	12 (5.8)	3 (7.9)	35 (4.9)
Subjects ongoing in study at data cut-off date	268 (73.4)	255 (69.5)	57 (75.0)	22 (66.7)	154 (70.0)	22 (57.9)	523 (71.4)
Subjects completed study	0	0	0	0	0	0	0
Subjects withdrawn from study	97 (26.6)	112 (30.5)	19 (25.0)	11 (33.3)	66 (30.0)	16 (42.1)	209 (28.6)
Death	76 (20.8)	86 (23.4)	13 (17.1)	8 (24.2)	52 (23.6)	13 (34.2)	162 (22.1)
Lost to follow-up	0	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0	0
Withdrawal by subject	20 (5.5)	25 (6.8)	6 (7.9)	3 (9.1)	13 (5.9)	3 (7.9)	45 (6.1)
Other	1 (0.3)	1 (0.3)	0	0	1 (0.5)	0	2 (0.3)

[a] Screened subjects are those who signed informed consent.
[b] For ICC arms percentages are based on the total number of subjects randomised to ICC. For Dato-DXd and total arms percentages are based on the number of subjects randomised.
[c] Percentages are based on the number of subjects started treatment.
Subjects are summarised in the arm to which they were randomised.
Percentages are based on the number of subjects randomised, with the exception of those marked [b] and [c].
ICC Investigator's choice chemotherapy. n Number of subjects per category.

- **Recruitment**

The pivotal study started recruitment 18 October 2021 and the current DCO is 17 July 2023 from 166 active sites in 20 countries/regions. Hence, the median duration of PFS follow-up in censored patients was 8.1 months (range: 0.0 to 15.4 months) in the Dato-DXd arm and 4.0 months (range: 0.0 to 15.4 months) in the ICC arm.

- **Conduct of the study**

The original CSP was dated 01 July 2021 and it was amended 3 times. Changes in the conduct of the study that were implemented by CSP amendments are shown and briefly described in below table.

Table 30 Protocol amendments related to changes in study conduct

Amendment Number/Date	Key details of amendment (substantial changes)	Main reason(s) for amendment
Amendments made *before* the start of patient recruitment		
1 (27 August 2021)	• Updated the ophthalmologic assessments in the SoA and Section 8.2.5.5 of the CSP • Ocular surface toxicity added as an AESI • Section 9.3.6 - added ophthalmologic analysis set • Section 9.6.3 - added details around the independent Ophthalmologic Data Review Committee	To provide additional guidance for investigators on the monitoring and management of ocular surface toxicities potentially associated with Dato-DXd.
	Oral care plan added to the SoA and Section 8.2.5.6	Clarification of the oral care protocol to be used to mitigate the risk of oral mucositis/stomatitis.
	Section 1.2 schema and inclusion criterion #3 – removed PARP inhibitors from being considered a prior line of chemotherapy	To ensure that enrolled patients had received at least one prior line of chemotherapy.
	Exclusion criterion #9 - Additional note added regarding ineligibility of patients found to have ILD/pneumonitis on baseline screening chest CT.	To ensure patients enrolled did not have active ILD.
	Section 6.2.1.2 - added guidance around dose re-calculation if patient's weight changed during the study.	Original wording was lacking information important for correct dose re-calculation.
	Section 6.6.1 Table 5 - amended dose reduction thresholds and added guidance around optimizing use of prophylactic and supportive medications.	For patient safety, emphasis was placed on providing prophylactic/supportive medications (when appropriate); in addition, dose reductions for Grade 3 toxicities (regardless of time of resolution) were added for most non-hematologic toxicities.
	Sections 9.4.2.1 and 9.4.2.1.3 – added 'subsequent anticancer therapy' to list of sensitivity analyses.	Additional sensitivity analysis to assess robustness of PFS dual primary analysis.
	Section 9.4.2.1.5 - added 2 additional subgroups: prior use of taxanes and/or anthracyclines, and pre-selected choice of chemotherapy. Clarified that forest plot of the PFS hazard ratios were to be produced for each level of the subgroups.	More detailed subgroup analysis to provide additional data, and terminology clarification.
Amendments made *after* the start of patient recruitment		
2 (19 April 2022)	Sections 1.1, and 5.1 - Removed requirement for patients in Japan to be ≥ 20 years	Update to the civil code for age of adulthood in Japan.
	Section 1.3 (SoA) - updated details to clarify that safety assessments did not have to be repeated if they had been performed within 72 hours prior to the day of dosing	To allow flexibility in patient management without compromising safety.
	Sections 2.3.1.1 and 8.3.11 - Labeled "stomatitis/oral mucositis" as an identified risk/AESI and established "mucosal inflammation other than oral mucositis/stomatitis" as a separate identified risk/AESI. Removed anaphylaxis in relation to IRR.	To align with latest Dato-DXd safety profile information.
	Inclusion criterion #8 - Limit of AST/ALT criteria extended to assess adequate organ and bone marrow function. Removed INR or prothrombin time, and either PTT or aPTT criteria.	To allow flexibility in patient enrollment without compromising safety.
	Inclusion criterion #15, Appendix G 1 – removed reference to HRT in relation to female patient contraception. Updated contraceptive requirement to 3 months before C1D1	HRT is contraindicated for HR-positive disease.
	Exclusion criterion #3 - removed allowance of study physician judgment and added examples of permitted toxicities related to previous anticancer therapy	To provide operational flexibility without compromising safety

	Exclusion criterion #19 - removed exclusion criteria to allow for the enrollment of patients using chronic systemic corticosteroids	To align with AstraZeneca Dato-DXd program standards
	Section 6.7 - added text regarding continuation of open-label treatment and alternative supply options should they have become available.	To align with AstraZeneca program standards
	Section 8.2.5.3 - added troponin assessment to the ILD/pneumonitis investigations. Clarified that bronchoscopy and bronchoalveolar lavage were options and added optional lung biopsy to the ILD/pneumonitis investigations	To align with AstraZeneca Dato-DXd program standards to rule out cardiac etiology
	Section 8.2.5.5 and 8.3.11 - added that the assessments were to be performed by an ophthalmologist, or if unavailable, another licensed eye care provider	To align with AstraZeneca Dato-DXd program standards
	Section 8.3.1 - added specific AEs that should have been reported within 24 hours of the investigator becoming aware	To align with AstraZeneca program standards
	Section 8.3.11 - Removed combined elevations of aminotransferases and bilirubin. Added the actions to be taken for ILD/pneumonitis cases. Clarified dry eye as an identified risk and keratitis as a potential risk within the ocular surface toxicity AESI	To align with AstraZeneca Dato-DXd program standards
	Section 8.3.14.1 - Added that AstraZeneca were to be notified of any female patient or partner of a male patient who may have become pregnant while receiving or within 7 months of discontinuing Dato-DXd	To align with AstraZeneca Dato-DXd program standards
3 (10 October 2022)	Exclusion criterion #6 - Updated definition of well controlled HIV infection. Clarified recommendation to monitor viral RNA load and CD4+ count, and that patients must have been tested for HIV if acceptable by local regulations or an IRB/IEC	To align with AstraZeneca Dato-DXd program standards
	Section 8.3.1 - Added Grade ≥ 2 keratitis events to list of AEs to be reported by the investigator in eCRF within 24 hours of awareness	To align with AstraZeneca Dato-DXd program standards
	Non-substantial changes to add possibility of mainland China cohort and to provide flexible language for the inclusion of a mainland China-specific recruitment tail, if required	

C1D1 = Cycle 1 Day 1.

Changes to the planned analyses are shown in the table below, indicating when any changes were made in relation to the unblinding of study data. The study was unblinded on 18 September 2023. The Sponsor study team remain blinded to OS data at IA1.

Table 31 Changes to planned analyses

Key details of change	Reason for change	SAP amendment?
Changes made before unblinding of study data		
Table 9 (population for analysis) in the CSP states that all PROs were to be analyzed using the FAS population, while the PRO endpoints that measured patient-reported symptomatic AEs and overall treatment tolerability should have been analyzed based on the safety population per Table 4 (objectives and endpoints) in the CSP, ie, among patients who received any amount of study intervention and according to the actual treatment received.	To clarify the inconsistent language in the CSP on the analysis population used for PRO endpoints between Table 4 Objectives and Endpoints and Table 9 Populations for Analysis and align the SAP with the analysis population as specified for each PRO endpoint in the CSP in Table 4 Objectives and Endpoints.	No
For the sensitivity analysis of attrition bias for PFS, the SAP states 2, or more, missed tumor assessments while the CSP stated 2, or more, non-evaluable tumor assessments.	To align the language with the current SAP template.	No
In Section 8.3.6 of the CSP, potential Hy's law was clarified and patients with elevated liver enzymes (ALT or AST ≥ 5 × ULN) that had liver metastases present at baseline were now permitted in the study.	To align the Hy's law definition which was different between CSP and SAP	Yes
In Section 3.2.4 of the SAP, the ophthalmologic analysis set was defined differently compared to the CSP. The SAP had additional conditions on the number of on-treatment assessments required to be included in the analysis set.	To make the analysis set more appropriate, extending it beyond the first Ophthalmologic data review.	Yes
For BICR the SAP mentioned a response of NED while the CSP did not. The study required measurable disease at baseline but encountered cases of no measurable disease at baseline in BICR data.	To ensure that NED which is a possible BICR response was captured in the SAP	Yes
Changes made after unblinding of study data		
An additional summary of ILD events, Table 14.3.6.3.4.IA1, was added.	To provide a summary of adjudicated ILD events that were either drug related or not drug related.	No

- **Baseline data**

Table 32 Demographic and Key Baseline Characteristics (Full Analysis Set)

Parameter, Statistic	Dato-DXd (N = 365)	ICC (N = 367)	Total (N = 732)
Age (years) [a], n	365	367	732
Mean (SD)	55.5 (11.62)	54.8 (11.09)	55.1 (11.36)
Median (range)	56.0 (29, 86)	54.0 (28, 86)	55.0 (28, 86)
Age group (years) [a], n (%)			
< 65	274 (75.1)	295 (80.4)	569 (77.7)
≥ 65	91 (24.9)	72 (19.6)	163 (22.3)
Sex, n (%)			
Female	360 (98.6)	363 (98.9)	723 (98.8)
Male	5 (1.4)	4 (1.1)	9 (1.2)

Parameter, Statistic	Dato-DXd (N = 365)	ICC (N = 367)	Total (N = 732)
Race, n (%)			
White	180 (49.3)	170 (46.3)	350 (47.8)
Asian	146 (40.0)	152 (41.4)	298 (40.7)
Black or African American	4 (1.1)	7 (1.9)	11 (1.5)
Other	3 (0.8)	6 (1.6)	9 (1.2)
Not reported	32 (8.8)	32 (8.7)	64 (8.7)
Ethnicity, n (%)			
Hispanic or Latino	40 (11.0)	43 (11.7)	83 (11.3)
Not Hispanic or Latino	322 (88.2)	318 (86.6)	640 (87.4)
Missing	3 (0.8)	6 (1.6)	9 (1.2)
ECOG performance status, n			
(0) Normal activity	197 (54.0)	220 (59.9)	417 (57.0)
(1) Restricted activity	165 (45.2)	145 (39.5)	310 (42.3)
(2) In bed less than or equal to 50% of the time	3 (0.8)	1 (0.3)	4 (0.5)
Missing	0	1 (0.3)	1 (0.1)
Previous lines of chemotherapy in the metastatic setting, n (%)			
1	229 (62.7)	225 (61.3)	454 (62.0)
2	135 (37.0)	141 (38.4)	276 (37.7)
3	1 (0.3)	0	1 (0.1)
4	0	1 (0.3)	1 (0.1)

[a] Age is calculated using the date of randomization.

n = number of subjects in analysis for a continuous variable and number of subjects per category for a categorical variable; N = number of subjects per treatment group SD, standard deviation

Table 33 Disease Characteristics at Study Entry (Full Analysis Set)

Parameter, Statistic	Dato-DXd (N = 365)	ICC (N = 367)	Total (N = 732)
Overall disease classification [a], n (%)	365 (100)	367 (100)	732 (100)
Locally advanced/inoperable	9 (2.5)	2 (0.5)	11 (1.5)
Metastatic	356 (97.5)	365 (99.5)	721 (98.5)
Visceral metastases [b], n (%)	352 (96.4)	360 (98.1)	712 (97.3)
Time from most recent disease progression to randomization (days)			
Median (range)	28.0 (1, 157)	28.0 (1, 754)	28.0 (1, 754)
Time from diagnosis to randomization (years)			
Median (range)	5.7166 (0.019, 46.683)	6.3751 (0.049, 29.136)	6.0876 (0.019, 46.683)

[b] Metastatic disease was for subjects with any metastatic site of disease. Locally advanced was for subjects with only locally advanced sites of disease.

[c] Visceral metastases includes all sites except bone.

n = number of subjects in analysis for a continuous variable and number of subjects per category for a categorical variable.

Table 34 Prior Anticancer Therapies at Study Entry (Full Analysis Set)

Therapy class	Dato-DXd (N = 365)	ICC (N = 367)	Total (N = 732)
Number of patients (%) who receive any prior cancer therapy	365 (100)	367 (100)	732 (100)
Cytotoxic chemotherapy	365 (100)	367 (100)	732 (100)
Hormonal therapy	348 (95.3)	353 (96.2)	701 (95.8)
Targeted therapy	322 (88.2)	317 (86.4)	639 (87.3)
Other	29 (7.9)	30 (8.2)	59 (8.1)
Immunotherapy	18 (4.9)	13 (3.5)	31 (4.2)
PARP inhibitor	8 (2.2)	17 (4.6)	25 (3.4)
ADC therapy	1 (0.3)	4 (1.1)	5 (0.7)
Prior use of CDK4/6 inhibitor	304 (83.3%)	300 (81.7%)	604 (82.5%)
Number of patients (%) who receive Prior Taxanes (overall)	295 (80.0)	296 (80.7)	591 (80.7)
Number of patients (%) who receive Prior Anthracycline (overall)	228 (62.5)	239 (65.1)	467 (63.8)
Number of patients (%) who receive Taxanes alone	91 (24.9)	85 (23.2)	176 (24.0)
Number of patients (%) who receive Anthracyclines alone	24 (6.6)	28 (7.6)	52 (7.1)
Number of patients (%) who receive both Taxanes and Anthracyclines	204 (55.9)	211 (57.5)	415 (56.7)
Number of patients (%) who receive neither Taxanes nor Anthracyclines	46 (12.6)	43 (11.7)	89 (12.2)

Table 35 Prior Anticancer Therapies in (neo)adjuvant Setting at Study Entry (Full Analysis Set)

Therapy class	Dato-DXd (N = 365)	ICC (N = 367)	Total (N = 732)
Number of patients (%) who received endocrine therapy	214 (58.6)	227 (61.9)	441 (60.2)
Duration of endocrine therapy (months)			
Median (min, max)	23.0 (1, 145.4)	23.5 (1, 199.8)	23.3 (1, 199.8)
Number of patients (%) who receive Taxanes	235 (64.4)	228 (62.1)	463 (63.3)
Number of patients (%) who receive Anthracycline	197 (54.0)	197 (53.7)	394 (53.8)
Number of patients (%) who receive Taxanes alone	49 (13.4)	41 (11.2)	90 (12.3)
Number of patients (%) who receive Anthracyclines alone	11 (3.0)	10 (2.7)	21 (2.9)
Number of patients (%) who receive both Taxanes and Anthracyclines	186 (51.0)	187 (51.0)	373 (51.0)

Table 36 Prior Anticancer Therapies in Metastatic Setting at Study Entry (Full Analysis Set)

Therapy class	Dato-DXd (N = 365)	ICC (N = 367)	Total (N = 732)
Any prior cancer therapy	365 (100)	367 (100)	732 (100)
Cytotoxic chemotherapy	365 (100)	366 (99.7)	731 (99.9)
Hormonal therapy	322 (88.2)	326 (88.8)	648 (88.5)
Targeted therapy	312 (85.5)	309 (84.2)	621 (84.8)
Immunotherapy	16 (4.4)	13 (3.5)	29 (4.0)
PARP inhibitor	8 (2.2)	16 (4.4)	24 (3.3)
ADC therapy	1 (0.3)	4 (1.1)	5 (0.7)
Other	24 (6.6)	24 (6.5)	48 (6.6)
Number of patients (%) who received endocrine therapy	322 (88.2)	326 (88.8)	648 (88.5)
Duration of endocrine therapy given in metastatic setting (months)			
Median (min, max)	24.6 (0, 217.7)	25.1 (0.8, 229)	24.8 (0, 229)
Number of patients (%) who receive Taxanes	81 (22.2)	70 (19.1)	151 (20.6)
Number of patients (%) who receive Anthracycline	54 (14.8)	52 (14.2)	106 (14.5)
Number of patients (%) who receive Taxanes alone	38 (10.4)	34 (9.3)	72 (9.8)
Number of patients (%) who receive Anthracyclines alone	11 (3.0)	16 (4.4)	27 (3.7)
Number of patients (%) who receive both Taxanes and Anthracyclines	43 (11.8)	36 (9.8)	79 (10.8)

Table 37 IA1 Extent of disease at study entry (FAS)

	Dato-DXd N=365 n (%)	ICC N=367 n (%)	Total N=732 n (%)
Breast and regional lymph node/other locally advanced sites			
Any site	110 (30.1)	104 (28.3)	214 (29.2)
Breast	71 (19.5)	69 (18.8)	140 (19.1)
Other Locally Advanced Sites	10 (2.7)	9 (2.5)	19 (2.6)
Regional Lymph Node	53 (14.5)	54 (14.7)	107 (14.6)
All other sites			
Any site	357 (97.8)	362 (98.6)	719 (98.2)
Adrenal Gland	6 (1.6)	11 (3.0)	17 (2.3)
Bladder	2 (0.5)	2 (0.5)	4 (0.5)
Bone	260 (71.2)	251 (68.4)	511 (69.8)
Brain	35 (9.6)	23 (6.3)	58 (7.9)
Central Nervous System	2 (0.5)	2 (0.5)	4 (0.5)
Cervix Uteri	1 (0.3)	0	1 (0.1)
Distant Lymph Node	72 (19.7)	82 (22.3)	154 (21.0)
Gastrointestinal System	1 (0.3)	0	1 (0.1)
Kidney	2 (0.5)	6 (1.6)	8 (1.1)
Large Intestine	2 (0.5)	0	2 (0.3)
Liver	275 (75.3)	251 (68.4)	526 (71.9)
Lung	92 (25.2)	87 (23.7)	179 (24.5)
Lung, Left Lower Lobe	2 (0.5)	5 (1.4)	7 (1.0)
Lung, Left Upper Lobe	5 (1.4)	3 (0.8)	8 (1.1)

Lung, Right Lower Lobe	3 (0.8)	7 (1.9)	10 (1.4)
Lung, Right Middle Lobe	2 (0.5)	4 (1.1)	6 (0.8)
Lung, Right Upper Lobe	5 (1.4)	6 (1.6)	11 (1.5)
Neck	2 (0.5)	4 (1.1)	6 (0.8)
Omentum	3 (0.8)	2 (0.5)	5 (0.7)
Ovary	6 (1.6)	1 (0.3)	7 (1.0)
Pancreas	2 (0.5)	2 (0.5)	4 (0.5)
Pelvis	1 (0.3)	0	1 (0.1)
Pericardium	2 (0.5)	2 (0.5)	4 (0.5)
Peritoneum	32 (8.8)	14 (3.8)	46 (6.3)
Pleura	46 (12.6)	50 (13.6)	96 (13.1)
Skin	13 (3.6)	8 (2.2)	21 (2.9)
Small Intestine	0	1 (0.3)	1 (0.1)
Soft Tissue	3 (0.8)	3 (0.8)	6 (0.8)
Spleen	6 (1.6)	2 (0.5)	8 (1.1)
Trachea	1 (0.3)	0	1 (0.1)
Uterus	0	1 (0.3)	1 (0.1)
Vagina	1 (0.3)	0	1 (0.1)
Other Metastatic Sites	91 (24.9)	70 (19.1)	161 (22.0)

The same subject may have both locally advanced and metastatic sites.
ICC Investigator's choice chemotherapy. n Number of subjects per category. N Number of subjects per treatment group.

- **Numbers analysed**

Table 38 Analysis Sets

	Dato-DXd n	ICC n	Total n
Enrolled set			1003
Full analysis set	365	367	732
Safety analysis set	360	351	711
Ophthalmologic analysis set [a]	244	164	408
Pharmacokinetic analysis set	221	0	221
Excluded from Pharmacokinetic analysis set	144	367	511
Did not receive treatment	5	16	21
Did not have any post-dose PK data available	7	351 [b]	358
Protocol deviation that affected PK analysis	132	0	132
ADA-evaluable set	352	0 [b]	352
Excluded from ADA-evaluable set	13	367	380
Did not receive treatment	5	16	21
Did not have ADA data available	8	351	359

[a] The ophthalmologic analysis set was added in CSP amendment 1 (27 August 2021) prior to the start of patient recruitment, in response to a request from a Health Authority.

[b] Per protocol, PK and ADA data were not collected from subjects in the ICC arm.

The same subject could have been excluded from an analysis set for more than one reason.

n = Number of subjects per category.

The primary and secondary endpoint analyses were conducted in the ITT (FAS) population.

- **Outcomes and estimation**

Primary endpoint PFS by BIRC (dual)

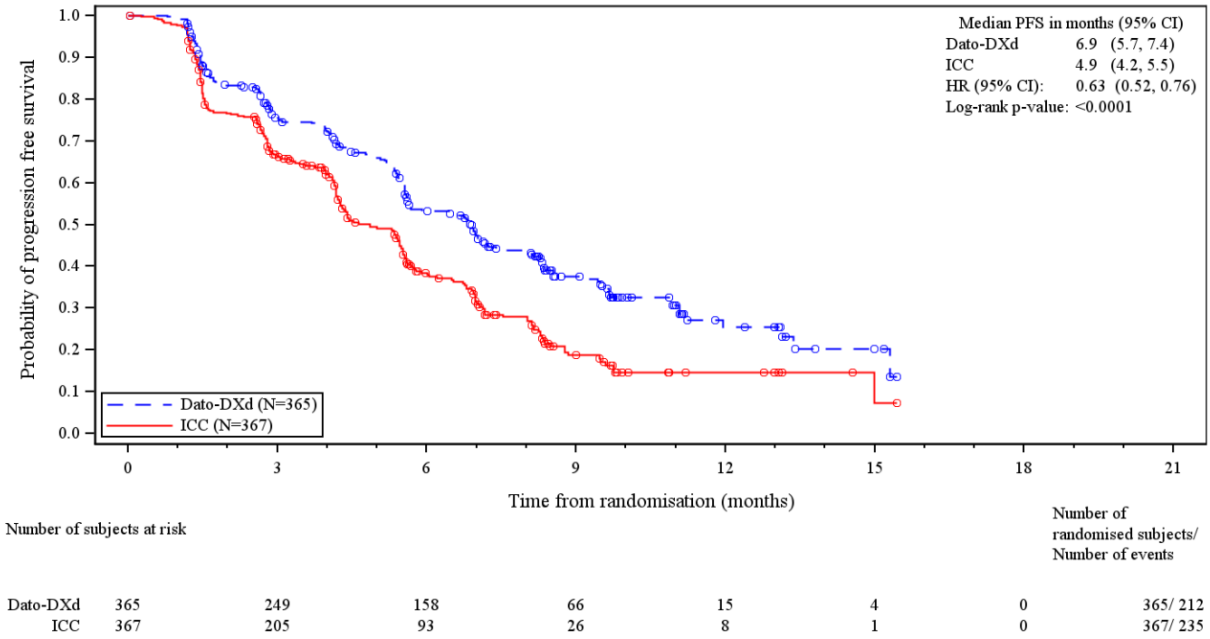
Table 39 Progression-free Survival, Primary Analysis, BICR Data (Full Analysis Set)

	Dato-DXd (N = 365)	ICC (N = 367)
Total events [a], n (%)	212 (58.1)	235 (64.0)
RECIST progression	201 (55.1)	218 (59.4)
Death in the absence of progression	11 (3.0)	17 (4.6)
Censored patients, n (%)	153 (41.9)	132 (36.0)
Censored RECIST progression [b]	3 (0.8)	3 (0.8)
Censored death [c]	9 (2.5)	15 (4.1)
Progression-free at the time of analysis	132 (36.2)	98 (26.7)
Lost to FU	0	0
Withdrawn consent	9 (2.5)	16 (4.4)
Discontinued study (any other specified reason for discontinuing study)	0	0
Median progression-free survival (months) [d]	6.9	4.9
95% CI for median progression-free survival [d]	5.7, 7.4	4.2, 5.5
Progression-free survival rate at 3 months (%) [d]	75.5	66.4
95% CI for progression-free survival rate at 3 months [d]	70.6, 79.7	61.1, 71.2
Progression-free survival rate at 6 months (%) [d]	53.3	38.5
95% CI for progression-free survival rate at 6 months [d]	47.7, 58.5	32.8, 44.1
Progression-free survival rate at 9 months (%) [d]	37.5	18.7
95% CI for progression-free survival rate at 9 months [d]	31.9, 43.2	13.8, 24.3
Hazard ratio [e]	0.63	-
95% CI for hazard ratio [e]	0.52, 0.76	-
99% CI for hazard ratio [e]	0.49, 0.80	-
2-sided p-value [f]	< 0.0001	-
Median (range) duration of FU in censored patients	8.1 (0.0 - 15.4)	4.0 (0.0 - 15.4)

[d] Only includes progression events that occur within 2 assessments of the last evaluable assessment.
[e] RECIST progression event occurred ≥ 2 visits after last evaluable RECIST assessment (or randomisation).
[f] Death occurred ≥ 2 visits after last evaluable RECIST assessment (or randomisation).
[g] Calculated using the Kaplan-Meier technique.
[h] The analysis was performed using a stratified Cox proportional hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favours Dato-DXd to be associated with a longer progression-free survival than ICC.
[i] Calculated using a stratified log-rank test adjusting for the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor.

Progression was determined by BICR assessment, RECIST 1.1.
BICR, blinded independent central review; CDK4/6, cyclin-dependent kinases 4 and 6; CI, confidence interval; FU, follow-up; ICC, investigators choice of chemotherapy; n, number of patients per category; N, number of patients per treatment group; RECIST 1.1, response evaluation criteria in solid tumours version 1.1.

Figure 20 Progression-free Survival, Kaplan-Meier Plot, BICR Data (Full Analysis Set)



A circle indicates a censored observation. RECIST version 1.1. 2-sided p-value.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ICC, Investigator's choice of chemotherapy; n, number of patients per category; N, number of patients per treatment group; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Final OS analysis (DCO 24 July 2024)

Table 40 Overall Survival, Final Analysis (FAS)

	Dato-DXd (N = 365)	ICC (N = 367)
Death, n (%)	223 (61.1)	213 (58.0)
Censored subjects, n (%)	142 (38.9)	154 (42.0)
Still in survival FU [a]	120 (32.9)	131 (35.7)
Terminated prior to death [b]	22 (6.0)	23 (6.3)
Lost to FU	5 (1.4)	2 (0.5)
Withdrawn consent	17 (4.7)	21 (5.7)
Other	0	0
Median overall survival (months) [c]	18.6	18.3
95% CI for median overall survival [c]	17.3, 20.1	17.3, 20.5
Survival rate at 6 months (%) [c]	93.3	87.9
95% CI for survival rate at 6 months [c]	90.2, 95.4	84.0, 90.9
Survival rate at 12 months (%) [c]	74.2	71.1
95% CI for survival rate at 12 months [c]	69.3, 78.5	66.0, 75.5
Survival rate at 18 months (%) [c]	52.0	50.9
95% CI for survival rate at 18 months [c]	46.7, 57.1	45.6, 56.0
Hazard ratio [d]	1.01	
95% CI for hazard ratio [d]	0.83, 1.22	
96.52% CI for hazard ratio – adjusted for multiplicity [d f]	0.83, 1.23	
2-sided p-value [e]	0.9445	
Median (range) duration of FU in censored patients	22.2 (0.0 - 32.0)	22.1 (0.0 - 31.1)
Median (range) duration of FU in all patients by treatment arm	17.8 (0.0 - 32.0)	17.5 (0.0 - 31.1)
Median (range) duration of FU in all patients	17.6 (0.0 - 32.0)	

[a] Includes patients known to be alive at DCO date.

[b] Includes patients with unknown survival status or patients who were lost to FU.

[c] Calculated using the Kaplan-Meier technique.

[d] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer overall OS than ICC.

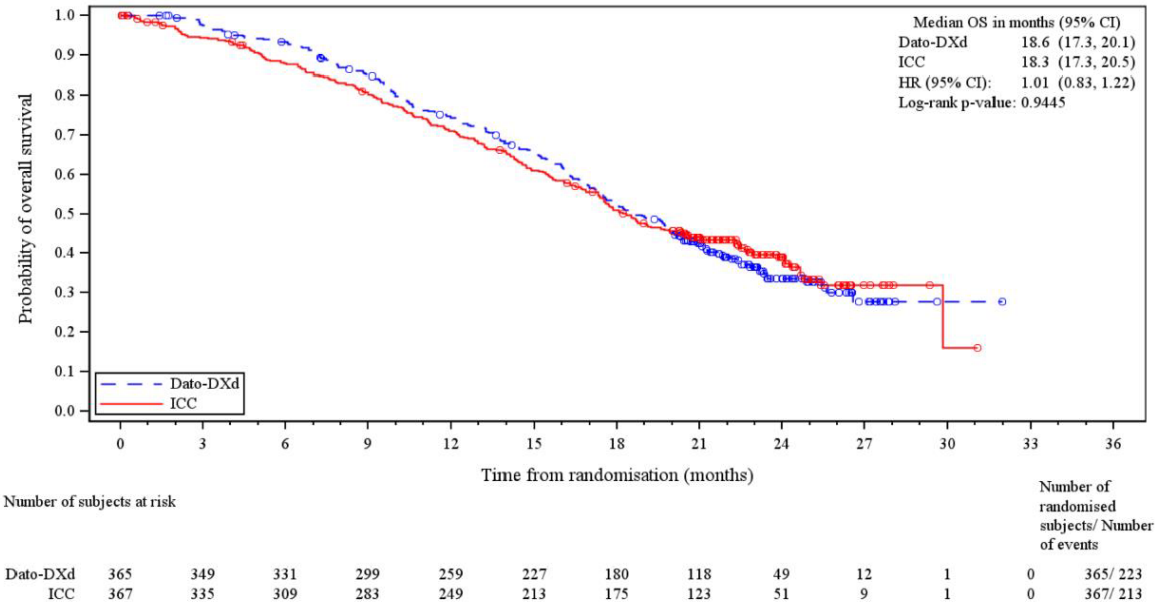
[e] Calculated using a stratified log-rank test adjusting for the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor.

[f] Lan-DeMets alpha spending function with O'Brien Fleming boundary with observed number of events, the boundary for declaring statistical significance was 4.03% for a 5% overall alpha.

n = number of patients per category; N = number of patients per treatment group.

Source: Table 14.2.2.1.FA

Figure 21 Overall Survival, Kaplan-Meier Plot (FAS)



Circle indicates a censored observation. 2-sided p-value.
HR = hazard ratio; N = number of patients per treatment group

Secondary endpoints: PFS by INV, ORR by BICR, ORR by INV, DCR, DoR, PFS2

Table 41 Study TB-01: Summary of Efficacy Data at DCO: 17 July 2023 (Full Analysis Set)

Efficacy endpoints	BICR assessment		Investigator assessment	
	Dato-DXd (N = 365)	ICC (N = 367)	Dato-DXd (N = 365)	ICC (N = 367)
Progression-free survival – by BICR (primary) and by Investigator (secondary)				
Total events, n (%) [a]	212 (58.1)	235 (64.0)	242 (66.3)	269 (73.3)
Median, months (95% CI) [b]	6.9 (5.7, 7.4)	4.9 (4.2, 5.5)	6.9 (5.9, 7.1)	4.5 (4.2, 5.5)
PFS rate (%) at 3 months (95% CI) [b]	75.5 (70.6, 79.7)	66.4 (61.1, 71.2)	77.7 (73.0, 81.7)	66.1 (60.8, 70.9)
PFS rate (%) at 6 months (95% CI) [b]	53.3 (47.7, 58.5)	38.5 (32.8, 44.1)	55.2 (49.8, 60.3)	36.9 (31.6, 42.2)
PFS rate (%) at 9 months (95% CI) [b]	37.5 (31.9, 43.2)	18.7 (13.8, 24.3)	34.7 (29.4, 40.0)	20.9 (16.3, 25.8)
Hazard ratio (95% CI; 2-sided p-value) [c, d]	0.63 (95% CI: 0.52, 0.76; p < 0.0001)		0.64 (0.53, 0.76; p < 0.0001)	
Overall survival data based on interim analysis				
Death, n (%)	NA		80 (21.9)	91 (24.8)
Median OS, months (95% CI) [b]			16.1 (16.1, NC)	NC (16.5, NC)
Survival rate (%) at 6 months (95% CI) [b]			93.0 (89.8, 95.2)	87.9 (84.0, 90.9)
Hazard ratio (95% CI) [c]			0.84 (0.62, 1.14)	
Best objective response				
Complete response	2 (0.5)	0	2 (0.5)	0

Efficacy endpoints	BICR assessment		Investigator assessment	
	Dato-DXd (N = 365)	ICC (N = 367)	Dato-DXd (N = 365)	ICC (N = 367)
Partial response	131 (35.9)	84 (22.9)	130 (35.6)	80 (21.8)
Stable disease ≥ 5 weeks	168 (46.0)	176 (48.0)	175 (47.9)	181 (49.3)
RECIST progression	57 (15.6)	67 (18.3)	50 (13.7)	66 (18.0)
Death	0	9 (2.5)	0	9 (2.5)
Total non-response	232 (63.6)	283 (77.1)	233 (63.8)	287 (78.2)
Objective response rate				
Number (%) of patients with response [f]	133 (36.44)	84 (22.89)	132 (36.16)	80 (21.80)
Adjusted response rate (%)	36.21	22.56	36.01	21.58
Odds ratio (95% CI; 2-sided p-value) [g]	1.95 (1.41, 2.71; nominal p < 0.0001)		2.04 (1.48, 2.85; nominal p < 0.0001)	
Disease control rate				
Number (%) of patients with response [h]	275 (75.34)	234 (63.76)	295 (80.82)	246 (67.03)
Odds ratio (95% CI; 2-sided p-value)	1.75 (1.27, 2.42; nominal p=0.0006)		2.09 (1.49, 2.96; nominal p<0.0001)	
Duration of response				
Median duration of response from onset of response, months (95% CI) [b, j]	6.7 (5.6, 9.8)	5.7 (4.9, 6.8)	6.9 (5.6, 8.3)	5.8 (4.6, 7.7)
Time to first subsequent therapy				
First subsequent anticancer therapy	NA		187 (51.2)	248 (67.6)
Median TFST, months (95% CI) [b]			8.2 (7.4, 8.9)	5.0 (4.6, 5.7)
Hazard ratio (95% CI) [c]			0.53 (0.45, 0.64)	
Time to second subsequent therapy				
Second subsequent anticancer therapy	NA		62 (17.0)	71 (19.3)
Median TSST, months (95% CI) [b]			13.3 (11.4, NC)	11.5 (10.3, 13.1)
Hazard ratio (95% CI) [c]			0.75 (0.59, 0.96)	
Time from Randomization to Second Progression				
Total events, n (%) [a]	NA		117 (32.1)	121 (33.0)
Median, months (95% CI) [b]			12.7	10.4
Hazard ratio (95% CI) [c]			0.71 (0.55, 0.92)	

[a] Only includes progression events that occur within 2 assessments of the last evaluable assessment.

[b] Calculated using the Kaplan-Meier technique.

[c] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables, number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer progression-free survival than ICC.

[d] The P-value is calculated using a stratified log-rank test adjusting for the stratification factors of the number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. Per the pooling strategy, the CDK4/6 strata was pooled.

[e] Response required confirmation.

[f] Responses exclude unconfirmed responses.

[g] The analysis was performed using a logistic regression model with factors for treatment, number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. An odds ratio > 1 favors Dato-DXd.

[h] Disease control rate at 12 weeks was defined as the percentage of patients who have a confirmed CR or PR or have demonstrated SD for at least 11 weeks after randomization without subsequent cancer therapy per RECIST 1.1.

[i] Duration of response is the time from the first documentation of confirmed response of CR/PR until the date of progression or death or the last evaluable RECIST assessment for patients that do not progress (or die) or do not progress (or die) within 2 missed visits of the last evaluable assessment (or randomization).

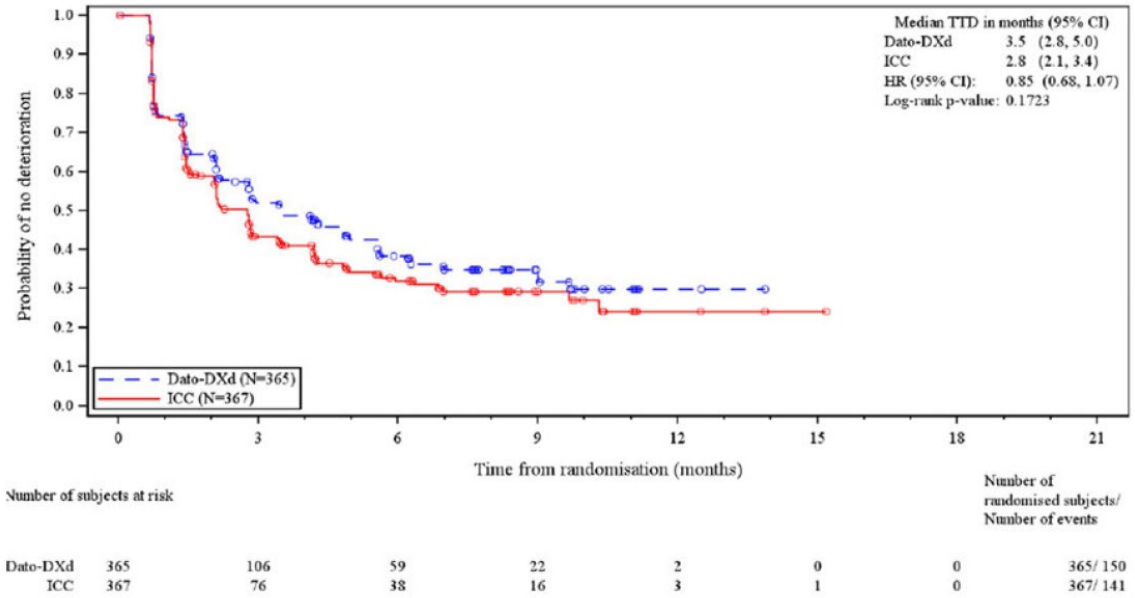
Secondary patient-reported endpoints: TTD in pain, physical functioning, and GHS/QoL

Table 42 Time to Deterioration in Pain, Primary Analysis (FAS)

	Dato-DXd (N = 365)	ICC (N = 367)
Total events [a], n (%)	150 (41.1)	141 (38.4)
Deterioration	150 (41.1)	141 (38.4)
Censored subjects, n (%)	215 (58.9)	226 (61.6)
Censored deterioration [b]	2 (0.5)	3 (0.8)
Impossible to deteriorate	8 (2.2)	14 (3.8)
No deterioration at time of analysis	77 (21.1)	68 (18.5)
No post-baseline data recorded at time of analysis	4 (1.1)	15 (4.1)
No baseline data recorded at time of analysis	94 (25.8)	106 (28.9)
Lost to FU	0	0
Withdrawn consent	4 (1.1)	2 (0.5)
Discontinued study	26 (7.1)	18 (4.9)
Median time to deterioration (months) [c]	3.5	2.8
95% CI for median time to deterioration [c]	2.8, 5.0	2.1, 3.4
Percentage of subjects without deterioration at 3 months (%) [c]	52.1	43.4
95% CI for percentage of subjects without deterioration at 3 months [c]	45.5, 58.2	36.4, 50.1
Percentage of subjects without deterioration at 6 months (%) [c]	38.4	31.9
95% CI for percentage of subjects without deterioration at 6 months [c]	31.8, 45.0	25.2, 38.9
Percentage of subjects without deterioration at 9 months (%) [c]	34.9	29.2
95% CI for percentage of subjects without deterioration at 9 months [c]	28.2, 41.5	22.4, 36.3
Hazard ratio [d]	0.85	-
95% CI for hazard ratio [d]	0.68, 1.07	-
2-sided p-value [e]	0.1723	-

[a] Only includes deterioration that occurred within 2 assessments of the previous evaluable PRO assessment respectively.
[b] Deterioration event occurred immediately after 2 or more missed PRO assessments.
[c] Calculated using the Kaplan-Meier technique.
[d] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer time to deterioration that ICC.
[e] Calculated using a stratified log-rank test adjusting for the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor.
Time to deterioration is defined as the time from date of randomization to date of first deterioration.
n = number of subjects per category; N = number of subjects per treatment group

Figure 22 Time to Deterioration in Pain, KM Plot, Primary Analysis (FAS)



Time to deterioration is defined as the time from date of randomization to date of first deterioration.
Circle indicates a censored observation. 2-sided p-value.
HR = hazard ratio; N = Number of subjects per treatment group.
Source: Figure 14.2.11.2.IA1

Table 43 Time to Deterioration in Physical Functioning, Primary Analysis (FAS)

	Dato-DXd (N = 365)	ICC (N = 367)
Total events [a], n (%)	129 (35.3)	131 (35.7)
Deterioration	129 (35.3)	131 (35.7)
Censored subjects, n (%)	236 (64.7)	236 (64.3)
Censored deterioration [b]	4 (1.1)	3 (0.8)
Impossible to deteriorate	1 (0.3)	1 (0.3)
No deterioration at time of analysis	104 (28.5)	83 (22.6)
No post-baseline data recorded at time of analysis	4 (1.1)	18 (4.9)
No baseline data recorded at time of analysis	94 (25.8)	106 (28.9)
Lost to FU	0	0
Withdrawn consent	5 (1.4)	2 (0.5)
Discontinued study	24 (6.6)	23 (6.3)
Median time to deterioration (months) [c]	5.6	3.5
95% CI for median time to deterioration [c]	3.5, 10.5	2.2, 4.9
Percentage of subjects without deterioration at 3 months (%) [c]	58.7	52.7
95% CI for percentage of subjects without deterioration at 3 months [c]	52.3, 64.6	45.8, 59.2
Percentage of subjects without deterioration at 6 months (%) [c]	47.6	39.5
95% CI for percentage of subjects without deterioration at 6 months [c]	40.9, 54.0	32.3, 46.5
Percentage of subjects without deterioration at 9 months (%) [c]	46.5	35.2
95% CI for percentage of subjects without deterioration at 9 months [c]	39.6, 53.1	27.8, 42.8
Hazard ratio [d]	0.77	-
95% CI for hazard ratio [d]	0.61, 0.99	-
2-sided p-value [e]	0.0438	-

[a] Only includes deterioration that occurred within 2 assessments of the previous evaluable PRO assessment respectively.

[b] Deterioration event occurred immediately after 2 or more missed PRO assessments.

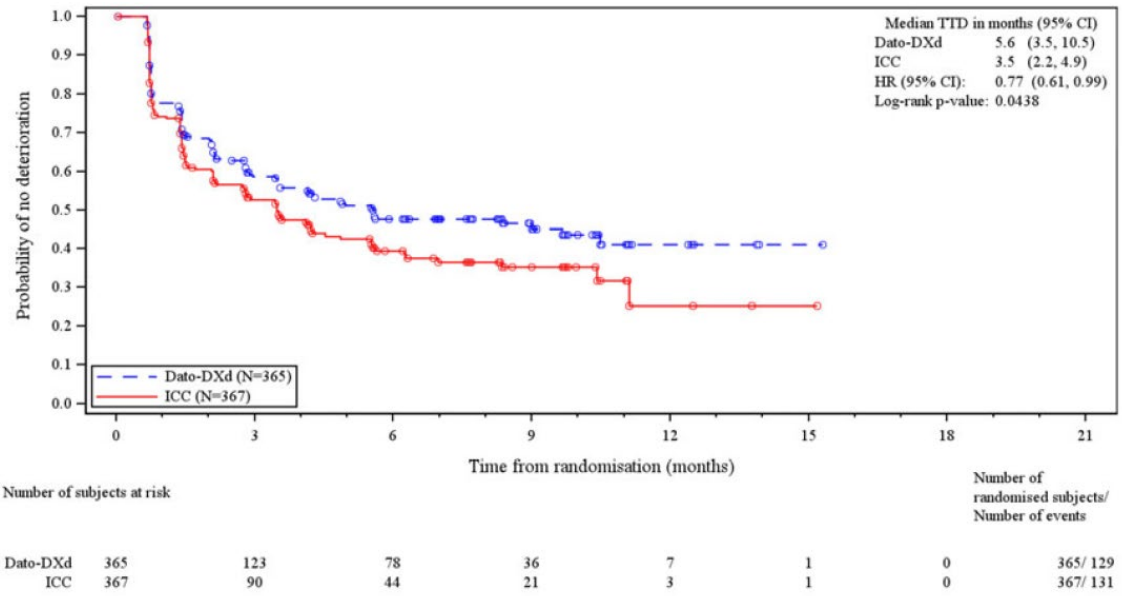
[c] Calculated using the Kaplan-Meier technique.

[d] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer time to deterioration that ICC.

[e] Calculated using a stratified log-rank test adjusting for the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor.

n = number of subjects per category; N = number of subjects per treatment group

Figure 23 Time to Deterioration in Physical Functioning, KM Plot, Primary Analysis (FAS)



Number of subjects at risk								Number of randomised subjects/ Number of events
Dato-DXd	365	123	78	36	7	1	0	365/ 129
ICC	367	90	44	21	3	1	0	367/ 131

Time to deterioration is defined as the time from date of randomization to date of first deterioration.
Circle indicates a censored observation. 2-sided p-value.
HR = hazard ratio; N = Number of subjects per treatment group.

Table 44 Time to Deterioration in the GHS/QoL Scale, Primary Analysis (FAS)

	Dato-DXd (N = 365)	ICC (N = 367)
Total events [a], n (%)	160 (43.8)	147 (40.1)
Deterioration	160 (43.8)	147 (40.1)
Censored subjects, n (%)	205 (56.2)	220 (59.9)
Censored deterioration [b]	6 (1.6)	3 (0.8)
Impossible to deteriorate	0	4 (1.1)
No deterioration at time of analysis	76 (20.8)	66 (18.0)
No post-baseline data recorded at time of analysis	4 (1.1)	18 (4.9)
No baseline data recorded at time of analysis	94 (25.8)	106 (28.9)
Lost to FU	0	0
Withdrawn consent	4 (1.1)	3 (0.8)
Discontinued study	21 (5.8)	20 (5.4)
Median time to deterioration (months) [c]	3.4	2.1
95% CI for median time to deterioration [c]	2.1, 5.0	1.5, 2.9
Percentage of subjects without deterioration at 3 months (%) [c]	50.7	43.2
95% CI for percentage of subjects without deterioration at 3 months [c]	44.4, 56.8	36.4, 49.8
Percentage of subjects without deterioration at 6 months (%) [c]	39.9	34.1
95% CI for percentage of subjects without deterioration at 6 months [c]	33.4, 46.2	27.4, 41.0
Percentage of subjects without deterioration at 9 months (%) [c]	31.0	26.1
95% CI for percentage of subjects without deterioration at 9 months [c]	24.2, 38.0	18.6, 34.2
Hazard ratio [d]	0.85	-
95% CI for hazard ratio [d]	0.68, 1.06	-
2-sided p-value [e]	0.1612	-

[a] Only includes deterioration that occurred within 2 assessments of the previous evaluable PRO assessment respectively.

[b] Deterioration event occurred immediately after 2 or more missed PRO assessments.

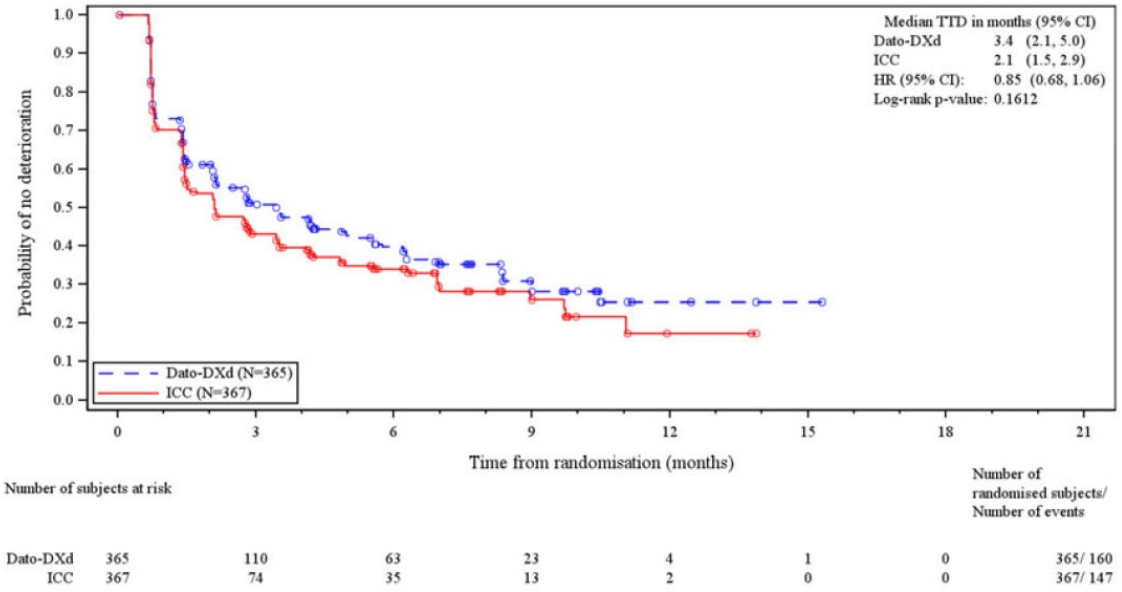
[c] Calculated using the Kaplan-Meier technique.

[d] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer time to deterioration that ICC.

[e] Calculated using a stratified log-rank test adjusting for the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor.

n = number of subjects per category; N = number of subjects per treatment group

Figure 24 Time to Deterioration in the GHS/QoL Scales, KM Plot, Primary Analysis (FAS)



Number of subjects at risk								Number of randomised subjects/ Number of events
Dato-DXd	365	110	63	23	4	1	0	365/ 160
ICC	367	74	35	13	2	0	0	367/ 147

Time to deterioration is defined as the time from date of randomization to date of first deterioration.
Circle indicates a censored observation. 2-sided p-value.
HR = hazard ratio; N = Number of subjects per treatment group.

- **Ancillary analyses**

PFS

Table 45 Disagreements between Investigator and Central Reviews of RECIST Progression (FAS)

Progression	Dato-DXd (N = 365)	ICC (N = 367)
RECIST progression [a] determined by:		
Investigator and central review	170 (46.6)	188 (51.2)
Progression date agreement (within 2 weeks)	81 (22.2)	104 (28.3)
Progression date ≥ 2 weeks earlier by central review than by investigator	70 (19.2)	66 (18.0)
Progression date ≥ 2 weeks earlier by investigator than by central review	19 (5.2)	18 (4.9)
Investigator but not central review	63 (17.3)	62 (16.9)
Central review but not investigator	31 (8.5)	30 (8.2)
Overall concordance rate [b]	74.2%	74.9%
	74.6%	
No progression by both	101 (27.7)	87 (23.7)
Early discrepancy rate [c]	0.35	0.32
Late discrepancy rate [d]	0.55	0.55
Difference in early discrepancy rate (Dato-DXd – ICC)	0.03	
Difference in late discrepancy rate (Dato-DXd – ICC)	0.01	

[a] Progression events that do not occur within 2 assessments of the last evaluable assessment (or randomization) are censored.

[b] Overall concordance rate was calculated as 100 – (% investigator but not central review + % central review but not investigator).

[c] Early discrepancy rate is the frequency of investigator declared progressions before central review as a proportion of all investigator progressions.

[d] Late discrepancy rate is the frequency of investigator declared progressions after central review as a proportion of all discrepancies.

RECIST 1.1

N = number of subjects per treatment group

Table 46 Progression-free Survival, Sensitivity Analysis, BICR Data (Full Analysis Set)

Group	N	Number (%) of subjects with events	Median (months)	Comparison between groups		
				Hazard ratio	95% CI	2-sided p-value
Evaluation-time bias [a]						
Dato-DXd	365	212 (58.1)	6.2	0.63	0.52, 0.76	< 0.0001
ICC	367	235 (64.0)	4.7	-	-	-
Attrition bias [b]						
Dato-DXd	365	203 (55.6)	6.9	0.63	0.51, 0.76	< 0.0001
ICC	367	212 (57.8)	5.3	-	-	-
Ascertainment bias [c]						
Dato-DXd	365	242 (66.3)	6.9	0.64	0.53, 0.76	< 0.0001
ICC	367	269 (73.3)	4.5	-	-	-
Subsequent anticancer therapy [d]						
Dato-DXd	365	198 (54.2)	6.9	0.63	0.52, 0.77	< 0.0001
ICC	367	208 (56.7)	5.4	-	-	-
Stratification according to eCRF						
Dato-DXd	365	212 (58.1)	6.9	0.63	0.52, 0.76	< 0.0001
ICC	367	235 (64.0)	4.9	-	-	-

[a] Analysis was performed using midpoint between time of progression and previous evaluable RECIST assessment using a stratified log-rank test.

[b] Analysis was performed using the actual PFS event times, rather than the censored times, of subjects who progressed or died in the absence of progression following 2 or more missed tumor assessments. Subjects who took subsequent therapy prior to their last evaluable RECIST assessment or progression or death were censored at their last evaluable assessment prior to taking subsequent therapy.

[c] Analysis was performed using site investigator data using a stratified log-rank test.

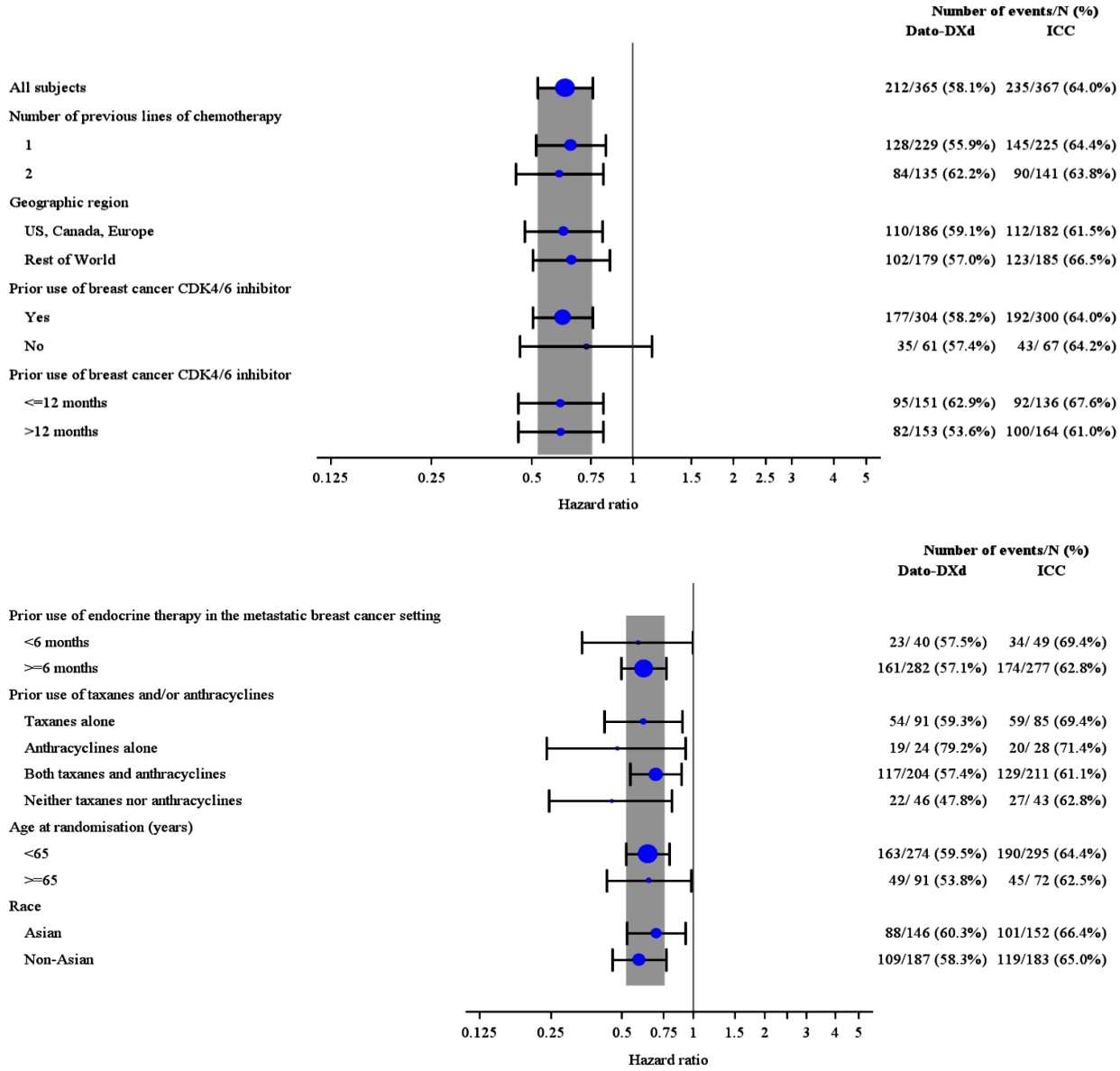
[d] Analysis was performed using a modified censoring rule so that subjects who took subsequent therapy prior to their last evaluable RECIST assessment or progression or death were censored at their last evaluable assessment prior to taking the subsequent anticancer therapy.

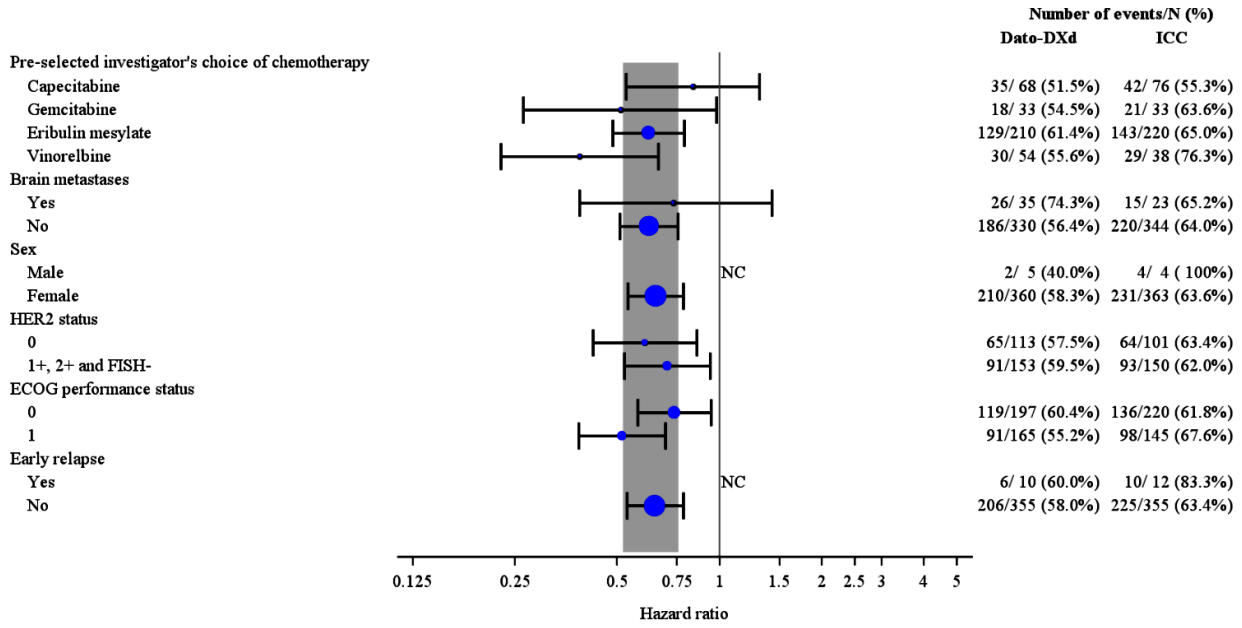
A hazard ratio < 1 favors Dato-DXd

RECIST 1.1

N = number of subjects per treatment group

Figure 25 Progression-free Survival, Forest Plot, by Subgroup, BICR Data (Full Analysis Set)





Hazard ratio (Dato-DXd: ICC) and 95% CI. A hazard ratio < 1 implies a lower risk of progression on Dato-DXd.

The overall analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The subgroup analysis was performed using a Cox Proportional Hazards model with treatment as the only covariate. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all subjects) hazard ratio.

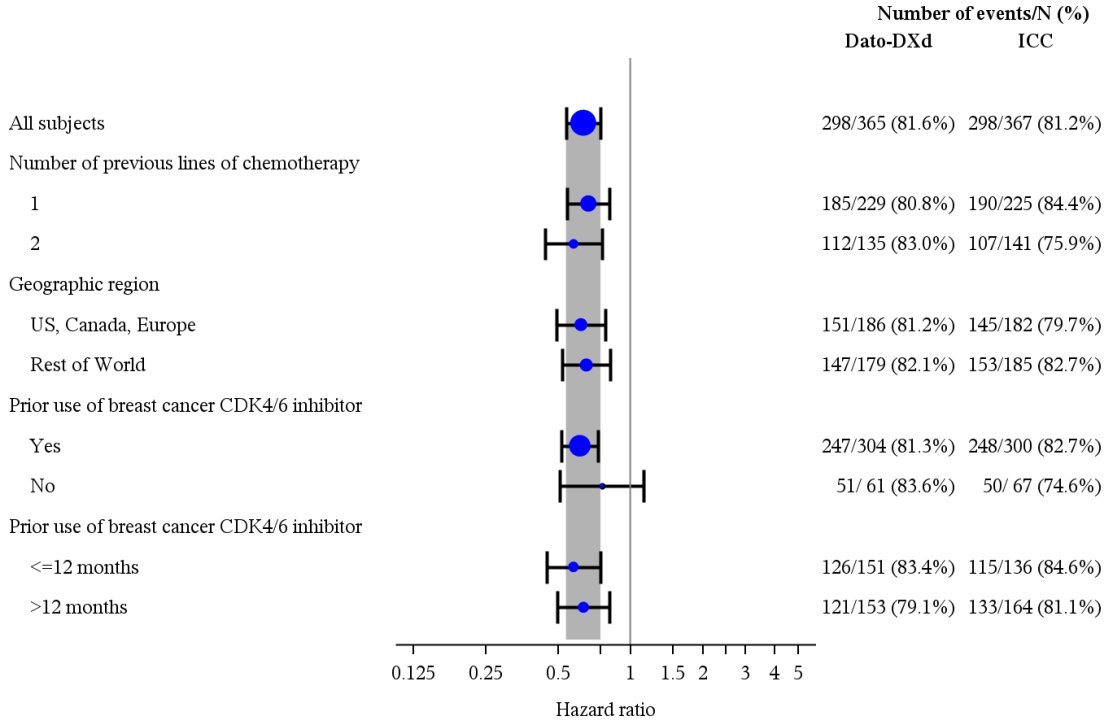
Progression includes deaths in the absence of RECIST progression. Progression events that did not occur within 2 assessments of the last evaluable assessment (or randomization) are censored.

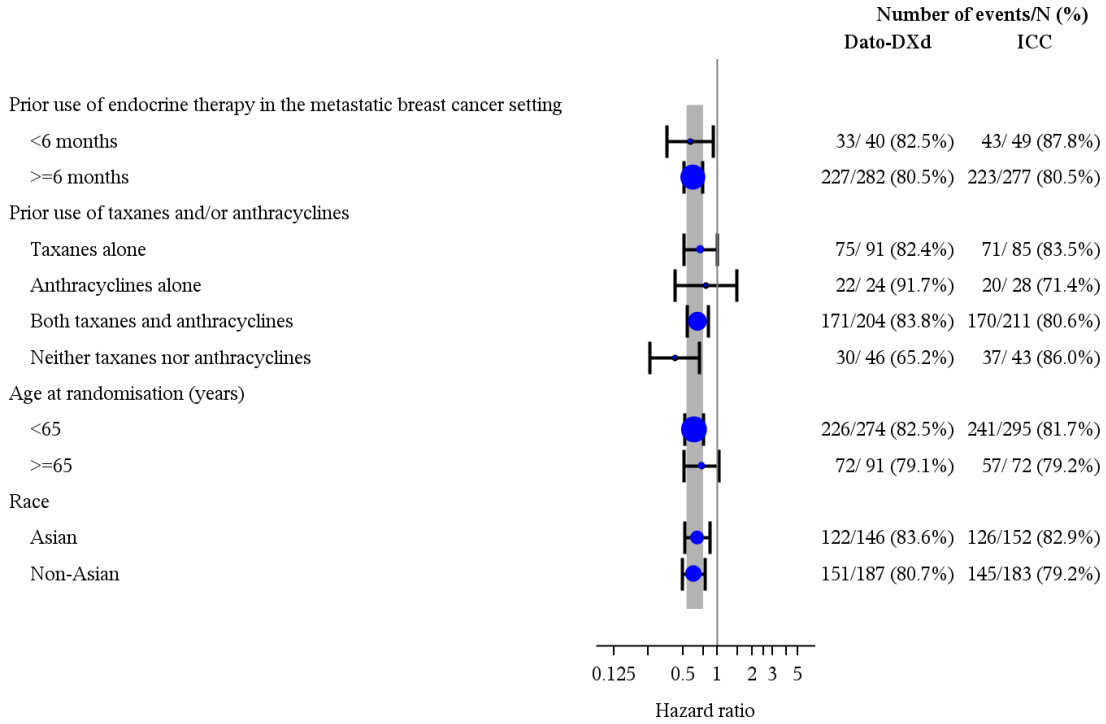
RECIST 1.1. Three Canadian subjects were incorrectly stratified to rest of world rather than United States, Canada, Europe.

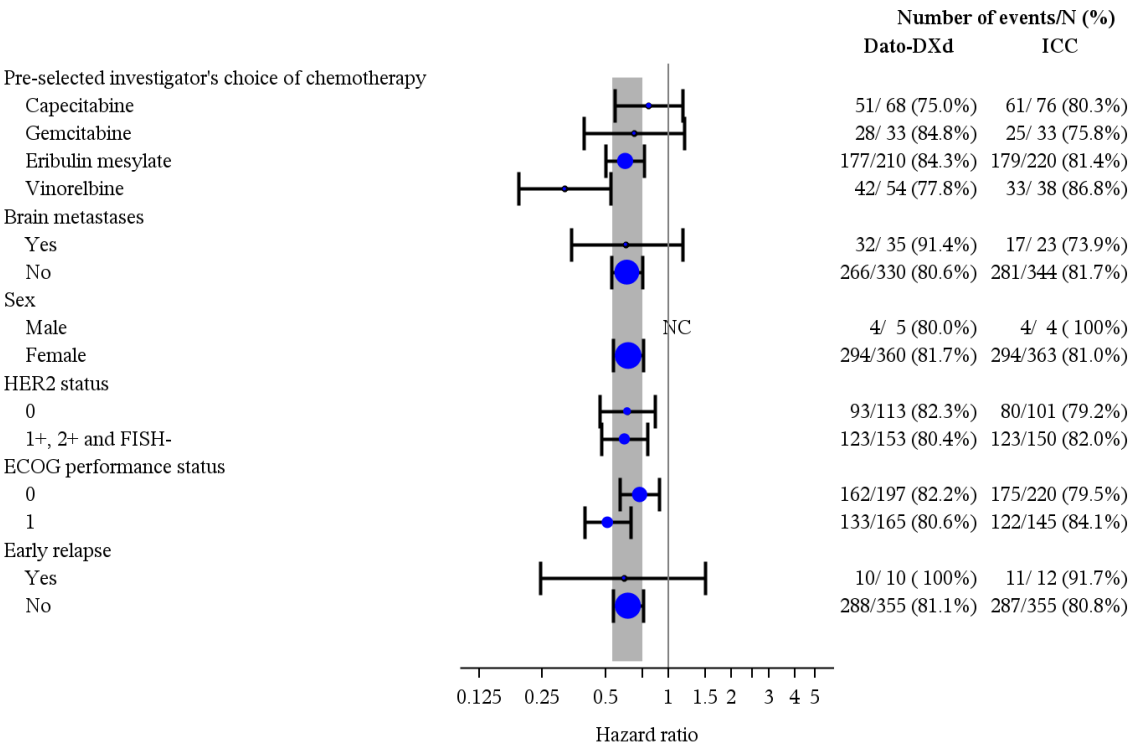
FISH = Fluorescence in-situ hybridization; N = number of subjects per treatment group Source: Figure 14.2.1.14.IA1, Study TB01 CSR in Module 5.3.5.1

Updated subgroup analyses for PFS by BICR at IA2

Figure 26 Progression-free Survival, Forest Plot, by Subgroup, Investigator Data (Full Analysis Set)



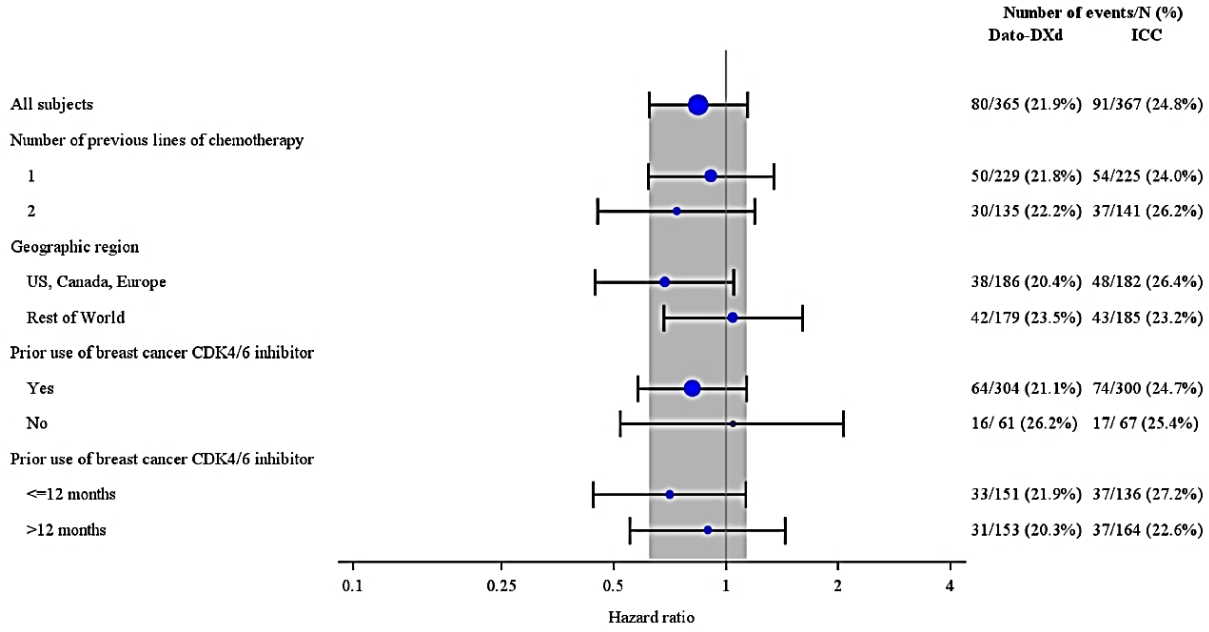


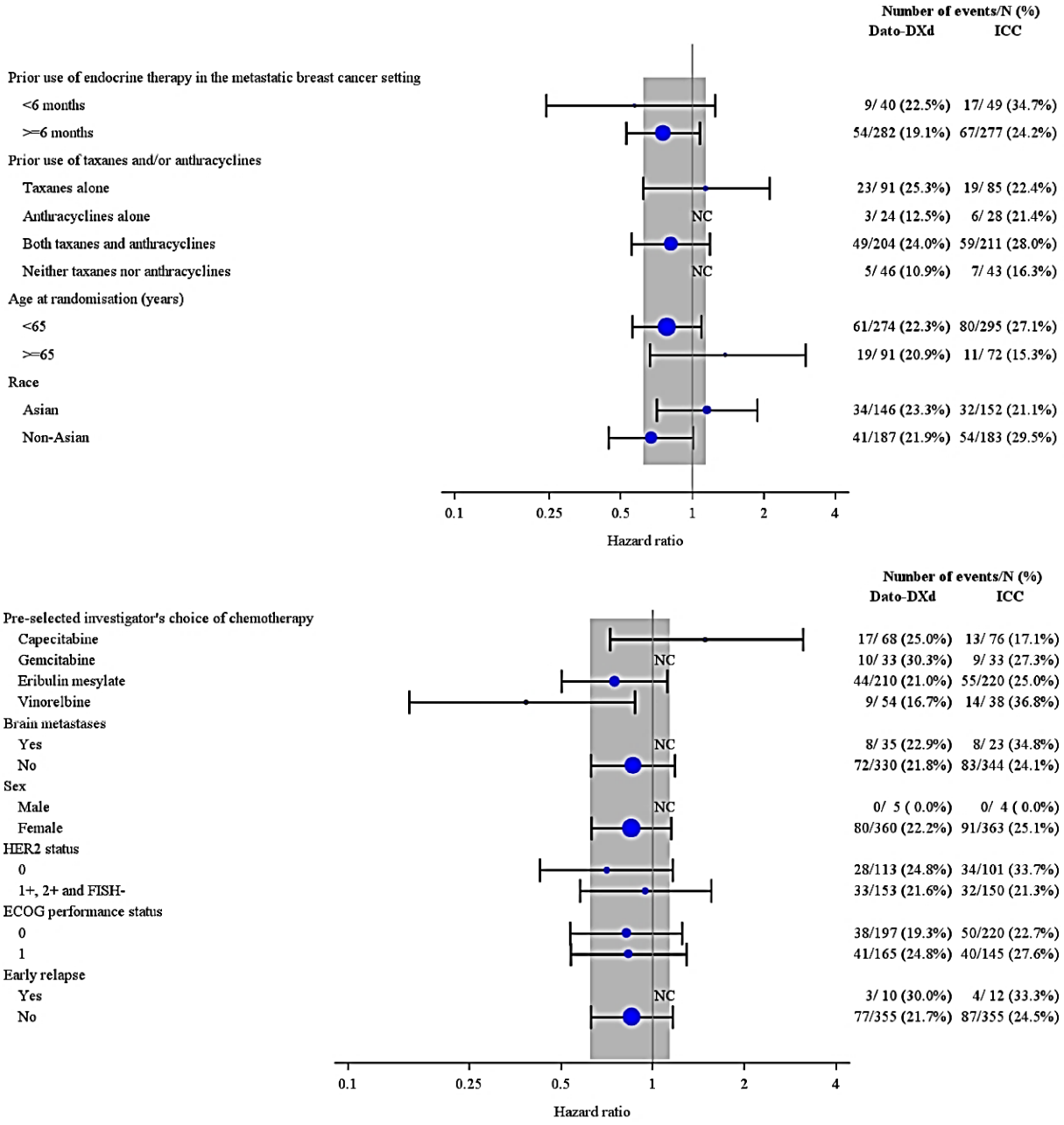


Hazard ratio (Dato-DXd: ICC) and 95% CI. A hazard ratio < 1 implies a lower risk of progression on Dato-DXd. The overall analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The subgroup analysis was performed using a Cox proportional hazards model with treatment as the only covariate. Size of circle is proportional to the number of events. Grey band represents the 95% confidence interval for the overall (all patients) hazard ratio. Progression includes deaths in the absence of RECIST progression. Progression events that do not occur within 2 assessments of the last evaluable assessment (or randomisation) are censored. RECIST version 1.1. Three Canadian patients were incorrectly stratified to geographic region rest of world rather than US, Canada, Europe. Per the pooling strategy, the CDK4/6 inhibitor strata was pooled.CN, Number of patients per treatment group.

OS

Figure 27 IA1 Overall Survival, Forest Plot, by Subgroup (Full Analysis Set)

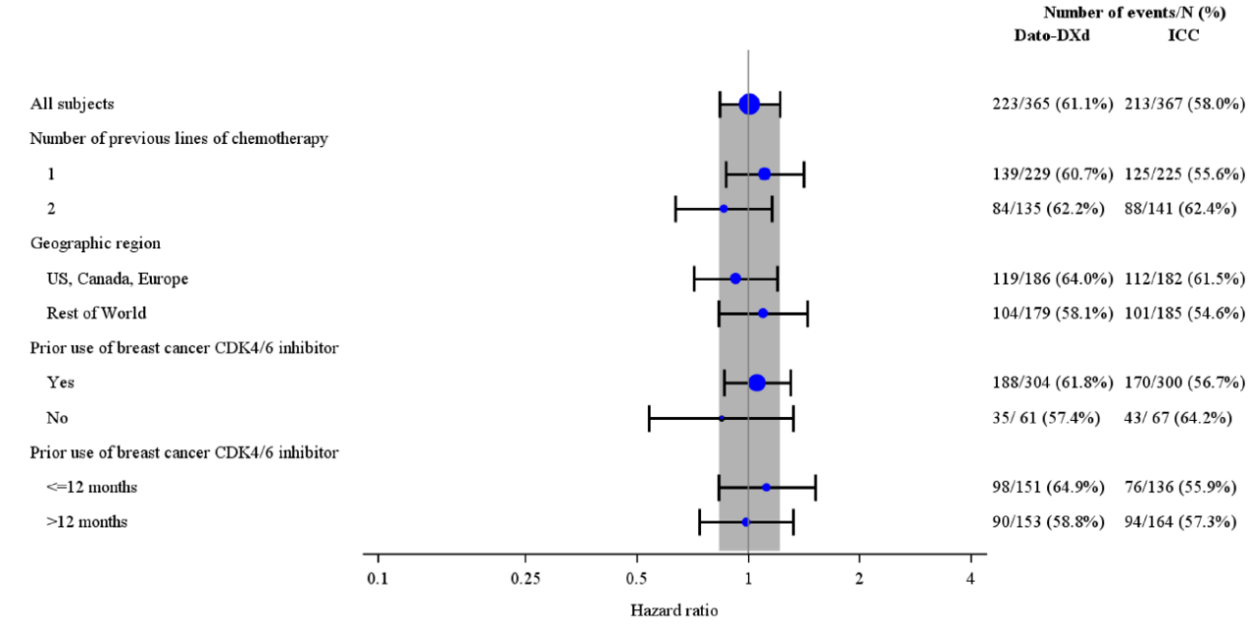


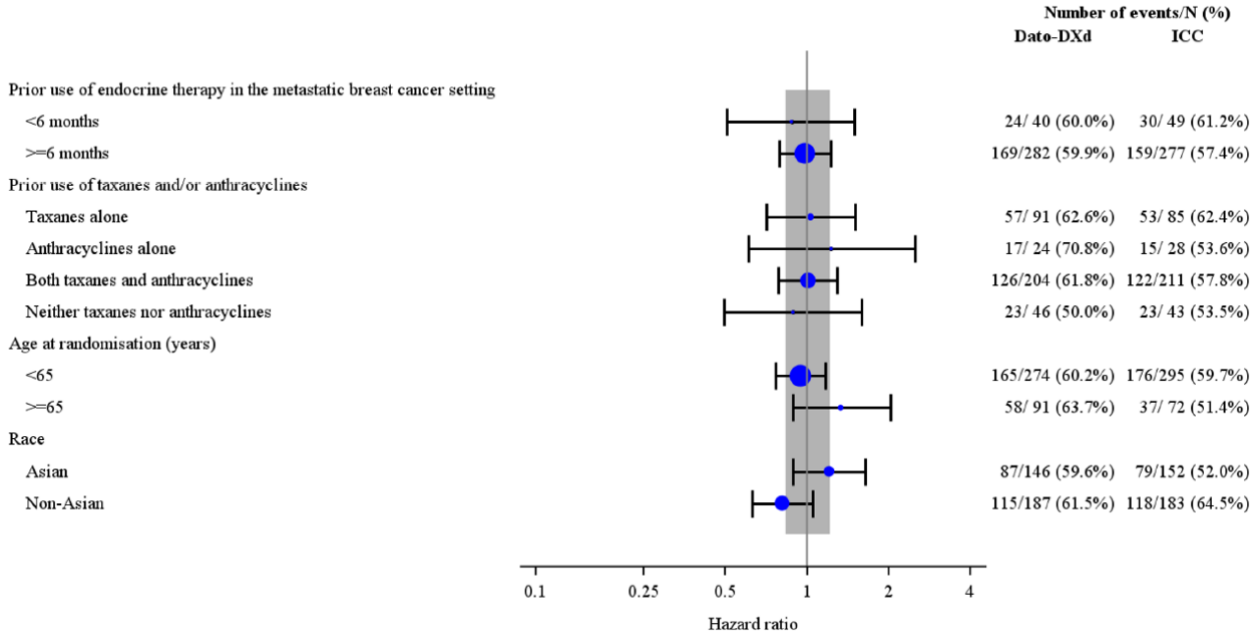


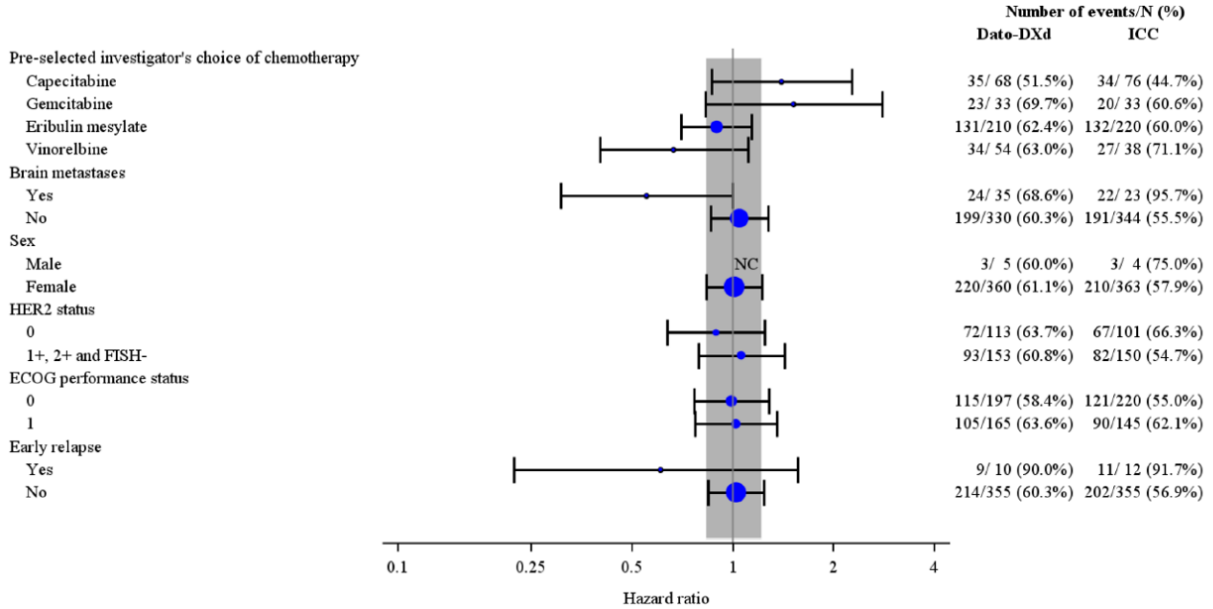
Hazard ratio (Dato-DXd: ICC) and 95% CI. A hazard ratio <1 implies a lower risk of death on Dato-DXd. The overall analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The subgroup analysis was performed using a Cox proportional hazards model with treatment as the only covariate. Size of circle is proportional to the number of events. Grey band represents the 95% confidence interval for the overall (all subjects) hazard ratio.
Three Canadian subjects were incorrectly stratified to geographic region rest of world rather than US, Canada, Europe. Per the pooling strategy, the CDK4/6 strata was pooled.
CI Confidence interval. ECOG Eastern cooperative oncology Group. HER2 Human epidermal growth factor receptor 2.
ICC Investigator's choice chemotherapy. N Number of subjects per treatment group. NC Not calculated. US United States.

Updated OS subgroup analyses (DCO 24 July 2024)

Figure 28 Overall Survival, Forest Plot, by Subgroup (Full Analysis Set) (DCO 24 July 2024)







Hazard ratio (Dato-DXd: ICC) and 95% CI. A hazard ratio < 1 implies a lower risk of death on Dato-DXd. The overall analysis was performed using a stratified Cox Proportional hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The subgroup analysis was performed using a Cox proportional hazards model with treatment as the only covariate. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) hazard ratio.
Three Canadian patients were incorrectly stratified to geographic region rest of world rather the US, Canada, Europe. Per the pooling strategy, the CDK4/6 strata was pooled.
CDK4/6 = Cyclin-dependent kinases 4 and 6; CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; HER2 = human epidermal growth factor receptor 2; ICC = investigator's choice chemotherapy; NC = not calculated; US = United States.

Table 47 PFS, Cox proportional hazards model, subgroup analysis, BICR (FAS)

				Comparison between groups	
Subgroup	Group	N	Number (%) of subjects with events [a]	Hazard ratio	95% CI
Pre-selected investigator's choice of chemotherapy					
Capecitabine	Dato-DXd	68	35 (51.5)	0.83	0.53, 1.31
	ICC	76	42 (55.3)		
Gemcitabine	Dato-DXd	33	18 (54.5)	0.51	0.26, 0.98
	ICC	33	21 (63.6)		
Eribulin mesylate	Dato-DXd	210	129 (61.4)	0.62	0.48, 0.79
	ICC	220	143 (65.0)		
Vinorelbine	Dato-DXd	54	30 (55.6)	0.39	0.23, 0.66
	ICC	38	29 (76.3)		
Brain metastases					
Yes	Dato-DXd	35	26 (74.3)	0.73	0.39, 1.42
	ICC	23	15 (65.2)		
No	Dato-DXd	330	186 (56.4)	0.62	0.51, 0.75
	ICC	344	220 (64.0)		

[a] Progression events that do not occur within 2 assessments of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events. The overall analysis was performed using a stratified Cox Proportional Hazards model with stratification variables number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. The subgroup analysis was performed using a Cox proportional hazards model with treatment as the only covariate. A hazard ratio < 1 favours Dato-DXd. CI calculated using Profile Likelihood. Pre-selected ICC are from IRT system. All other factors are from eCRF. Three Canadian subjects were incorrectly stratified to rest of world rather than US, Canada, Europe. RECIST version 1.1. Per the pooling strategy, the CDK4/6 strata was pooled.
BICR Blinded independent central review. CI Confidence interval. eCRF Electronic case report form. IRT Interactive response technology. N Number of subjects per treatment group. RECIST Response evaluation criteria in solid tumours. US United States.

Table 48 Baseline Characteristics and Median Treatment Duration

	TROPION-Breast01	Blum et al	EMBRACE trial Cortes et al		Kaufman et al		Jones et al	DESTINY-Breast04 trial Modi et al	TROPiCS-02 trial Rugo et al
	ICC [a] N=367	Capecitabine N=162	Eribulin N=508	TPC [b] N=254	Eribulin N=554	Capecitabine N=548	Vinorelbine N=115	TPC [c] N=163	TPC [d] N=271
Median age (range) years	54.0 (28, 86)	55.8 [mean] (26, 78)	55.0 (28, 85)	56.0 (27, 81)	54.0 (24, 80)	53.0 (26, 28)	53 (29, 83)	55.7 (28.4, 80)	55 (48, 63)
Hormone receptor-positive, no. (%)	366 (99.7)	NR	327 (64)	162 (64)	ER: 259 (46.8) PgR: 227 (41.0)	ER: 278 (50.7) PgR: 234 (42.7)	ER: 59 (51)	162 (99.4)	ER: 1%-10% 15 (6), >10% 246 (91) PgR: 1%-10% 44 (16), >10% 120 (44)
HER2-negative / low status, no. (%)	366 (99.7)	NR	373 (73)	192 (76)	375 (67.7)	380 (69.3)	NR	IHC 1+: 95 (58.3) IHC2+ and ISH-ve: 68 (41.7)	HER2 low: 134 (57) IHC0: 116 (43)
ECOG PS – n (%)									
0	220 (59.9)	NR	217 (43)	103 (41)	250 (45.1)	230 (42.0)	NR	95 (58.3)	NR
1	145 (39.5)	NR	244 (48)	126 (50)	293 (52.9)	301 (54.9)	NR	68 (41.7)	NR
Other	1 (0.3)	NR	39 (8)	22 (9)	11 (2.0)	17 (3.1)	NR	0	NR
Number of lines of previous chemotherapy in the metastatic setting – no. of patients (%)									
0	0	NR [e]	0	0	116 (20.9)	104 (19.0)	NR [f]	0	0
1	225 (61.3)		1 (<1)	0	280 (50.5)	293 (53.5)		14 (8.6)	2 (1)
≥ 2	142 (38.7)		505 (99.4)	253 (100)	158 (28.5)	151 (27.5)		149 (91.4)	269 (99.3)
Previous CDK4/6i – n (%)	300 (81.7)	NR	NR	NR	NR	NR	NR	115 (70.6)	268 (98.9)
Prior ET – n (%)	326 (88.8)	NR	NR	NR	NR	NR	78 (68)	160 (98.2)	234 (86)
Median duration of treatment (range) - months	4.1 (0.2, 17.4)	NR	3.9 (0.7, 16.3)	2.1 (0.03, 21.2)	4.1 (0.7, 45.1)	3.9 (0.7, 47.4)	NR	3.5 (0.3, 17.6)	2.3 (IQR: 1.0, 5.1)

[a] TB-01 study control arm consisted of capecitabine, gemcitabine, eribulin mesylate, and vinorelbine.
[b] EMBRACE control arm therapy consisted of vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines, and other chemotherapies.
[c] DESTINY-Breast04 trial control arm (all patients) consisted of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

[d] TROPiCS-02 trial control arm consisted of eribulin, vinorelbine, capecitabine, or gemcitabine.
[e] 100% of patients received prior chemotherapy in the gemcitabine + paclitaxel arm; 99.2% of patients received prior chemotherapy in the paclitaxel arm.
[f] Patients enrolled in the study had experienced treatment failure after one or 2 cytotoxic regimens for advanced disease, at least one of which contained chemotherapy agents (anthracycline).
Source: TB01 study CSR, Module 5.3.5.1; Blum et al 1999; Cortes et al 2011; Jones et al 1995; Kaufman et al 2015; Modi et al 2022a; Rugo et al 2022; Rugo et al 2023; Tolaney et al 2023.

Table 49 Treatment Outcomes of ICC Arm and Chemotherapy (historic data)

	TROPION-Breast01	Blum et al	EMBRACE trial Cortes et al		Kaufman et al		Jones et al	DESTINY-Breast04 trial Modi et al	TROPiCS-02 trial Rugo et al
	ICC [a] (N=367)	Capecitabine (N=162)	Eribulin (N=508)	TPC [b] (N=254)	Eribulin (N=554)	Capecitabine (N=548)	Vinorelbine (N=115)	TPC [c] (N=163)	TPC [d] (N=271)
PFS /TPP (n)	235	135	NR	NR	385	360	115	110	NR
Median PFS (TDP) in months	4.9	3.1	3.7	2.2	4.1	4.2	2.8	5.4	4.0
95% CI	4.2, 5.5	2.8, 3.53	3.3, 3.9	2.1, 3.4	3.5, 4.3	3.9, 4.9	NR	4.4, 7.1	NR
Overall Survival (n)	91	NR	274	148	446	459	115	163	199
Median OS in months	Immature [e]	12.8	13.1	10.6	15.9	14.5	8.1	17.5	11.2
95% CI	NC	NR	11.8, 14.3	9.3, 12.5	15.2, 17.6	13.1, 16.0	NR	15.2, 22.4	10.1, 12.7
ORR, %	22.9	20	12	5	11	11.5	16	16.3	14
95% CI	NR	14, 28	9.4, 15.5	2.3, 8.4	8.5, 13.9	8.9, 14.5	NR	11, 22.8	NR
DoR, months	5.7	8.1	4.2	6.7	NR	NR	NR	6.8	5.6
(95% CI)	4.9, 6.8	NR	3.8, 5.0	6.7, 7.0	NR	NR	NR	NR	3.8, 7.9

1. TB-01 study control arm consisted of capecitabine, gemcitabine, eribulin mesylate, and vinorelbine.
2. EMBRACE control arm therapy consisted of vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines, and other chemotherapies.
3. DESTINY-Breast04 trial control arm (HR+ cohort) consisted of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.
4. TROPiCS-02 trial control arm consisted of eribulin, vinorelbine, capecitabine, or gemcitabine.
5. Data for OS were not mature at this interim analysis (23.4% maturity, 38.5% information fraction), with a median follow-up of 9.7 months for OS (range: 0 to 20.2 months). The study is ongoing.

Source: Table 18, Table 21, Table 23, Table 27 in TB01 CSR, Module 5.3.5.1; Blum et al 1999; Cortes et al 2011; Jones et al 1995; Kaufman et al 2015; Modi et al 2022a; Modi et al 2022b; Rugo et al 2023.

Table 50 Progression-free Survival, Primary Analysis, Pre-selected Chemotherapy Subgroup Analysis, BICR Data (Full Analysis Set)

Subgroup	Group	N	Number (%) of patients with events [a]	Median progression-free survival (months) [b]	95% CI for median progression-free survival [b]
Pre-selected investigator's choice of chemotherapy					
Capecitabine	Dato-DXd	68	35 (51.5)	7.2	5.6, 13.4
	ICC	76	42 (55.3)	7.2	6.7, 8.3
Gemcitabine	Dato-DXd	33	18 (54.5)	5.6	2.7, 12.0
	ICC	33	21 (63.6)	3.9	1.7, 5.5
Eribulin mesylate	Dato-DXd	210	129 (61.4)	6.8	5.6, 8.2
	ICC	220	143 (65.0)	4.4	4.2, 5.5
Vinorelbine	Dato-DXd	54	30 (55.6)	6.6	4.9, NC
	ICC	38	29 (76.3)	3.6	1.5, 5.3

[a] Progression events that do not occur within 2 assessments of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.

[b] Calculated using the Kaplan-Meier technique.

Pre-selected ICC are from the IRT system. Dato-DXd arm is also being presented as in the pre-selected chemotherapy from IRT.

Median PFS for the ICC treatments overall are presented in Table 49 Treatment Outcomes of ICC Arm and Chemotherapy (historic data), while median PFS is estimated by pre-selected ICC subgroup and actual treatment received (ICC or Dato-DXd) in Table 50.

HER2-testing results

The updated HER2-associated PFS by investigator and OS data (HER2 IHC0 versus HER2-low) based on central assessment of HER2, including data on HER2 status for the majority of cases with missing HER2 information are presented in the table below. For 81/732=11% numerical HER2 IHC data are still missing. For n=6 (0.8%) information on HER2 status is completely missing.

Table 51 PFS, BICR by central HER2 IHC and Treatment Arm (Biomarker FAS) (DCO 17 July 2023)

HER2 IHC Group	Statistics	Dato-DXd	ICC
0	N	168	174
	Total events, n (%) [a]	104 (61.9)	113 (64.9)
	RECIST progression	100 (59.5)	107 (61.5)
	Death in the absence of progression	4 (2.4)	6 (3.4)
	Censored patients, n (%)	64 (38.1)	61 (35.1)
	Median months (95% CI) [b]	5.7 (5.5-7.1)	5.5 (4.3-6.2)
	Hazard ratio (95% CI)	0.75 (0.57-0.98)	
1+ and 2+	N	66	50
	Total events, n (%) [a]	37 (56.1)	31 (62.0)
	RECIST progression	35 (53.0)	27 (54.0)
	Death in the absence of progression	2 (3.0)	4 (8.0)
	Censored patients, n (%)	29 (43.9)	19 (38.0)
	Median months (95% CI) [b]	6.9 (5.6-10.9)	4.3 (2.7-7.0)
	Hazard ratio (95% CI)	0.65 (0.40-1.06)	

[a] Only includes progression events that occur within 2 assessments of the last evaluable assessment.
[b] Calculated using the Kaplan-Meier technique.
Progression is determined by BICR assessment, RECIST 1.1.
A hazard ratio < 1 favours Dato-DXd to be associated with a longer progression-free survival than ICC.
One patient with a central testing result of IHC 3+ is excluded from this analysis.
BICR = blinded independent central review; CI = confidence interval; Dato-DXd = datopotamab deruxtecan; DCO = data cut-off; HER2 = Human epidermal growth factor receptor 2; IA1 = interim analysis 1; ICC = Investigator's choice chemotherapy; IHC = immunohistochemistry; NC = not calculable; RECIST = Response Evaluation Criteria in Solid Tumours.

Table 52 OS by central HER2 IHC and Treatment Arm (Biomarker FAS) (DCO 24 July 2024)

HER2 IHC Group	Statistics	Dato-DXd	ICC
0	N	168	174
	Death, n (%)	106 (63.1)	110 (63.2)
	Censored patients, n (%)	62 (36.9)	64 (36.8)
	Median months (95% CI) [a]	19.6 (17.2-21.2)	17.6 (16.3-20.3)
	Hazard ratio (95% CI)	0.98 (0.75-1.27)	
1+ and 2+	N	66	50
	Death, n (%)	38 (57.6)	23 (46.0)
	Censored patients, n (%)	28 (42.4)	27 (54.0)
	Median months (95% CI) [a]	18.5 (14.2-NC)	29.8 (15.5-NC)
	Hazard ratio (95% CI)	1.33 (0.79-2.29)	

[a] Only includes progression events that occur within 2 assessments of the last evaluable assessment.
A hazard ratio < 1 favours Dato-DXd to be associated with a longer progression-free survival than ICC.
One patient with a central testing result of IHC 3+ is excluded from this analysis.
CI = confidence interval; Dato-DXd = datopotamab deruxtecan; HER2 = Human epidermal growth factor receptor 2; ICC = Investigator's choice chemotherapy; IHC = immunohistochemistry; NC = not calculable.

- **Summary of main efficacy results**

The following table summarises 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 53 Summary of efficacy for trial D9268C00001 TROPION-Breast01

Title: A Phase 3, Open-label, Randomised Study of Dato-DXd Versus Investigator's Choice of Chemotherapy in Participants with Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer Who Have Been Treated With One or Two Prior Lines of Systemic Chemotherapy (TROPION-Breast01)		
Study identifier	D9268C00001	
Design	Phase III, randomised, multicentre, open label, sponsor-blinded study of Dato-DXd versus Investigator's choice of chemotherapy in patients with inoperable or metastatic hormone receptor-positive, HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	21 Months (15 October 2021 to 17 July 2023) Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Dato-DXd	Dato-DXd (6 mg/kg IV on Day 1, Q3W) N=365

	Investigator's Choice of Chemotherapy		Capecitabine (1000 or 1250 mg/m^2 oral BID on Days 1 to 14, Q3W); choice between the 2 doses will be determined by standard institutional practice. Gemcitabine (1000 mg/m2 IV on Day 1 and Day 8, Q3W) Eribulin mesylate (1.4 mg/m2 IV on Days 1 and 8, Q3W) Vinorelbine (25 mg/m2 IV on Days 1 and 8, Q3W) N=367
Endpoints and definitions	Dual Primary endpoints	PFS by BICR	Progression free survival Time from the date of randomisation until the date of objective disease progression or death. Per RECIST Version 1.1, by blinded independent central review (BICR) assessment.
		OS	Overall survival Time from the date of randomisation until death due to any cause.
	Secondary endpoints	ORR	Objective response rate The proportion of participants who have a confirmed complete response (CR) or partial response (PR), per RECIST 1.1 using BICR assessments.
		DoR	Duration of response The time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. Per RECIST 1.1 using BICR assessments.
		BOR	Best objective response
		PFS by INV	Time from the date of randomisation until the date of disease progression or death. Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, by Investigator
		DCR	DCR at 12 weeks per RECIST 1.1
		PFS2	Time from the randomization to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy, or death.
Database lock	31-08-2023 (Final PFS analysis and First Interim analysis for OS)		
Results and Analysis			
Analysis description	**Primary Analysis (PFS and Interim analysis OS)**		
Analysis population and time point description	Intent to treat (all randomised patients). The final PFS analysis was performed based on a data cut-off (DCO) date of 17 July 2023, when 447 PFS events from the global cohort had occurred across Dato-DXd + ICC treatment arms (61% maturity). The first interim analysis of OS a was performed based on a DCO date of 17th of July 2023, when 171 OS events had occurred across Dato-DXd + ICC treatment arms (23.4% maturity).		

Descriptive statistics and estimate variability	Treatment group	Dato-DXd	ICC
	Number of subjects	365	367
	PFS (months) [a] Median (95% CI)	6.9 (5.7, 7.4)	4.9 (4.2, 5.5)
	Overall survival (months) [a] Median (95% CI)	16.1 (16.1, NC)	NC (16.5, NC)
	Confirmed ORR, n/N (%)	133/365 (36.44)	84/367 (22.89)
	DoR (months) [b] Median (25th, 75th percentiles), BICR	6.7 (5.6, 9.8)	5.7 (4.9, 6.8)
	BOR (% of patients) [b] CR = complete response PR = partial response SD = stable disease PD = progressive disease	CR 2 (0.5) PR 131 (35.9) SD>= 5 weeks 168 (46.0) PD 58 (15.9)	CR 0 (0) PR 84 (22.9) SD>= 5 weeks 176 (48.0) PD 76 (20.7)
	PFS2 (months) [a] Median (95% CI)	12.7 (11.1, NC)	10.4 (9.5,12.6)
	DCR, n/N (%)	275/365 (75.35)	234/367 (63.76)
Effect estimate per comparison	Dual Primary endpoint: PFS	Comparison groups	Dato-DXd vs ICC
		Hazard ratio [c,d]	0.63
		95% CI [c]	0.52, 0.76
		Two-sided p-value [e]	<0.0001
	Dual Primary endpoint: OS	Comparison groups	Dato-DXd vs ICC
		Hazard ratio [c,d]	0.84
		95% CI c	0.62, 1.14
		Two-sided p-value[e]	0.2615
	Secondary endpoint: ORR, confirmed by BICR	Comparison groups	Dato-DXd vs ICC
		Odds ratio [f,g]	1.95
		95% CI [f]	1.41,2.71
		Two-sided p-value (nominal) [f]	<0.0001
	Secondary endpoint: PFS2	Comparison groups	Dato-DXd vs ICC
		Hazard ratio [c,d]	0.71
		95% CI [c]	0.55,0.92

Notes	[a] Calculated using the Kaplan-Meier technique. [b] Includes confirmed responses. [c] The hazard ratio (HR) and confidence interval (CI) were estimated from a stratified Cox proportional hazards model with the Efron method to control for ties, the stratification factors of number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitors, and the CI calculated using a profile likelihood approach. [d] A HR < 1 favors Dato DXd to be associated with a longer OS or PFS than ICC. [e] P-values were generated using the stratified log-rank test adjusting for number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitors. [f] The analysis was performed using logistic regression adjusting for for number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitors with the CI calculated using a profile likelihood approach and the p-value calculated based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model. [g] An odds ratio > 1 favors Dato-DXd compared to ICC. NC, not calculated.

2.6.5.3. Clinical studies in special populations

The definitions for renal impairment and hepatic impairment used in Dato-DXd studies were as follows.

Renal function status at Baseline was defined as follows:

- Normal: serum creatinine clearance ≥ 90 mL/min (Stage 1)
- Mild impairment: serum creatinine clearance ≥ 60 but < 90 mL/min (Stage 2)
- Moderate impairment: serum creatinine clearance ≥ 30 but < 60 mL/min (Stage 3)
- Severe impairment: serum creatinine clearance ≥ 15 but < 30 mL/min (Stage 4 and Stage 5)

Hepatic function status at Baseline is now defined as follows:

Normal

1. Total bilirubin ≤ ULN and AST ≤ ULN (except for Gilbert syndrome patients)
2. Total bilirubin ≤ 3 × ULN and (AST ≤ ULN) for patients with Gilbert syndrome

Mild impairment

1. Total bilirubin > ULN but ≤ 1.5 × ULN and any AST except for patients with Gilbert syndrome
2. Total bilirubin > ULN but ≤ 3 × ULN and (AST > ULN) for patients with Gilbert syndrome
3. Total bilirubin ≤ ULN and (AST > ULN) regardless of Gilbert syndrome

Moderate impairment

1. Total bilirubin ≥ 1.5 x ULN, ≤ 3.0 x ULN and any AST except for patients with Gilbert syndrome

Severe impairment

1. Total bilirubin ≥ 3.0 x ULN and any AST regardless of Gilbert syndrome

Table 54 Number of Special Populations in Controlled and Non-controlled Breast Cancer Clinical Trials

Special population	Number of patients	
	Controlled trials TB01 (Dato-DXd arm) N = 360	Non-controlled trials TP01 (Breast cancer cohort) N = 83
Renal impairment patients	40	8
Hepatic impairment patients	6	1
Paediatric patients <18 years	0	0
Adult patients 18 to <65 years	269	71
Age 65 to < 75	72	10
Age 75 to < 85	18	2
Age ≥ 85	1	0
Missing	0	0

TB01, TROPION-Breast01; TP01, TROPION-PanTumor01.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein widely expressed in solid tumors, including breast cancer. Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed antibody-drug conjugate composed of a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload (an exatecan derivative, DXd), via a tetrapeptide-based cleavable linker. Following internalization of Dato-DXd into TROP2-expressing cells, the plasma-stable linker is cleaved by tumor-cell enriched lysosomal enzymes to release the payload, leading to tumor cell death and a bystander antitumor effect, resulting in elimination of both target and neighboring cells.

TROP2 analysis by immunohistochemistry (IHC) has previously shown that 97% (1959/2008) of breast tumors expressed TROP2 (Dum et al 2022). However, it is not known whether the level of TROP2 protein expression could be related to the extent of clinical response in the HR-positive HER2-negative patient population included in this study. Therefore, the TROPION-Breast01 study includes an exploratory objective to assess whether TROP2 protein expression level may correlate with clinical response from Dato-DXd used to treat breast cancer.

TROP2 expression was measured by the exploratory TROP2 (EPR20043) IHC Robust Prototype Assay (RPA) by Ventana in tumor samples obtained as close as possible to the time of diagnosis of metastatic or inoperable disease (refer to EPR20043 intracellular domain TROP2). TROP2 tumor cell membrane IHC expression in tumor cells was assessed by pathologists by membrane H-score (low, medium, and high). Samples that were not evaluable (NE) or missing were included in a missing/NE category. The following groups were assessed: Low H-score: 0 to 99; Medium H-score: 100 to 199; High H-score: 200 to 300; Missing or NE.

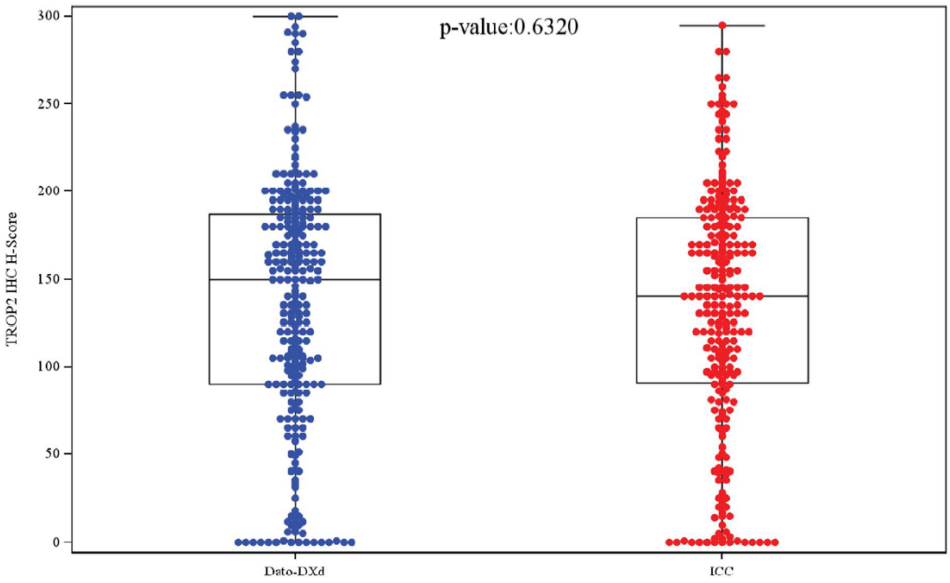
A total of 732 subjects (who constitute the ITT population) were included in the BFAS, of which 545 subjects (74.5%) had an evaluable result with numerical value available for the H-score and were included in the IHC-EAS.

Table 55 Subject Disposition (BFAS)

	Dato-DXd n (%)	ICC n (%)	Total n (%)
Subjects in Biomarker Full Analysis Set	365	367	732
Subjects with TROP2 IHC evaluable	277 (75.9)	268 (73.0)	545 (74.5)
Subjects with TROP2 IHC non-evaluable or missing	88 (24.1)	99 (27.0)	187 (25.5)

Percentages and summary statistics are based on the number of subjects in the BFAS subgroup.
Subjects are summarized in the arm to which they were randomized.

Figure 29 Boxplot of TROP2 IHC H-Score by Treatment Arm (IHC-EAS)



Nominal p-value derived from Wilcoxon Rank-Sum test.

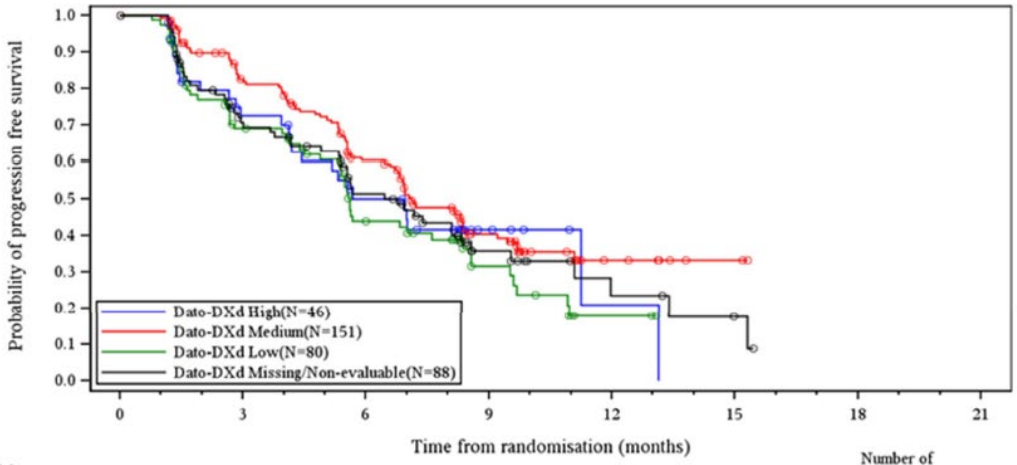
Table 56 PFS (BICR) by TROP2 IHC H-Score and Treatment Arm (BFAS)

TROP2 IHC H-Score group	Statistics	Dato-DXd	ICC
High	N	46	40
	Total events [a], n (%)	26 (56.5)	25 (62.5)
	RECIST progression	25 (54.3)	23 (57.5)
	Death in the absence of progression	1 (2.2)	2 (5.0)
	Censored subjects, n (%)	20 (43.5)	15 (37.5)
	Median months (95% CI) [b]	5.7 (4.2 - NC)	4.4 (2.7 - 7.1)
	Hazard ratio (95% CI) [c]	0.71 (0.40 - 1.26)	
Medium	N	151	150
	Total events [a], n (%)	82 (54.3)	101 (67.3)
	RECIST progression	80 (53.0)	91 (60.7)
	Death in the absence of progression	2 (1.3)	10 (6.7)
	Censored subjects, n (%)	69 (45.7)	49 (32.7)
	Median months (95% CI) [b]	7.1 (6.6 - 8.4)	4.6 (4.2 - 5.6)
	Hazard ratio (95% CI) [c]	0.53 (0.40 - 0.72)	
Low	N	80	78
	Total events [a], n (%)	52 (65.0)	51 (65.4)
	RECIST progression	50 (62.5)	49 (62.8)
	Death in the absence of progression	2 (2.5)	2 (2.6)
	Censored subjects, n (%)	28 (35.0)	27 (34.6)
	Median months (95% CI) [b]	5.6 (4.9 - 8.3)	5.3 (4.0 - 5.6)
	Hazard ratio (95% CI) [c]	0.78 (0.52 - 1.17)	
Missing or non-evaluable	N	88	99
	Total events [a], n (%)	52 (59.1)	58 (58.6)
	RECIST progression	46 (52.3)	55 (55.6)
	Death in the absence of progression	6 (6.8)	3 (3.0)
	Censored subjects, n (%)	36 (40.9)	41 (41.4)
	Median months (95% CI) [b]	6.5 (5.4 - 8.3)	5.4 (3.4 - 6.0)
	Hazard ratio (95% CI) [c]	0.66 (0.44 - 0.97)	

[a] Only includes progression events that occurred within 2 assessments of the last evaluable assessment.
[b] Calculated using the Kaplan-Meier technique.
[c] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables: number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer PFS than ICC.

Per the pooling strategy, for the high subgroup CDK4/6 and previous lines of chemotherapy strata were pooled. For the medium, low, and missing or non-evaluable subgroups the CDK4/6 strata were pooled.
Progression is determined by BICR assessment, RECIST 1.1.

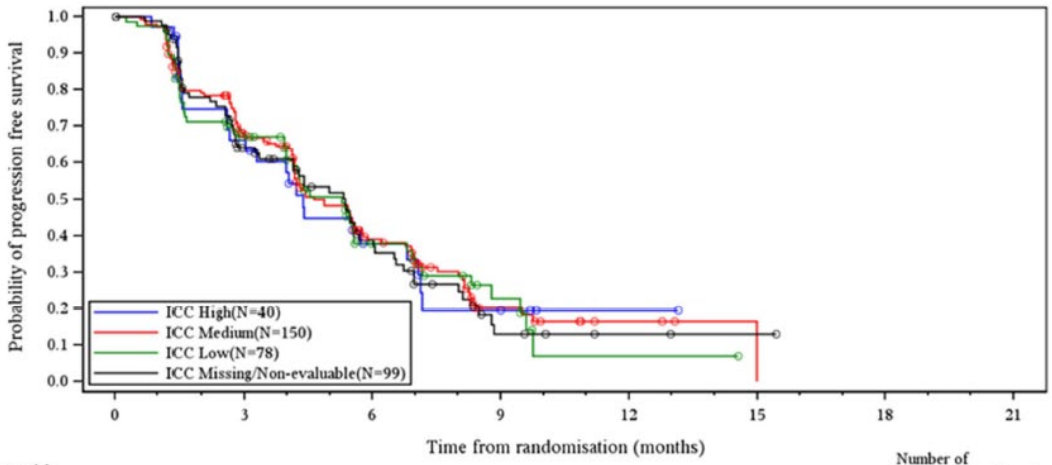
Figure 30 PFS, Kaplan-Meier Plot, BICR data by Dato-DXd TROP2 Subgroup (BFAS)



Number of subjects at risk								Number of randomised subjects/ Number of events
Dato-DXd High	46	30	19	6	1	0	0	46/ 26
Dato-DXd Medium	151	114	76	35	7	2	0	151/ 82
Dato-DXd Low	80	51	28	12	2	0	0	80/ 52
Dato-DXd Missing/Non-evaluable	88	54	35	13	5	2	0	88/ 52

Circle indicates a censored observation. RECIST 1.1.
HR = hazard ratio

Figure 31 PFS, Kaplan-Meier Plot, BICR data by ICC TROP2 Subgroup (BFAS)



Number of subjects at risk								Number of randomised subjects/ Number of events
ICC High	40	23	9	4	1	0	0	40/ 25
ICC Medium	150	90	43	11	4	0	0	150/ 101
ICC Low	78	46	18	6	1	0	0	78/ 51
ICC Missing/Non-evaluable	99	46	23	5	2	1	0	99/ 58

Circle indicates a censored observation. RECIST 1.1.
HR = hazard ratio

Table 57 OS by TROP2 IHC H-Score and Treatment Arm (BFAS)

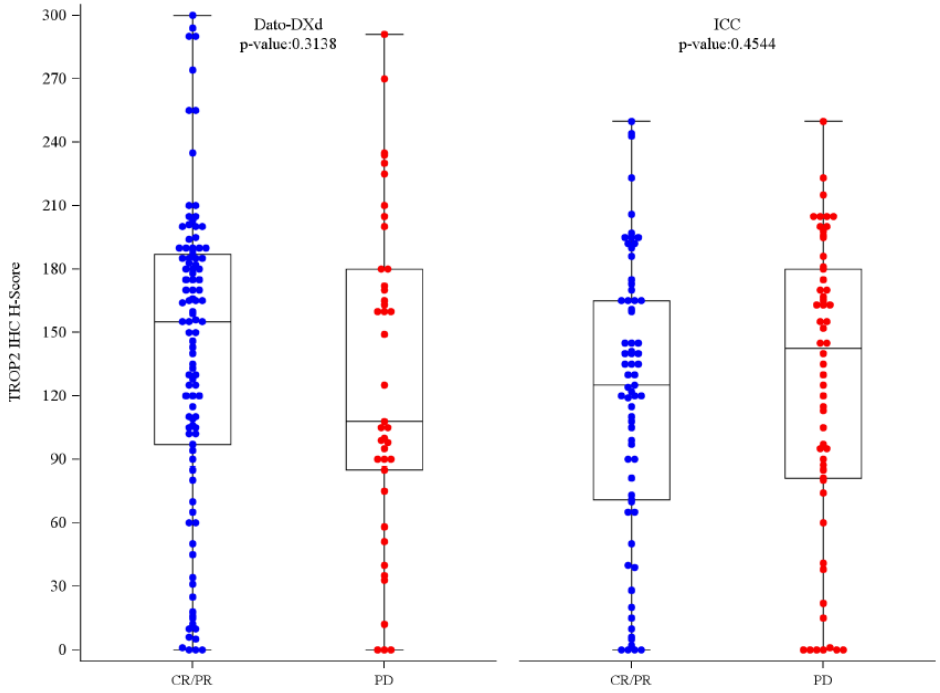
TROP2 IHC H-score group	Statistics	Dato-DXd	ICC
High	N	46	40
	Death, n (%)	12 (26.1)	10 (25.0)
	Censored subjects, n (%)	34 (73.9)	30 (75.0)
	Median months (95% CI) [a]	16.1 (13.7 - NC)	NC (11.2 - NC)
	Hazard ratio (95% CI) [b]	0.92 (0.39 - 2.22)	
Medium	N	151	150
	Death, n (%)	26 (17.2)	38 (25.3)
	Censored subjects, n (%)	125 (82.8)	112 (74.7)
	Median months (95% CI) [a]	NC (15.1 - NC)	NC (14.3 - NC)
	Hazard ratio (95% CI) [b]	0.62 (0.37 - 1.02)	
Low	N	80	78
	Death, n (%)	23 (28.8)	19 (24.4)
	Censored subjects, n (%)	57 (71.3)	59 (75.6)
	Median months (95% CI) [a]	NC (13.3 - NC)	NC (16.5 - NC)
	Hazard ratio (95% CI) [b]	1.15 (0.62 - 2.14)	
Missing or non-evaluable	N	88	99
	Death, n (%)	19 (21.6)	24 (24.2)
	Censored subjects, n (%)	69 (78.4)	75 (75.8)
	Median months (95% CI) [a]	NC (13.3 - NC)	NC (13.8 - NC)
	Hazard ratio (95% CI) [b]	0.97 (0.52 - 1.77)	

[a] Calculated using the Kaplan-Meier technique.

[b] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables: number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer OS than ICC.

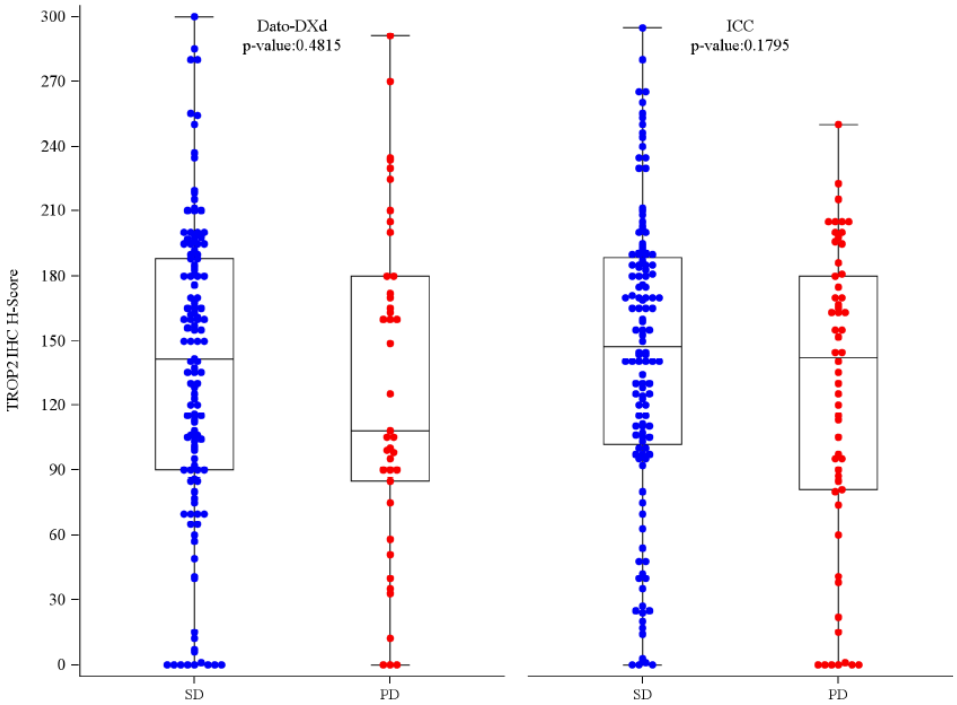
Per the pooling strategy, for the high subgroup CDK4/6, previous lines of chemotherapy and geographic region strata were pooled. For the medium, low, and missing or non-evaluable subgroups the CDK4/6 and previous lines of chemotherapy strata were pooled.

Figure 32 Boxplot of TROP2 IHC H-Score by BOR of CR/PR and PD and Treatment Arm (BFAS)



Response required confirmation. Nominal p-value derived from Wilcoxon Rank-Sum test. RECIST version 1.1.

Figure 33 Boxplot of TROP2 IHC H-Score by BOR of SD and PD and Treatment Arm (BFAS)



Response required confirmation. Nominal p-value derived from Wilcoxon Rank-Sum test. RECIST version 1.1.
Source: 14.3.1.7.IA1

Table 58 PFS (BICR) by TROP2 IHC H-Score Quantile and Treatment Arm, IA1 (Biomarker Full Analysis Set)

TROP2 IHC HScore quantile group	Statistics	Dato-DXd	ICC
Quantile (≥ 0, < 20%)	N	54	55
	Total events [a], n (%)	33 (61.1)	35 (63.6)
	RECIST progression	31 (57.4)	35 (63.6)
	Death in the absence of progression	2 (3.7)	0
	Censored patients, n (%)	21 (38.9)	20 (36.4)
	Median months (95% CI) [b]	5.7 (4.5 - 9.6)	5.4 (4.3 - 6.9)
	Hazard ratio (95% CI) [c]	0.76 (0.46 - 1.25)	
Quantile (≥ 20%, < 40%)	N	54	45
	Total events [a], n (%)	37 (68.5)	31 (68.9)
	RECIST progression	35 (64.8)	28 (62.2)
	Death in the absence of progression	2 (3.7)	3 (6.7)
	Censored patients, n (%)	17 (31.5)	14 (31.1)
	Median months (95% CI) [b]	5.6 (4.1 - 7.0)	4.0 (2.8 - 7.0)
	Hazard ratio (95% CI) [c]	0.74 (0.44 - 1.24)	
Quantile (≥ 40%, < 60%)	N	54	61

TROP2 IHC HScore quantile group	Statistics	Dato-DXd	ICC
	Total events a, n (%)	28 (51.9)	36 (59.0)
	RECIST progression	28 (51.9)	32 (52.5)
	Death in the absence of progression	0	4 (6.6)
	Censored patients, n (%)	26 (48.1)	25 (41.0)
	Median months (95% CI) [b]	8.1 (5.6 - NC)	5.9 (4.2 - 8.1)
	Hazard ratio (95% CI) [c]	0.63 (0.38 - 1.04)	
Quantile (≥ 60%, < 80%)	N	56	55
	Total events a, n (%)	29 (51.8)	40 (72.7)
	RECIST progression	29 (51.8)	36 (65.5)
	Death in the absence of progression	0	4 (7.3)
	Censored patients, n (%)	27 (48.2)	15 (27.3)
	Median months (95% CI) [b]	8.4 (5.6 - NC)	4.2 (2.8 - 5.4)
	Hazard ratio (95% CI) [c]	0.31 (0.18 - 0.52)	
Quantile (≥ 80%, ≤ 100%)	N	59	52
	Total events a, n (%)	33 (55.9)	35 (67.3)
	RECIST progression	32 (54.2)	32 (61.5)
	Death in the absence of progression	1 (1.7)	3 (5.8)
	Censored patients, n (%)	26 (44.1)	17 (32.7)
	Median months (95% CI) [b]	6.8 (5.2 - 11.2)	4.4 (2.9 - 7.1)
	Hazard ratio (95% CI) [c]	0.72 (0.44 - 1.18)	
Missing	N	88	99
	Total events a, n (%)	52 (59.1)	58 (58.6)
	RECIST progression	46 (52.3)	55 (55.6)
	Death in the absence of progression	6 (6.8)	3 (3.0)
	Censored patients, n (%)	36 (40.9)	41 (41.4)
	Median months (95% CI) [b]	6.5 (5.4 - 8.3)	5.4 (3.4 - 6.0)
	Hazard ratio (95% CI) [c]	0.66 (0.44 - 0.97)	

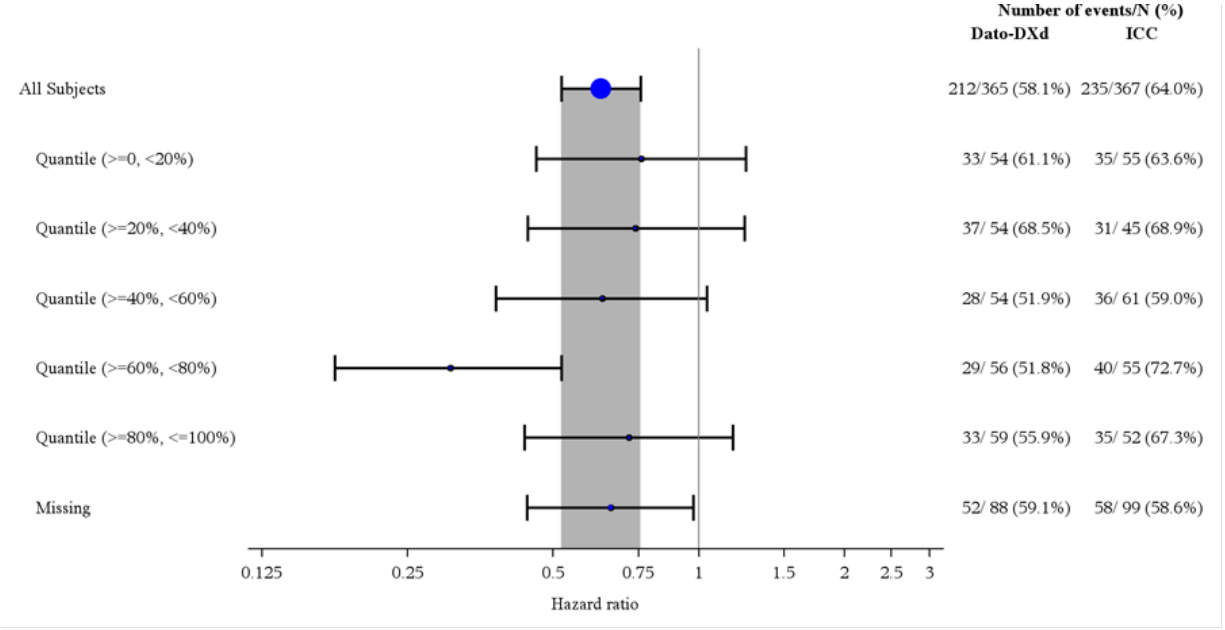
[a] Only includes progression events that occurred within 2 assessments of the last evaluable assessment.

[b] Calculated using the Kaplan-Meier technique.

[c] The analysis was performed using a stratified Cox Proportional Hazards model with stratification variables: number of previous lines of chemotherapy, geographic region, and prior use of CDK4/6 inhibitor. A hazard ratio < 1 favors Dato-DXd to be associated with a longer PFS than ICC.

Per the pooling strategy, for the 0-25, 50-75, 75-100, and missing quantile subgroups, the CDK4/6 inhibitor strata was pooled. For the 25-50 quantile subgroup, number of previous lines of chemotherapy and CDK4/6 inhibitor stratas were pooled. Progression is determined by BICR assessment, RECIST 1.1.

Figure 34 Progression-free Survival, Forest Plot, by TROP2 IHC H-score Quantile and Treatment Arm, BICR Data, IA1 (Biomarker Full Analysis Set)



Hazard ratio (Dato-DXd: ICC) and 95% CI.

A hazard ratio < 1 favours Dato-DXd.

Table 59 PFS (BICR) by TROP2 IHC H-Score and Treatment Arm, Samples Collected Within 6 Weeks of Treatment Start Date, IA1 (Biomarker Full Analysis Set)

TROP2 IHC H-Score quantile group	Statistics	Dato-DXd	ICC
High	N	9	6
	Total events [a], n (%)	5 (55.6)	5 (83.3)
	RECIST progression	5 (55.6)	4 (66.7)
	Death in the absence of progression	0	1 (16.7)
	Censored patients, n (%)	4 (44.4)	1 (16.7)
	Median months (95% CI) [b]	11.2 (1.3 - NC)	3.7 (1.3 - NC)
	Hazard ratio (95% CI) [c]	0.31 (0.06 - 1.27)	
Medium	N	14	16
	Total events [a], n (%)	9 (64.3)	12 (75.0)
	RECIST progression	9 (64.3)	12 (75.0)
	Censored patients, n (%)	5 (35.7)	4 (25.0)
	Median months (95% CI) [b]	8.1 (3.1 - NC)	4.2 (1.4 - 5.6)
	Hazard ratio (95% CI) [c]	0.38 (0.14 - 0.96)	
Low	N	10	12
	Total events [a], n (%)	8 (80.0)	8 (66.7)
	RECIST progression	8 (80.0)	8 (66.7)
	Censored patients, n (%)	2 (20.0)	4 (33.3)
	Median months (95% CI) [b]	4.4 (1.2 - 5.5)	5.4 (1.4 - NC)
	Hazard ratio (95% CI) [c]	1.21 (0.42 - 3.37)	
Missing or Non-evaluable	N	4	5
	Total events [a], n (%)	1 (25.0)	3 (60.0)
	RECIST progression	1 (25.0)	3 (60.0)
	Censored patients, n (%)	3 (75.0)	2 (40.0)
	Median months (95% CI) [b]	NC (1.6 - NC)	6.2 (1.7 - NC)
	Hazard ratio (95% CI) [c]	0.32 (0.02 - 2.53)	

[a] Only includes progression events that occurred within 2 assessments of the last evaluable assessment.

[b] Calculated using the Kaplan-Meier technique.

[c] The analysis was performed using an unstratified Cox Proportional Hazards model. A hazard ratio < 1 favors Dato-DXd to be associated with a longer PFS than ICC.

Progression is determined by BICR assessment, RECIST 1.1.

Table 60 PFS (BICR) by TROP2 IHC H-Score Quantile and Treatment Arm, Samples Collected Within 6 Weeks of Treatment Start Date, IA1 (Biomarker Full Analysis Set)

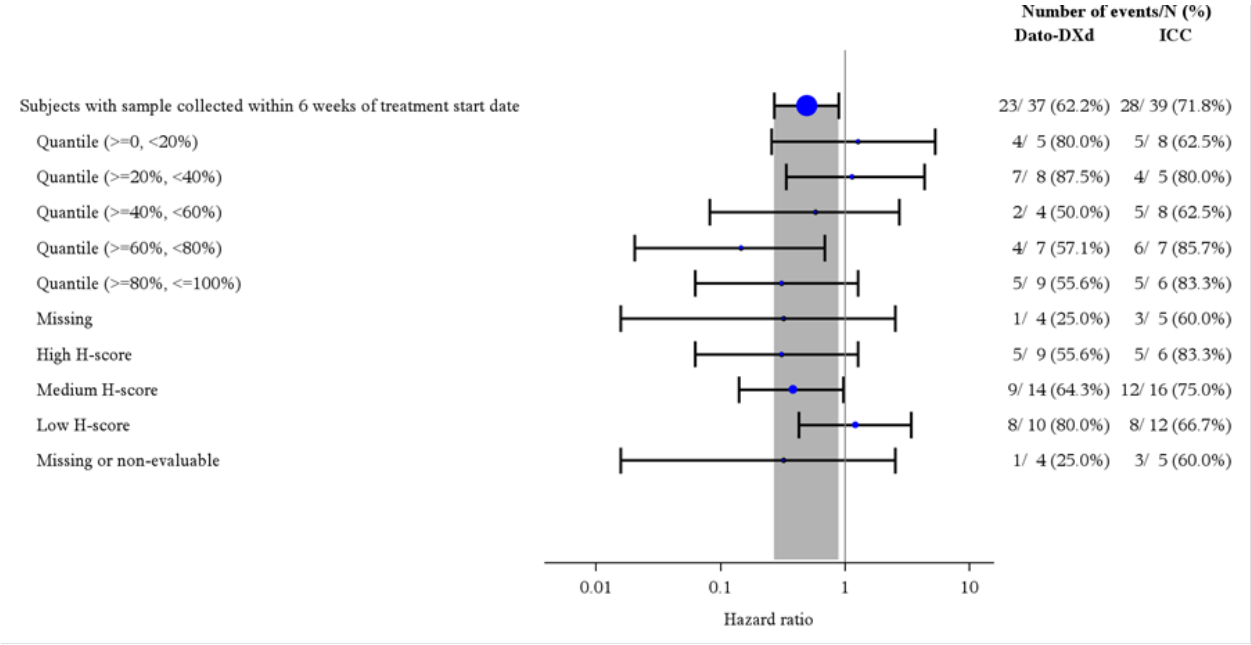
TROP2 IHC H-Score quantile group	Statistics	Dato-DXd	ICC
Quantile (≥ 0, < 20%)	N	5	8
	Total events a, n (%)	4 (80.0)	5 (62.5)
	RECIST progression	4 (80.0)	5 (62.5)
	Censored patients, n (%)	1 (20.0)	3 (37.5)
	Median months (95% CI) b	4.4 (1.2 - NC)	5.4 (1.1 - NC)
	Hazard ratio (95% CI) c	1.27 (0.26 - 5.25)	
Quantile (≥ 20%, < 40%)	N	8	5
	Total events a, n (%)	7 (87.5)	4 (80.0)
	RECIST progression	7 (87.5)	4 (80.0)
	Censored patients, n (%)	1 (12.5)	1 (20.0)
	Median months (95% CI) b	4.2 (1.2 - 5.5)	2.7 (1.4 - NC)
	Hazard ratio (95% CI) c	1.13 (0.34 - 4.34)	
Quantile (≥ 40%, < 60%)	N	4	8
	Total events a, n (%)	2 (50.0)	5 (62.5)
	RECIST progression	2 (50.0)	5 (62.5)
	Censored patients, n (%)	2 (50.0)	3 (37.5)
	Median months (95% CI) b	NC (3.1 - NC)	4.4 (0.7 - NC)
	Hazard ratio (95% CI) c	0.57 (0.08 - 2.70)	
Quantile (≥ 60%, < 80%)	N	7	7
	Total events a, n (%)	4 (57.1)	6 (85.7)
	RECIST progression	4 (57.1)	6 (85.7)
	Censored patients, n (%)	3 (42.9)	1 (14.3)
	Median months (95% CI) b	9.7 (1.0 - NC)	3.5 (1.3 - NC)
	Hazard ratio (95% CI) c	0.15 (0.02 - 0.68)	
Quantile (≥ 80%, 100%)	N	9	6
	Total events a, n (%)	5 (55.6)	5 (83.3)
	RECIST progression	5 (55.6)	4 (66.7)
	Death in the absence of progression	0	1 (16.7)
	Censored patients, n (%)	4 (44.4)	1 (16.7)
	Median months (95% CI) b	11.2 (1.3 - NC)	3.7 (1.3 - NC)
	Hazard ratio (95% CI) c	0.31 (0.06 - 1.27)	
Missing	N	4	5
	Total events a, n (%)	1 (25.0)	3 (60.0)
	RECIST progression	1 (25.0)	3 (60.0)
	Censored patients, n (%)	3 (75.0)	2 (40.0)
	Median months (95% CI) b	NC (1.6 - NC)	6.2 (1.7 - NC)

Table 60 PFS (BICR) by TROP2 IHC H-Score Quantile and Treatment Arm, Samples Collected Within 6 Weeks of Treatment Start Date, IA1 (Biomarker Full Analysis Set)

TROP2 IHC H-Score quantile group	Statistics	Dato-DXd	ICC
	Hazard ratio (95% CI) c	0.32 (0.02 - 2.53)	

[a] Only includes progression events that occurred within 2 assessments of the last evaluable assessment.
[B] Calculated using the Kaplan-Meier technique.
[C] The analysis was performed using an unstratified Cox Proportional Hazards model. A hazard ratio < 1 favors Dato-DXd to be associated with a longer PFS than ICC.
Progression is determined by BICR assessment, RECIST 1.1.

Figure 35 Progression-free Survival, Forest Plot, by TROP2 IHC H-score Quantile and Treatment Arm for Samples Collected Within 6 Weeks of Treatment Start Date, BICR Data, IA1 (Biomarker Full Analysis Set)



Hazard ratio (Dato-DXd: ICC) and 95% CI.

A hazard ratio < 1 favours Dato-DXd.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study – TP01 (BC cohort)

Disposition and Exposure

A total of 41 patients with HR-positive/HER2-negative metastatic breast cancer (mBC) were enrolled and received at least 1 dose of the study drug. As of 22 July 2022, 5 (12.2%) of these patients were continuing to receive study treatment and 36 (87.8%) patients discontinued study treatment. The primary reason for study treatment discontinuation in HR-positive/HER2-negative mBC patients was progressive disease in 24 (58.5%) patients. The median (range) study duration was 13.7 (range: 9 to 16) months. The median treatment duration was 4.83 (range: 0.7 to 14.9) months. and the median total number of treatment cycles initiated was 7.0 (range: 1 to 20).

Demographics and Baseline Characteristics

The median age was 57.0 years (range: 33 to 75 years), and most patients were White (29 [70.7%]) or Asian (8 [19.5%]), and female (40 [97.6%]).%]) By region, 85.4% of patients were treated in the United States, and 14.6% of patients were treated in Japan. The baseline ECOG status in patients was either 0 (48.8%) or 1 (51.2%), with an overall median (range) of baseline body mass index of 27.54 kg/m^2 (18.49 to 43.39 kg/m^2). The target tumor sizes measured at baseline per BICR were ≤5 cm in 43.9% of patients, >5 to <10 cm in 39.0% of patients, and ≥10 cm in 14.6% of patients.

Prior Cancer History and Therapy

All 41 (100%) patients received prior systemic cancer treatments. The majority (≥50%) of patients were BRCA- (ie, BRCA1 and BRCA2 negative). In terms of prior systemic cancer treatment, all of patients received endocrine therapy (100%), chemotherapy (100%), and majority of the patients received CDK4/6 inhibitors (95.1%), capecitabine (82.9), taxanes (58.5%), and anthracycline (53.7%).

Efficacy Results in Patients with HR-positive/HER2-negative BC (N=41)

All patients with HR-positive/HER2-negative mBC received a Dato-DXd IV dose of 6 mg/kg 21-day cycle.

- Confirmed ORR (CR + PR; 95% CI) as assessed by BICR was 26.8% (14.2, 42.9) and 29.3% (16.1, 45.5) as assessed by the investigator.
- DCR (confirmed CR + confirmed PR+SD [or non-CR/non-PD]; 95% CI) as assessed by BICR was 85.4% (70.8, 94.4) and 80.5% (65.1, 91.2) as assessed by the investigator.
- CBR ([confirmed CR + confirmed PR+SD [non-CR/non-PD] for at least 6 months]; 95% CI) as assessed by BICR was 43.9% (28.5, 60.3) and 36.6% (22.1, 53.1) as assessed by the investigator.
- The median DoR (95% CI) was NE (4.4, NE) and the median TTR (min, max) was 2.76 (1.2, 5.6) months as assessed by BICR. As assessed by the investigator, the median DoR (95% CI) was NE (2.9, NE) months, and the median TTR (min, max) was 2.76 (1.2, 5.9) months.
- The median PFS (95% CI) was 8.3 (5.5, 11.1) and 5.6 (4.1, 6.9) months as assessed by BICR and the investigator, respectively.
- The median OS (95% CI) was NE (10.1, NE) months. The OS rate at 12 months (95% CI) was 56.8% (39.1, 71.2).

2.6.6. Discussion on clinical efficacy

Dosing recommendation

The recommended dosing regimen was also supported by data from the TP01 study from NSCLC patients, where 3 different dose levels were tested (4, 6, and 8 mg/kg), that indicated that 6 mg/kg of Dato-DXd has a better efficacy compared to a 4 mg/kg dose. The tolerability profile was also deemed manageable at this dose. The observed plasma concentrations of Dato-DXd and DXd was similar in both indications. This is further supported by same population PK model and similar estimated PK parameters between two indications.

No new covariates were found in the updated PK analysis using TB01 data. The ER analysis using TB01 data showed that there is no clear exposure-response relationship, although patients with lower exposure tended to show lower efficacy. The TGI analysis indicated that 6 mg/kg is likely to provide

better tumour regression compared to 4 mg/kg, which is similar to simulations from NSCLC analysis. The exposure safety analysis and simulations indicated that doses greater than 6 mg/kg are likely to lead to more AEs. Overall, the totality of observed clinical efficacy and safety data, population PK analysis, and ER analyses of efficacy and safety support to use Dato-DXd at the proposed dose of 6 mg/kg administered on Day 1 of each 21-day cycle.

In conclusion, TP01 provided supportive data of the efficacy of Dato-DXd in mBC and supportive data for the chosen proposed dose of 6 mg/kg administered on Day 1 of each 21-day cycle. Since an RCT (TB01) serves as the pivotal study for this application, these data are considered supportive of the use of Dato-DXd in a heavily pre-treated patient population. Therefore, no update is required of these non-comparative data although the DCO was 22 July 2022.

Design and conduct of clinical studies

The efficacy of Datopotamab deruxtecan (Dato-DXd) in the proposed indication is based on the pivotal study TROPION-Breast01 and supportive data from the BC cohort in the TP01 study (n=41). TROPION-Breast01 is a phase 3, open-label, randomised study of Dato-DXd versus single-agent chemotherapy of Investigator's choice (ICC) in patients with unresectable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with one or 2 prior lines of systemic therapy. Patients should have progressed or not suitable for endocrine therapy, and should have progressed following most recent chemotherapy. Targeted agents (e.g. PARP inhibitors, CDK4/6 inhibitors) do not count as a prior line of chemotherapy, unless combined with chemotherapy. Patients were included from 166 active sites in 20 countries/regions over less than 2 years and the current DCO is 17 July 2023, so the median duration of PFS follow-up in censored patients was 8.1 months in the Dato-DXd arm and 4.0 months in the ICC arm. A total of 732 patients were randomised 1:1 to received either Dato-DXd (n=365) or ICC (eribulin, vinorelbine, capecitabine or gemcitabine as single-agent chemotherapy) (N=367). The randomisation was stratified by the following factors: Number of previous lines of chemotherapy, geographic region and prior use of a CDK4/6-inhibitor. The study design was open-label, which is considered acceptable, as it is agreed that the Investigator's choice of chemotherapy (ICC) could not be blinded. The dual primary endpoints of the pivotal study were PFS by blinded independent central review (BICR) and OS. Relevant secondary endpoints include PFS by investigator, ORR, DoR, and PFS2. Multiple sensitivity analyses for PFS were conducted to address potential biases, and the procedures to support the integrity of the study results are endorsed. The methodologies employed to analyse the multiple secondary endpoints and subgroup analysis are acceptable. The utilization of various analysis sets is agreed (ITT, SAS, PAS). The calculation of the smallest detectable HR at 0.775 for PFS and between 0.824 and 0.817 for OS is acceptable. The methodology behind the setup of interim analyses is considered to be sound. The utilization of a conservative error-spending approach for the primary endpoints is acknowledged to respect the overall type I error rate. Secondary endpoints and subgroup analysis have not been included in the confirmatory testing strategy and, thus, cannot be interpreted as confirmatory evidence. Changes to the planned analyses were intended to clarify language and align with established templates without altering the analytical methodology, therefore, the potential for bias is considered low. Overall, the statistical analysis plan is considered acceptable.

Baseline characteristics showed that the median age was ~55 years , with the vast majority (~77%) being less than 65 years of age, while ~22% of the patients were ⩾65 years, which is reflective of the targeted patient population. Nine male patients were included, which is acceptable since breast cancer is rare in men, and the results from the pivotal trial is considered extrapolatable to men with HR-positive, HER2-negative metastatic breast cancer in line with previous EMA decisions. Nearly half of the patients were White, while ~40% were Asian, so the fraction of patients representative of the EU population is considered acceptable for the interpretation of the study results. Although only 1.5% of the patients included were locally advanced /inoperable, the data from the metastatic patients are

considered extrapolatable to the unresectable patients based on the scientific rationale for efficacy and the mode of action for Dato-DXd.

Patients had good ECOG Performance status (PS) with either of ECOG PS 0 (~60%) or ECOG PS 1 (~40%). The vast majority of the patients had prior CDK4/6 inhibitors (82.5%), which was balanced between the arms. The median number of previous lines of anticancer therapies was 3, most commonly chemotherapy and endocrine therapy. As mentioned, prior ADC, immunotherapy and PARP inhibitors were less frequently used; however, this is considered reflective of the standard of care and is acceptable. Disease characteristics show that most patients had visceral metastases at baseline with the most common sites of metastasis in the liver, bone, lung, pleura, other metastatic sites, and the brain. Overall, the study population is considered reflective of the targeted 2L+ patient population with advanced HR+, HER2-negative BC and the proposed indication.

Efficacy data and additional analyses

The dual endpoint of **PFS by BICR** was met and showed a statistically significant improvement of 2 months from 4.9 months for ICC to 6.9 months with Dato-DXd, HR 0.63 (95%CI: 0.52, 0.76). The PFS data is mature at the time of the primary and final analysis of PFS, as 58.1% events in the Dato-DXd arm and 64.0% events in the ICC arm were observed, respectively. The KM curves for PFS by BICR separate after approximately 2 months and stay separated, which generally suggests no violation of the PH assumption. This PFS benefit was statistically significant and given that the pivotal study is considered to be a substitution trial using relevant comparators, the 2-months difference in median PFS between Dato-DXd and single-agent chemotherapy per Physicians' choice, can be considered clinically relevant.

Most of the patients in the control arm received either eribulin (59.9%), followed by capecitabine (20.7%), vinorelbine (10.4%), and gemcitabine (9.0%). In the ICC arm, 43% of patients had not received prior anthracyclines and/or taxanes, so they would probably have been offered these important standard of care options in the studied treatment setting. For this reason, the performance of the control arm may have been better if inclusion of anthracyclines and taxanes had been allowed. This leads to the uncertainty that PFS benefit of Dato-DXd compared to chemotherapy may have been overestimated; and although this issue will not be further pursued, it has to be weighed in the B/R assessment as an uncertainty.

An overview of the efficacy of treatments administered in the ICC comparator arm was provided indicating a median PFS for gemcitabine, eribulin and vinorelbine treatment groups ranging from 3.5 to 4.4 months. This is comparable to the reported historical studies, although the median PFS was longer than expected for the capecitabine group, and comparable with the median PFS on Dato-DXd i.e. 7.2 months. This observation is in line with the assumption that capecitabine is not an inferior treatment in comparison with Dato-DXd. The overall observed efficacy for the control arm is in line with historical controls, hence the control arm is not considered to underperform for the ICC options allowed in the study.

Of note, the SOC chemotherapy choice in a given patient was determined before randomization, but this was not a stratification factor.

The other dual primary endpoint was **OS** and at the time of the first IA of OS (DCO: 17 July 2023), there were 21.9 % and 24.8% events in the Dato-DXd and the ICC arm, respectively. First interim analysis of OS analysis showed a hazard ratio of 0.84 (95%CI: 0.62, 1.14; p = 0.2615). At the second OS interim analysis (DCO: 29 April 2024), the HR was 0.93 (95%CI: 0.76, 1.13) with a p-value of 0.4712 that did not cross the prespecified IA2 efficacy stopping boundary of 0.0348. The median OS in the Dato-DXd arm was 19.0 months versus 18.2 months in the ICC arm. At the final analysis of OS after 22.8 months of median follow up at DCO: 24 July 2024, 436 OS events had occurred (59.6%

maturity), and the final OS HR was 1.01 (95%CI: 0.83-1.22), with a median OS of the Dato-DXd arm of 18.6 months vs 18.3 months in the ICC arm, respectively. The p-value of 0.9445 that did not cross the prespecified final analysis efficacy stopping boundary of 0.0403. Hence, the PFS benefit is not supported by OS benefit as well, which may be due to subsequent treatments. An imbalance in ADC therapies given after study drug was identified and more patients had received subsequent ADC treatment in the ICC arm at the final analysis of OS. Subsequent Enhertu use was 21.8% in the ICC arm versus 9.3% in the Dato-DXd arm, and subsequent Trodelvy use was 7.1% in the ICC arm versus 4.1% in the Dato DXd arm. Subsequent ADC use was dependent on the investigators' preference for subsequent therapy with respect to different mechanism of action, potential resistance mechanisms, and toxicity profiles; however, it is also based on the patients' performance status (ECOG PS), which may be impacted after toxic treatment. In this context, the lower use of subsequent ADCs in the Dato-DXd arm may be due to the severe toxicity from the treatment and subsequent need for a treatment with a different toxicity profile, especially regarding pneumonitis, which is a known severe toxicity of both Dato-DXd and Enhertu. The data available do not show an apparent OS detriment (OS HR was 1.01 (95%CI: 0.83-1.22)), supporting the efficacy of Dato-DXd.

Relevant secondary endpoints were: PFS by investigator (INV), ORR, DoR, and PFS2. The primary analysis of PFS by INV was 6.9 vs 4.9 months in the Dato-DXd arm vs ICC, respectively, HR 0.64 (0.53, 0.76); which is in line with the PFS by BICR results. The updated PFS by INV at IA2 (HR 0.64; 95%CI 0.54, 0.75; median PFS 6.9 months vs 4.5 months for Dato-DXd vs ICC, respectively) is consistent with the results from the primary analysis. No updated PFS by BICR analysis was provided.

The confirmed **ORR by BICR** was 36.44% for Dato-DXd vs 22.89% for ICC. The median DoR was 1 month longer in the Dato-DXd arm (6.7 months) than in the ICC arm (5.7 months), with a similar median time to onset of response (2.7 months for Dato-DXd and 2.6 months for ICC). Time from randomisation to second progression (PFS2) was 12.7 months with Dato-DXd vs 10.4 months on ICC, HR 0.71 (95%CI: 0.55, 0.92). Overall, the relevant secondary endpoints are in favour of Dato-DXd and considered supportive of one of the dual primary endpoints, PFS by BIRC. A reasonable justification for the absence of multiplicity adjustments for secondary endpoints was provided. By clarifying that these endpoints were meant to support, rather than confirm, the primary findings, the concerns about potential error rate inflation were appropriately addressed.

The proposed sensitivity analyses for the dual endpoint PFS and OS are generally acceptable. Sensitivity analysis of PFS by BICR showed robust results regarding patients who had subsequent therapy prior to their last evaluable RECIST assessment or progression or death and are not censored (HR 0.64, 95%CI:0.53,0.77), which was consistent with the primary analysis. Sensitivity analysis of PFS by BICR regarding patients, who had progressive disease or died after two or more missed visits was also in line with the primary analysis (HR 0.65, 95%CI:0.54; 0.78).

Supportive efficacy data of the efficacy of Dato-DXd in mBC was submitted form the BC cohort of the TP01 study, which also supported the chosen proposed dose of 6 mg/kg administered on Day 1 of each 21-day cycle. Since an RCT (TB01) serves as the pivotal study for this application, these data are only considered supportive of the use of Dato-DXd in a heavily pre-treated patient population. Therefore, no update is required of these non-comparative data although the DCO was 22 July 2022.

Subgroup analyses showed that the PFS benefit observed with Dato-DXd was consistent across the prespecified subgroups of prior lines of chemotherapy, geographic region, prior use of taxanes and/or anthracyclines, age and race, HER2 status and ECOG performance status. For the subgroup, who had no prior use of CDK 4/6 inhibitors, the HR estimate for PFS was not significantly improved with Dato-DXd; however, this is considered due to the small size of this subgroup and not clinically relevant. Although not predefined, an additional subgroup analysis was requested for patients with invasive lobular breast cancer (n=49). At the time of updated DCO (29 April 2024) a total of 29 out of 49

patients were recorded as having OS events, with 13 (48.1%) events in the Dato-DXd arm and 16 (72.7%) events in the ICC arm (HR 0.45; 95%CI: 0.21, 0.93). These results for patients with invasive lobular breast cancer are in line with those for the overall study population. In addition, subgroup analyses were requested for other age cut-offs and patients with de novo stage IV disease at diagnosis (n=219), versus patients with stage I-III at diagnosis (n=454), as the prognosis from the moment of M1 disease is better for de novo stage IV disease (de Maar, Breast Cancer Res Treat 2023; Dawood, Ann Oncol 2010). The median PFS and OS results according to other age cut-offs are in line with those for the cut-off of age 65. No signals of a detriment are observed for patients aged ≥ 75 years. PFS and OS benefit are also similar for stage I-III versus de novo stage IV patients.

Updated OS subgroups analyses showed trends which could be further explored in other studies with similar ADCs include a HR point estimate for OS of Dato-DXd versus control >1.1 for the following subgroups: patients who had received 1 line of previous chemotherapy; Asian patients; patients 65 years and older; and patients eligible for capecitabine or gemcitabine treatment. Updated analyses show that the HER2-associated dual endpoint (PFS and OS) data, categorized in HER2 IHC0 versus HER2-low suggest that Dato-DXd PFS benefit (vs ICC) is more pronounced for the HER2-low subgroup, while OS data suggest no benefit of Dato-DXd (vs ICC) in the HER2 IHC0 subgroup (HR of 0.98; 95% CI: 0.75-1.27).

Biomarker analyses were conducted, since Dato-DXd is a TROP2-directed ADC and Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein, which is expressed in solid tumors, including breast cancer. The TROP2 (EPR20043) IHC Robust Prototype Assay by Ventana used in the pivotal study has been analytically validated by Ventana and an Assay Validation Report have been provided as part of the MAA. Of the 732 patients included in the ITT population, ~75% had an evaluable result with numerical value available for the H-score. The presented data from the biomarker report showed apparent efficacy from Dato-DXd across the whole spectrum of TROP2 expression (Low, Medium, High) in the pivotal study TB01. Based on these data on advanced HR+, HER2-negative breast cancer, a biomarker-restriction for the currently applied indication is not considered pertinent. Nevertheless, a signal suggesting that specifically tumors with higher TROP2 expression levels might be sensitive to Dato-DXd cannot be ruled out, especially in case a tumour biopsy was taken and examined for TROP2 expression within 6 weeks of starting Dato-DXd. Such tumour biopsies may better reflect the actual biomarker status than archival tumour tissues. Moreover, it should be noted that these results are not considered applicable to other cancer disease settings, where TROP2 expression may be associated with efficacy.

Considering the open-label design of the pivotal study, the patient-reported outcomes (PROs) are considered somewhat biased and should not be reflected in the SmPC.

The Applicant has provided **supportive efficacy data** from 41 patients HR positive/HER2 negative mBC included in the TP01 study, who received the proposed dose of Dato-DXd, which was conducted in heavily pre-treated patients. Hence, all of the mBC patients had received prior endocrine therapy (100%), chemotherapy (100%), and majority of the patients had received CDK4/6 inhibitors (95.1%), capecitabine (82.9), taxanes (58.5%), and anthracycline (53.7%). The median age was 57 years, most patients were White (70.7%) or Asian (19.5%). By region, 85.4% of patients were treated in the United States, and 14.6% of patients were treated in Japan. The baseline ECOG status in patients was either 0 or 1.

The confirmed ORR by BICR was 26.8% (95%CI: 14.2, 42.9), the median DoR NE (4.4, NE) and the median OS was NE (10.1, NE) months.

The finally agreed indication is as follows: *Dato-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast*

cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting (see section 5.1).

The revised wording is acceptable as it is now aligned with that of other ADC indications for advanced HR-positive, HER2-negative breast cancer.

2.6.7. Conclusions on the clinical efficacy

The results from the pivotal Study TROPION-Breast01 show a statistically significant 2-month improvement of median PFS by BICR with Dato-DXd in comparison with single-agent chemotherapy of Investigator's choice in in patients with HR-positive, HER2-negative, unresectable or metastatic breast cancer. The final update of OS, the other dual primary endpoint, do not show apparent OS detriment supporting the efficacy of Dato-DXd.

2.6.8. Clinical safety

Safety data collection

Table 61 Overview of Key Clinical Studies Providing Safety and Tolerability Data in this Application

Study number and name / DCO date of data included in this submission	Phase / study design	Patient population	Key patient selection criteria	Treatment duration	Overall number of patients enrolled / randomised	Number of patients contributing to the overall Dato-DXd 6 mg/kg safety pool	Location in module 5
D9268C00001 TB01 Ongoing DCO: 24 July 2024	Phase III, open-label, randomised study of Dato-DXd versus ICC	Patients with inoperable or metastatic HR-positive, HER2-negative breast cancer who had been treated with one or 2 prior lines of systemic chemotherapy in the inoperable or metastatic setting	Patients were to have progressed on, and not be suitable for endocrine therapy and have documented progression on most recent line of chemotherapy	Until disease progression according to RECIST 1.1, or until unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation was met	732 Dato-DXd 6 mg/kg: 365 ICC: 367 • Capecitabine 1000 mg/m^2: 76 • Gemcitabine 1000 mg/m^2: 33 • Eribulin mesylate 1.4 mg/m^2: 220 • Vinorelbine 25 mg/m^2: 38	360	Module 5.3.5.1
DS1062-A-J101 TP01 DCO: 22 July 2022 for TNBC and HR-positive/ HER2-negative breast cancer	Phase I, two-part (dose escalation and dose expansion), open-label, multidose, FIH, study of Dato-DXd monotherapy	Dose escalation: Patients with TNBC Dose expansion: Patients with TNBC, HR-positive breast cancer	Patients were to have relapsed or progressed following local standard treatments or for which no standard treatment was available. Patients who had measurable disease based on RECIST v1.1	Until disease progression, unacceptable toxicity, or withdrawal of consent	TNBC: 44 HR-positive/ HER2-negative: 41 NSCLC: 210 TNBC: Dato-DXd 6 mg/kg: 42 HR-positive/ HER2-negative: Dato-DXd 6 mg/kg: 41	TNBC: 42 HR-positive/ HER2-negative: 41	Module 5.3.3.2

Assessments including safety evaluation in the pivotal trial TB01 are shown in the below table.

Table 62 Schedule of Activities

Procedure	Screening (up to 28 days before C1D1)	Intervention Period				Post-intervention FU Period				Details in CSP Section or Appendix
		Cycle 1		Cycle 2 +		EoT (within 7 days of decision to stop treatment)	Safety FU (28 days after last dose [+7 days]) [a]	At PD	Survival FU (Every 3 months [±14 days]) relative to the date of Safety FU Visit	
		Day 1	Day 8 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)					
Informed consent: main study [b]	X									Section 5.1 and Appendix A 3
Informed consent: genetic sample and analysis (optional)	X									Section 5.1 and Appendix A 3
Study Procedures and Assessments										
Inclusion and exclusion criteria	X									Sections 5.1 & 5.2
Randomization		X [c]								Section 6.3
Demography	X									Section 5.1
Full physical examination (including weight and height)	X									Section 8.2.1
Targeted physical examination (including weight)		X [d]		X [e, f]		X	X			Section 8.2.1
Medical history [g]	X									Sections 5.1 & 5.2
Past and current medical conditions and prior anticancer therapy use	X									Sections 5.1 & 5.2
ECOG performance status	X	X [d]		X [f]		X	X			Section 8.2.5.4
12-lead ECG [h]	X	As clinically indicated				X				Section 8.2.3
Echocardiogram or MUGA (LVEF) [i]	X	As clinically indicated								Section 8.2.5.1
Vital signs including SpO_2 [j]	X	X		X [e]		X	X			Section 8.2.2
Pulmonary function tests [k]	X	If ILD/pneumonitis is suspected								Section 8.2.5.2
ILD/pneumonitis investigation, including HRCT		If ILD/pneumonitis is suspected								Section 8.2.5.3
Ophthalmologic assessments [l]	X	<-------every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1 etc) within 14 days prior to scheduled Cycle Day 1 visit (but not after the scheduled visit) and as clinically indicated-------->				X				Section 8.2.5.5
Oral care plan [m]	X	<----------								Section 8.2.5.6
AE [n, o]	X	<----------				X	X			Section 8.3
Prior and concomitant medication [o]	X	<----------				X	X			Section 6.5
Subsequent anticancer therapy							X		X	
Clinical Safety Laboratory Assessments										
Serum/urine pregnancy test (WOCBP only) [p]	X	X		X		X	X			Sections 5.1, 5.2 & 8.2.4
Hepatitis B and C serology [q]	X									Sections 5.2 & 8.2.4
HIV antibody test (as required by local regulations or IRB/IEC) [q, r]	X									Sections 5.2 & 8.2.4
Clinical safety laboratory assessments (clinical chemistry and hematology)	X	X [d]		X [d, e]		X	X			Section 8.2.4
Urinalysis	X	As clinically indicated								Section 8.2.4
Pharmacokinetics Assessments (for patients randomized to Dato-DXd only)										
PK blood sampling (before infusion) [s]		X		X (C2, C4, C6, C8, and C12, then every 4 cycles)		X				Section 8.5.1

PK blood sampling (end of infusion) [t]		X[u]		X (C2, C4, C6, C8)						Section 8.5.1
Immunogenicity Assessments (for patients randomized to Dato-DXd only)										
Blood sample for immunogenicity testing (ADA)		X[s]		X[s] (C2, C4, C6, C8, and C12; then every 4 cycles)		X	X			Section 8.5.2
Biomarker Assessments										
Mandatory tumor sample available (FFPE)	X									Section 8.6.1
Optional tumor biopsy (FFPE/FF) at progression [v]								X		Section 8.6.2
Optional paired tumor biopsy (FFPE/FF) [v]	X			X (C2D1 to C2D7 only)						Section 8.6.2
Optional bronchoalveolar lavage and lung biopsy sample on suspected ILD/diagnosis of ILD (added in CSP amendment 3)	As clinically indicated									Section 8.6.2
Plasma samples for biomarker analysis [v]	X	X		X (C2, C4)		X		X		Section 8.6.1
Serum samples for biomarker analysis [v]	X	X		X (C2, C4)		X		X		Section 8.6.1

Plasma samples for biomarker analysis on suspected ILD/diagnosis of ILD	As clinically indicated									Section 8.6.1
Serum samples for biomarker analysis on suspected ILD/diagnosis of ILD	As clinically indicated									Section 8.6.1
Whole blood sample for gene expression analysis (RNA) [v]	X	X		X (C2, C4)				X		Section 8.6.1
Whole blood sample for gene expression analysis (DNA) [v]	X	X		X (C2, C4)				X		Section 8.6.1
Plasma samples for ctDNA analysis [v]	X	X		X (C2-C6; then Q6W)		X		X		Section 8.6.1
Genomics Initiative (optional)										
Optional exploratory genetic blood sample for Genomics Initiative [v,w]		X								Section 8.7 & Appendix D
Efficacy Assessments										
Tumor imaging (RECIST 1.1) [x]	X	Every 6 weeks (±7 days) from randomization for 48 weeks, then every 9 weeks (±7 days) thereafter until RECIST 1.1 disease progression (as assessed by the investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional FU scan should be performed as per imaging schedule (ie, either 6 weeks or 9 weeks later).								Section 8.1.1
Brain MRI/CT imaging [y]	X	Mandated for patients who had brain metastases documented at baseline, per RECIST 1.1 schedule.								Section 8.1.1
Whole body bone scan [z]	X	As clinically indicated								Section 8.1.1

Survival status									X	Section 7.1.3 & 8.1.4
Time to second progression or death (PFS2)							X		X	Section 8.1.3
Clinical Outcome Assessments										
ePRO training and setup		X								Section 8.1.5
EORTC QLQ-C30, EORTC IL 116, PGIS, EQ-5D-5L		C1D1, Q3W from C1D1 for the first 48 weeks, and Q6W thereafter until EoT				At EoT visit, then Q6W (relative to C1D1) after EoT until 18 weeks after PD				Section 8.1.5
PRO-CTCAE, EORTC IL 117, PGI-TT		C1D1, every week from C1D1 for the first 12 weeks, and Q3W thereafter until EoT				X				Section 8.1.5
PGIC		Q6W from C1D1 for the first 12 weeks (ie, 6 weeks and 12 weeks from C1D1)								Section 8.1.5
Medical Resource Utilization										
HOSPAD [aa]		X	X [bb]	X	X [bb]	X				Section 8.8
Study Intervention Administration										
Dato-DXd administration (IV)		X		X						Section 6
Capecitabine administration (oral)		Days 1 to 14 only, BID		Days 1 to 14 only, BID						Section 6
Eribulin administration (IV)		X	X	X	X					Section 6
Vinorelbine administration (IV)		X	X	X	X					Section 6
Gemcitabine administration (IV)		X	X	X	X					Section 6

[a] The safety FU visit was to be performed 28 (+7) days after the last study intervention administration. If the date of discontinuation was over 35 days from last study intervention administration, then the EoT assessments could also function as the Safety FU visit.

[b] Written informed consent and any locally required privacy act document authorization had to be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[c] Every effort was to be made to minimize the time between randomization and starting treatment (ie, no more than 3 days from the date of randomization).

[d] If safety assessments were performed within 72 hours prior to starting Day 1 of a cycle, they did not have to be repeated, if the patient's condition had not changed.

[e] For patients randomized to ICC, routine clinical care was to be performed in accordance with local practice.

[f] Within 3 days prior to administration of study intervention.

[g] Includes ocular history (since prior ocular events may predispose to or cause dry eye/keratitis), as well as history, type and frequency of tobacco use, e-cigarette use, vaping (including dates).

[h] Triplicate ECGs were to be taken at screening and EoT. Triplicate ECGs were to be taken in close succession, while in a supine/semi-recumbent position. Single ECGs were to be taken during treatment as clinically indicated.

[i] The same test had to be used for the patient throughout the study. ECHO/MUGA not required at EoT unless clinically indicated.

[j] Vital signs and SpO_2 were to be performed both before and after study intervention administration (where applicable), and as clinically indicated during treatment. Patients were to remain at the site for at least 1-hour post-infusion (where applicable) for close observation for IRRs.

[k] Pulmonary function tests at a minimum were to include spirometry (minimum requirement of: FVC [L], FVC % predicted, FEV1 [L], FEV1 % predicted, FEV1/FVC %). DLCO will be performed (when feasible); however, for patients with prior severe and/or clinically significant pulmonary disorders, DLCO was a requirement.

[l] Ophthalmologic assessments (by a licensed eye care provider) including visual acuity testing, fluorescein staining, intraocular pressure, slit lamp examination and fundoscopy were to be performed at screening, and then every 3 cycles from C1D1 onwards (eg, C4D1, C7D1, C10D1, etc) within 14 days prior to scheduled cycle Day 1 visit (but not after the scheduled visit), in addition to as clinically indicated while on trial, and at EoT (see CSP Section 8.2.5.5 [Appendix 16.1.1] for additional information). Assessment schedule amended to every 3 cycles in CSP amendment 1.

[m] A daily OCP was to be started before study drug initiation, and had to be maintained throughout the study until 28 days after last dose. An oral care kit was provided at study enrollment and monthly thereafter until the Safety FU visit, which included a toothbrush, toothpaste, dental floss, and an alcohol-free mouthwash. An oral care plan patient information guide was to be given to each randomized patient before study drug initiation. Initiation of dexamethasone oral solution was to be strongly considered (see CSP Section 8.2.5.6 [Appendix 16.1.1] for details). Oral care plan added in CSP amendment 1.

[n] Data collection could be conducted by phone if not tied to a visit.

[o] All AEs occurring after the patient signed the ICF and up to 28 (+7) days after the last dose of study drug (ie, the safety FU period), whether observed by the investigator or reported by the patient, were to be recorded on the AE eCRF page (see CSP Section 8.3 [Appendix 16.1.1] for additional information).

[p] Negative serum pregnancy test performed within 72 hours before study intervention at screening and repeat urine or serum pregnancy tests (per institutional guideline) performed within 72 hours before infusion of each cycle and at EoT and during safety FU. A positive urine pregnancy test result had to immediately be confirmed using a serum test.

[q] Prior HIV serology (anti-HIV with or without HIV RNA, as appropriate), hepatitis B serology (HBsAg, anti-HBs, and anti-HBc with or without HBV DNA, as appropriate), and hepatitis C serology (anti-HCV antibody with or without HCV RNA, as appropriate) testing results could be used if performed within 120 days before enrollment. In this case, there was no need for a repeat test during the 28-day screening period.

[r] Patients had to be tested for HIV if acceptable by local regulations or an IRB/IEC. If an HIV infection met the criteria outlined in CSP Section 5.2 (see Appendix 16.1.1), the patients' viral RNA load and CD4+ cell count were to be monitored per local SoC (eg, every 3 months).

[s] To be performed within 8 hours prior to the start of Dato-DXd infusion, except for the EoT visit, during which samples could be collected anytime during this visit.

[t] To be performed within 1 hour after the end of Dato-DXd infusion.

[u] An additional PK sample was to be taken 5 hours (± 1 hour) from the start of Dato-DXd infusion on C1D1.

[v] Not applicable to patients in mainland China.

[w] The sample for genetic research was to be obtained at Day 1 pre-dose. If, for any reason, the sample was not drawn at Day 1, it could be taken at any visit until the last study visit. Only 1 sample was to be collected per patient for genetics during the study.

[x] The baseline tumor assessment had to be performed within 28 days before randomization and as close as possible to the start of treatment. The assessment was to include CT (preferred) or MRI, with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis. Any other areas of disease involvement were to be additionally imaged at screening based on known metastasis sites or by the signs and symptoms of individual patients. The FU assessments were to include CT/MRI with IV contrast of the chest, abdomen and pelvis and any other area where disease was identified at baseline. The assessment had to continue until **1 visit (per original schedule)** after radiographic disease progression (as assessed by investigator), whether or not the patient was still on treatment. The same imaging technique (CT or MRI) used to characterize each identified and reported lesion at baseline was to be used in the subsequent tumor assessments.

[y] Patients with brain metastases at baseline had to have the lesions recorded as part of the RECIST assessment and have a brain scan performed per the tumor imaging schedule until radiological progression per RECIST. For patients in whom CNS metastases were first discovered at the time of screening, the treating investigator was to consider delay of randomization and study intervention to document stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, repeat of all screening activity could have been required).

[z] Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray were to be recorded as NTLs and followed by the same method (CT, MRI, or X-ray), as indicated in the SoA.

[aa] The site was to complete the "Hospital Admission (HOSPAD)" form at the site at every scheduled clinic visit up to and including the post-study treatment discontinuation FU visit. If the patient discontinued study treatment for reasons other than RECIST progression, the HOSPAD form administration was continued until progression was confirmed. Study mandated visits were not to be included as a hospital admission.

[bb] Only applicable to patients who were required to attend study visits on Day 8 of each cycle (ie, those randomized to receive ICC which are administered by IV infusion).

Note: All assessments on treatment days were to be performed prior to study intervention administration, unless otherwise indicated. Following the DCO for the primary analysis, PK assessments were to be discontinued. Data collection following final study analysis until the end of the study is described in Section 8 of the CSP (see Appendix 16.1.1).

2.6.8.1. Patient exposure

Table 63 Study treatment exposure and treatment compliance in pivotal study and BC pool (safety analysis set)

Parameter	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Treatment duration (months) [b]						
Mean (SD)	6.7 (3.73)	4.81 (3.47)	8.3 (6.33)	5.34 (4.74)	6.6 (4.00)	7.9 (6.15)
Median	6.7	4.1	6.8	4.1	6.2	6.2
Min, Max	0.7, 16.1	0.2, 17.4	0.7, 28.5	0.2, 27.9	0.7, 21.8	0.7, 28.5
Total amount of dose taken (mg/kg)						
Mean (SD)	52.1 (29.23)	NA	63.6 (48.23)	NA	50.8 (30.00)	60.2 (46.25)
Median	48.0	NA	48.0	NA	48.0	48.0
Min, Max	6.0, 138.0	NA	6.0, 234.0	NA	6.0, 162.1	6.0, 234.0
Actual dose intensity (mg/kg/cycle) [c]						
Mean (SD)	5.5 (0.70)	NA	5.4 (0.73)	NA	5.5 (0.74)	5.4 (0.76)
Median	5.8	NA	5.7	NA	5.8	5.7
Min, Max	3.0, 6.3	NA	3.0, 6.3	NA	2.3, 6.5	2.3, 6.5
Relative dose intensity (%) [d]						
Mean (SD)	91.3 (11.66)	82.32 (20.87)	90.4 (12.14)	83.04 (19.13)	91.2 (12.28)	90.5 (12.65)
Median	97.1	87.5	95.5	87.5	97.3	95.5
Min, Max	49.3, 105.0	0.0, 138.9	49.3, 105.0	0.0, 138.9	37.9, 107.6	37.9, 107.6
Total number of cycles initiated						
Mean (SD)	9.2 (5.17)	6.3 (NC)	11.4 (8.62)	6.7 (NC)	9.1 (5.50)	10.8 (8.37)
Median	9.0	6.0	9.0	6.0	8.0	8.0
Min, Max	1, 23	NC	1, 39	NC	1, 31	1, 39
Treatment duration category, n (%)						
>0 to ≤3 months	83 (23.1)	NA	83 (23.1)	NA	111 (25.1)	111 (25.1)
>3 to ≤6 months	85 (23.6)	NA	85 (23.6)	NA	107 (24.2)	107 (24.2)
>6 to ≤9 months	95 (26.4)	NA	70 (19.4)	NA	111 (25.1)	86 (19.4)
>9 to ≤12 months	65 (18.1)	NA	37 (10.3)	NA	70 (15.8)	42 (9.5)
>12 to ≤18 months	32 (8.9)	NA	48 (13.3)	NA	40 (9.0)	56 (12.6)

Parameter	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
>18 to ≤24 months	0	NA	28 (7.8)	NA	4 (0.9)	32 (7.2)
>24 months	0	NA	9 (2.5)	NA	0	9 (2.0)
Relative dose intensity, by category, n (%)						
≥95%	204 (56.7)	NA	189 (52.5)	NA	252 (56.9)	237 (53.5)
<95% to ≥90%	36 (10.0)	NA	43 (11.9)	NA	47 (10.6)	54 (12.2)
<90% to ≥80%	58 (16.1)	NA	60 (16.7)	NA	67 (15.1)	69 (15.6)
<80% to ≥60%	58 (16.1)	NA	63 (17.5)	NA	68 (15.3)	73 (16.5)
<60%	4 (1.1)	NA	5 (1.4)	NA	9 (2.0)	10 (2.3)

[a] TB01 (n=360) + TP01 BC (n=83).

[b] For Dato-DXd arm in TB01 and pooled studies, treatment duration (months) = (date of last dose – date first dose date + 21) / 30.4375. For ICC arm in TB01, total exposure of capecitabine = (min (last capecitabine dose where > 0, date of death, date of DCO) – first capecitabine dose date + 1 / (365.25/12); total exposure of gemcitabine, vinorelbine, and eribulin mesylate = (min (last dose date where dose > 0 + W, date of death, date of DCO) – first dose date + 1 / (365.25/12), where W = 6 if the last dose was scheduled on Day 1 and W = 13 if the last dose was scheduled on Day 8.

[c] Dose intensity for Dato-DXd (mg/kg/cycle) = Total amount of doses taken (mg/kg) / (Treatment duration [days] / 21).

[d] For Dato-DXd arm in TB01 and pooled studies, relative dose intensity for Dato-DXd (%) = 100 × Dose intensity (mg/kg/cycle) / Planned dose intensity (mg/kg/cycle). For ICC arm in TB01, relative dose intensity is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation.

NA denotes not applicable. NC denotes not calculated.

Source: **IA1 columns:** Table 2.7.4.2.1, ISS, Module 5.3.5.3 and Table 14.3.1.1.IA1, Table 14.3.1.2.IA1, and Table 14.3.1.4.IA1, TB01 original CSR, Module 5.3.5.1; **FA columns:** Table 2.7.4.2.1, ISS Final Analysis, Module 5.3.5.3 and Table 14.3.1.1.FA and Table 14.3.1.2.FA, TB01 CSR Addendum 2 Final Analysis, Module 5.3.5.1.

Table 64 Summary of Exposure by Subgroup in Pivotal and Pooled Studies (Safety Analysis Set)

Parameter	Pivotal Study TB01 Dato-DXd 6 mg/kg N = 360						BC Pool [a] Dato-DXd 6 mg/kg N = 443					
	IA1			FA			IA1			FA		
	n	Median (mo)	Range (mo)	n	Median (mo)	Range (mo)	n	Median (mo)	Range (mo)	n	Median (mo)	Range (mo)
Age group [b]												
<65	269	6.41	0.7, 16.1	269	6.41	0.7, 28.5	340	5.85	0.7, 21.8	340	5.85	0.7, 28.5
≥65	91	6.87	1.4, 15.9	91	6.87	1.4, 26.3	103	6.87	1.4, 18.1	103	6.87	1.4, 26.3
Race												
Caucasian/ White	179	6.90	0.7, 16.1	179	6.93	0.7, 28.5	230	6.26	0.7, 21.8	230	6.26	0.7, 28.5
Asian	142	6.03	0.7, 15.9	142	6.03	0.7, 26.9	164	6.03	0.7, 16.1	164	6.03	0.7, 26.9
Black/ African American	4	2.18	1.4, 8.5	4	2.18	1.4, 8.5	7	2.83	1.4, 11.5	7	2.83	1.4, 11.5
Other	3	7.46	3.0, 10.3	3	7.46	3.0, 22.3	10	5.59	1.4, 14.8	10	5.59	1.4, 22.3
Missing	32	6.11	1.4, 14.0	32	6.11	1.4, 20.7	32	6.11	1.4, 14.0	32	6.11	1.4, 20.7

Renal function status at baseline [c]												
Normal	178	7.10	0.7, 15.2	178	7.28	(0.7, 26.9)	227	6.90	0.7, 19.6	227	6.90	(0.7, 26.9)
Mild	142	5.65	0.7, 16.1	142	5.62	(0.7, 28.5)	168	5.60	0.7, 21.8	168	5.60	(0.7, 28.5)
Moderate	40	6.57	1.4, 13.3	40	6.57	(1.4, 24.6)	48	5.62	1.3, 13.3	48	5.62	(1.3, 24.6)
Severe	0	NA	NA	0	NA	NA	0	NA	NA	0	NA	NA
Hepatic function at baseline [d]												
Normal	184	6.92	0.7, 16.1	182	6.92	0.7, 28.5	234	6.87	0.7, 21.8	232	6.87	0.7, 28.5
Mild	170	5.83	0.7, 14.0	172	6.03	0.7, 25.3	202	5.62	0.7, 14.8	204	5.67	0.7, 25.3
Moderate	5	9.69	3.0, 11.2	5	9.69	3.0, 16.1	6	6.88	3.0, 11.2	6	6.88	3.0, 16.1
Severe	1	4.14	4.1, 4.1	1	4.14	4.1, 4.1	1	4.14	4.1, 4.1	1	4.14	4.1, 4.1
ECOG PS												
(0) Normal activity	196	6.21	0.7, 15.2	196	6.21	0.7, 26.9	233	5.82	0.7, 19.6	233	5.82	0.7, 26.9
(1) Restricted activity	161	7.00	0.7, 16.1	161	7.00	0.7, 28.5	207	6.90	0.7, 21.8	207	6.90	0.7, 28.5
(2) In bed ≤50% of the time	3	2.76	1.4, 9.2	3	2.76	1.4, 15.5	3	2.76	1.4, 9.2	3	2.76	1.4, 15.5
Missing	0	NA	NA	0	NA	NA	0	NA	NA	0	NA	NA

[a] TB01 (n=360) + TP01 BC (n=83).

[b] Age in years is calculated using the date of birth and the date of informed consent.

[c] Normal renal function = CrCl ≥ 90 mL/min; mild renal impairment = CrCl ≥ 60 mL/min, and < 90 mL/min; moderate renal impairment = CrCl ≥ 30 mL/min and <60 mL/min

[d] Normal hepatic function = TBL ≤ ULN and AST ≤ ULN; mild hepatic impairment = (TBL > ULN and ≤ 1.5 × ULN and any AST) or (TBL ≤ ULN and AST > ULN); moderate hepatic impairment = TBL > 1.5 × ULN and ≤ 3.0 × ULN and any AST.

NA denotes not applicable.

Table 65 Summary of Demographics in Pivotal and Pooled Studies (Safety Analysis Set)

Parameter	Pivotal Study TB01		Pooled Studies [a]			
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	BC Dato-DXd 6 mg/kg N = 443	NSCLC Dato-DXd 6 mg/kg N = 484	BC+NSCLC Dato-DXd 6 mg/kg N = 927	BC+NSCLC Dato-DXd ≥ 4 mg/kg N = 1067
Age (years), n [b]	360	351	443	484	927	1067
Mean (SD)	55.5 (11.68)	55.1 (11.05)	55.2 (11.54)	61.6 (9.89)	58.6 (11.17)	58.9 (11.24)
Median	56.0	55.0	55.0	63.0	60.0	60.0
(min, max)	(29, 86)	(28, 86)	(29, 86)	(26, 84)	(26, 86)	(26, 86)
Age group (years), n (%)						

Table 65 Summary of Demographics in Pivotal and Pooled Studies (Safety Analysis Set)

Parameter	Pivotal Study TB01		Pooled Studies [a]			
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	BC Dato-DXd 6 mg/kg N = 443	NSCLC Dato-DXd 6 mg/kg N = 484	BC+NSCLC Dato-DXd 6 mg/kg N = 927	BC+NSCLC Dato-DXd ≥ 4 mg/kg N = 1067
< 65	269 (74.7)	280 (79.8)	340 (76.7)	283 (58.5)	623 (67.2)	705 (66.1)
≥ 65	91 (25.3)	71 (20.2)	103 (23.3)	201 (41.5)	304 (32.8)	362 (33.9)
Sex, n (%)						
Female	355 (98.6)	347 (98.9)	437 (98.6)	220 (45.5)	657 (70.9)	724 (67.9)
Male	5 (1.4)	4 (1.1)	6 (1.4)	264 (54.5)	270 (29.1)	343 (32.1)
Race, n (%)						
Caucasian or White	179 (49.7)	160 (45.6)	230 (51.9)	191 (39.5)	421 (45.4)	501 (47.0)
Asian	142 (39.4)	148 (42.2)	164 (37.0)	214 (44.2)	378 (40.8)	428 (40.1)
Black or African American	4 (1.1)	6 (1.7)	7 (1.6)	9 (1.9)	16 (1.7)	20 (1.9)
Other	3 (0.8)	6 (1.7)	10 (2.3)	62 (12.8)	72 (7.8)	78 (7.3)
Missing [c]	32 (8.9)	31 (8.8)	32 (7.2)	8 (1.7)	40 (4.3)	40 (3.7)
Ethnicity, n (%)						
Hispanic or Latino	39 (10.8)	38 (10.8)	53 (12.0)	17 (3.5)	70 (7.6)	74 (6.9)
Not Hispanic or Latino	318 (88.3)	307 (87.5)	385 (86.9)	414 (85.5)	799 (86.2)	934 (87.5)
Missing [c]	3 (0.8)	6 (1.7)	5 (1.1)	53 (11.0)	58 (6.3)	59 (5.5)
Region, n (%)						
US, Canada, Europe	185 (51.4)	173 (49.3)	249 (56.2)	273 (56.4)	522 (56.3)	622 (58.3)
Rest of World	175 (48.6)	178 (50.7)	194 (43.8)	211 (43.6)	405 (43.7)	445 (41.7)
Height (cm), n	359	347	442	481	923	1063
Mean (SD)	160.6 (7.53)	160.7 (6.76)	160.7 (7.57)	166.4 (9.10)	163.6 (8.87)	164.0 (9.03)
Median (min, max)	160.0 (130, 185)	160.0 (136, 194)	160.0 (130, 185)	166.9 (144, 192)	163.0 (130, 192)	163.6 (130, 192)
Baseline Weight (kg), n	360	351	443	484	927	1067
Mean (SD)	65.1 (15.33)	65.3 (16.11)	65.9 (15.91)	67.4 (14.98)	66.7 (15.44)	67.2 (16.08)
Median (min, max)	62.0 (36, 141)	63.0 (35, 131)	62.3 (36, 141)	65.0 (37, 127)	64.0 (36, 141)	64.2 (36, 156)
BMI (kg/m^2), n	359	347	442	481	923	1063

Table 65 Summary of Demographics in Pivotal and Pooled Studies (Safety Analysis Set)

Parameter	Pivotal Study TB01		Pooled Studies [a]			
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	BC Dato-DXd 6 mg/kg N = 443	NSCLC Dato-DXd 6 mg/kg N = 484	BC+NSCLC Dato-DXd 6 mg/kg N = 927	BC+NSCLC Dato-DXd ≥ 4 mg/kg N = 1067
Mean (SD)	25.2 (5.38)	25.3 (5.76)	25.5 (5.48)	24.3 (4.46)	24.8 (5.01)	24.9 (5.10)
Median (min, max)	24.2 (15, 49)	24.2 (14, 50)	24.3 (15, 49)	23.7 (15, 45)	24.0 (15, 49)	24.1 (12, 49)
ECOG performance status, n (%)						
(0) Normal activity	196 (54.4)	208 (59.3)	233 (52.6)	143 (29.5)	376 (40.6) [d]	417 (39.1)
(1) Restricted activity	161 (44.7)	142 (40.5)	207 (46.7)	339 (70.0)	546 (58.9) [d]	645 (60.4)
(2) In bed less than or equal to 50% of the time	3 (0.8)	1 (0.3)	3 (0.7)	0	3 (0.3)	3 (0.3)
Missing	0	0	0	2 (0.4)	2 (0.2)	2 (0.2)
Baseline Brain Metastasis, n (%)						
Yes	35 (9.7)	22 (6.3)	47 (10.6)	96 (19.8)	143 (15.4) [d]	175 (16.4)
No	325 (90.3)	329 (93.7)	396 (89.4)	388 (80.2)	784 (84.6) [d]	892 (83.6)
Renal function status at baseline, n (%) [e]						
Normal	178 (49.4)	179 (51.0)	227 (51.2)	176 (36.4)	403 (43.5)	463 (43.4)
Mild	142 (39.4)	138 (39.3)	168 (37.9)	214 (44.2)	382 (41.2)	429 (40.2)
Moderate	40 (11.1)	33 (9.4)	48 (10.8)	93 (19.2)	141 (15.2)	173 (16.2)
Severe	0	0	0	1(0.2)	1(0.1)	2(0.2)
Missing	0	1(0.3)	0	0	0	0
Hepatic function at baseline, n (%) [f]						
Normal	184 (51.1)	183 (52.1)	234 (52.8)	406 (83.9)	640 (69.0) [d]	764 (71.6)
Mild	170 (47.2)	163 (46.4)	202 (45.6)	78 (16.1)	280 (30.2) [d]	296 (27.7)
Moderate [g]	5 (1.4)	3 (0.9)	6 (1.4)	0	6 (0.6)	6 (0.6)
Severe [g]	1 (0.3)	0	1 (0.2)	0	1 (0.1)	1 (0.1)
Missing	0	2 (0.6)	0	0	0	0

[a] See **Error! Reference source not found.** for an overview of studies included in the pooled analyses.

[b] Age informed in years is calculated using the main study consent date and the birth date.

[c] Missing row includes both Missing and Not Reported/Unknown

[d] Difference of ≥ 5% between the TB01 Dato-DXd arm and the BC + NSCLC 6 mg/kg pool.

[e] Renal function: Normal = CrCl ≥ 90 mL/min; mild = CrCl ≥ 60 and < 90 mL/min; moderate = CrCl ≥ 30 and < 60 mL/min; severe = CrCl < 30 mL/min.

[f] Hepatic function: Normal = (TBL ≤ ULN and AST ≤ ULN) except for subjects with Gilbert syndrome) or (TBL ≤ 3.0 × ULN and (AST ≤ ULN) for subjects with Gilbert syndrome); mild = (TBL > ULN and ≤ 1.5 × ULN and any AST with Gilbert syndrome) or (TBL ≤ ULN and AST > ULN and with Gilbert syndrome); moderate = TBL > 1.5 × ULN and ≤ 3.0 × ULN and any AST except for subjects with Gilbert syndrome; Severe = TBL > 3.0 × ULN and any AST regardless of Gilbert Syndrome.

[g] Moderate and Severe Categories were not enrolled into the TL01 study. These data are presented only for Studies TB01, TL05 and TP01.

Percentages are based on the number of subjects in the Safety Analysis Set.
Baseline is defined as the last available assessment prior to the start of study treatment.

2.6.8.2. Adverse events

Table 66 Criteria for Adverse Event Assessment

Criteria	Description
TEAE definition	Development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product (i.e. TEAE), whether or not considered causally related to the product. An undesirable medical condition could be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). Deterioration of protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments as compared to baseline in these parameters were only to be reported as AEs if they fulfilled any of the criteria for a SAE, were clinically significant, or were the reason for discontinuation of treatment with study drug unless clearly due to progression of disease under study.
TEAE reporting period	Defined as the period from the time of main informed consent, throughout the treatment period and including the safety follow-up period (28 days [+7 days, ie, 35 days] after study drug was discontinued, or until the day prior to starting any subsequent cancer therapy if within the 28-day [+7 days] period [where applicable]).
TEAE variables collected	The following variables were collected for each TEAE: TEAE term (verbatim), TEAE start and stop date, maximum CTCAE grade, TEAE seriousness, Investigator causality assessment against the study drug (yes or no), action taken with study drug, TEAE caused patient withdrawal from study (yes or no), and outcome of the TEAE.
Coding of TEAEs	The MedDRA version current at the time of reporting in the individual studies was used to assign standard terms for all reported TEAEs. Study TP01 used MedDRA Version 23.0 for NSCLC analysis and Version 25.0 for BC analysis. Studies TB01 and TL01 used MedDRA Version 26.0, and TL05 used Version 25.1. For the pooled safety analyses, the MedDRA version aligned with pivotal Study TB01 (Version 26.0) will be applied, regardless of it being the last study to lock or not.
Capturing TEAE severity	The severity of any TEAE was assessed by the Investigator according to National Cancer Institute CTCAE Version 5.0. In Study TP01, AE severity was captured using CTCAE version 4.03 early in the study until the protocol was updated to use CTCAE version 5.0.
Causality assessment	The investigator assessed causal relationship between investigational product and each adverse event, and answered 'yes' or 'no' to the question: *'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'*

Table 66 Criteria for Adverse Event Assessment

Criteria	Description
Dosing action taken due to TEAE	Both dose modifications and delays were allowed, per standard toxicity management guidelines.

Overall adverse events in pivotal (TB01) and pooled studies

Table 67 Overall Summary of Treatment-emergent Adverse Events in Pivotal Study and BC Pool (Safety Analysis Set)

AE Category	6 mg/kg N = 360	N = 351	6 mg/kg N = 360	N = 351	6 mg/kg N = 443	6 mg/kg N = 443
Any TEAE	350 (97.2)	337 (96.0)	353 (98.1)	339 (96.6)	433 (97.7)	436 (98.4)
Any TEAE of CTCAE Grade ≥ 3	117 (32.5)	190 (54.1) [b]	126 (35.0)	195 (55.6) [b]	155 (35.0)	164 (37.0)
Any treatment-related TEAE	337 (93.6)	303 (86.3)	341 (94.7)	303 (86.3)	419 (94.6)	423 (95.5)
Any treatment-related TEAE of CTCAE Grade ≥ 3	75 (20.8)	157 (44.7) [b]	80 (22.2)	160 (45.6) [b]	95 (21.4)	100 (22.6)
Any serious TEAE	54 (15.0)	64 (18.2)	62 (17.2)	67 (19.1)	67 (15.1)	75 (16.9)
Any serious TEAE CTCAE Grade ≥ 3	47 (13.1)	60 (17.1)	51 (14.2)	63 (17.9)	60 (13.5)	64 (14.4)
Any treatment-related serious TEAE	21 (5.8)	32 (9.1)	22 (6.1)	32 (9.1)	24 (5.4)	25 (5.6)
Any treatment-related serious TEAE Grade ≥ 3	17 (4.7)	31 (8.8)	17 (4.7)	31 (8.8)	20 (4.5)	20 (4.5)
Any TEAE associated with death	0 [c]	3 (0.9)	1 (0.3) [c]	3 (0.9)	1(0.2) [c]	2 (0.5) [c]
Any treatment-related TEAE associated with death	0 [c]	1 (0.3)	0 [c]	1 (0.3)	0 [c]	0 [c]
Any TEAE associated with dose reduction	83 (23.1)	113 (32.2)	95 (26.4)	113 (32.2)	94 (21.2)	106 (23.9)
Any treatment-related TEAE associated with dose reduction	75 (20.8)	106 (30.2)	87 (24.2)	106 (30.2)	86 (19.4)	98 (22.1)
Any serious TEAE associated with dose reduction	6 (1.7)	12 (3.4)	6 (1.7)	12 (3.4)	6 (1.4)	6 (1.4)
Any treatment-related serious TEAE associated with dose reduction	4 (1.1)	8 (2.3)	4 (1.1)	8 (2.3)	4 (0.9)	4 (0.9)
Any TEAE associated with drug interruption	78 (21.7)	120 (34.2) [b]	95 (26.4)	119 (33.9)	104 (23.5)	121 (27.3)

AE Category	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any treatment-related TEAE associated with drug interruption	43 (11.9)	86 (24.5) [b]	57 (15.8)	85 (24.2)	60 (13.5)	74 (16.7)
Any serious TEAE associated with drug interruption	9 (2.5)	21 (6.0)	11 (3.1)	21 (6.0)	13 (2.9)	15 (3.4)
Any treatment-related serious TEAE associated with drug interruption	4 (1.1)	10 (2.8)	4 (1.1)	9 (2.6)	4 (0.9)	4 (0.9)
Any TEAE associated with drug withdrawn	11 (3.1)	10 (2.8)	15 (4.2)	11 (3.1)	17 (3.8)	21 (4.7)
Any treatment-related TEAE associated with drug withdrawn	9 (2.5)	9 (2.6)	12 (3.3)	9 (2.6)	15 (3.4)	18 (4.1)
Any serious TEAE associated with drug withdrawn	4 (1.1)	4 (1.1)	5 (1.4)	5 (1.4)	5 (1.1)	6 (1.4)
Any treatment-related serious TEAE associated with drug withdrawn	3 (0.8)	4 (1.1)	3 (0.8)	4 (1.1)	4 (0.9)	4 (0.9)

[a] TB01 (n=360) + TP01 BC (n=83).

[b] Notable difference (≥ 10%) between the Dato-DXd arm and the ICC arm in TB01 study.

[c] One patient had an event of pneumonitis and died (initially assessed as Grade 3 and death due to disease progression) that was subsequently assessed by the ILD Adjudication Committee as fatal drug related ILD (see Section 2.1.8.1.1).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01.

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarisation, a subject is counted once if the subject reported one or more AEs.

Drug interrupted includes both infusion interruption and dose delay.

Table 68. Treatment-emergent Adverse Events by SOC in TB01 Study and BC Pool (Safety Analysis Set)

System Organ Class	Number (%) of patients [a]		
	Individual Study		BC Pool
	Dato-DXd (6 mg/kg) N = 360	ICC N = 351	Dato-DXd (6 mg/kg) (N=443)
Any AE	**351 (97.5)**	**338 (96.3)**	**434 (98.0)**
Infections and Infestations	198 (55.0)	133 (37.9)	231 (52.1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	3 (0.8)	2 (0.6)	3 (0.7)
Blood and Lymphatic System Disorders	84 (23.3)	161 (45.9)	100 (22.6)
Immune System Disorders	3 (0.8)	4 (1.1)	3 (0.7)
Endocrine Disorders	3 (0.8)	3 (0.9)	3 (0.7)
Metabolism and Nutrition Disorders	115 (31.9)	113 (32.2)	151 (34.1)
Psychiatric Disorders	26 (7.2)	31 (8.8)	36 (8.1)
Nervous System Disorders	92 (25.6)	130 (37.0)	129 (29.1)
Eye Disorders	194 (53.9)	97 (27.6)	234 (52.8)
Ear and Labyrinth Disorders	9 (2.5)	14 (4.0)	10 (2.3)
Cardiac Disorders	20 (5.6)	10 (2.8)	28 (6.3)
Vascular Disorders	35 (9.7)	31 (8.8)	40 (9.0)
Respiratory, Thoracic and Mediastinal Disorders	126 (35.0)	68 (19.4)	159 (35.9)
Gastrointestinal Disorders	305 (84.7)	212 (60.4)	384 (86.7)
Hepatobiliary Disorders	7 (1.9)	19 (5.4)	8 (1.8)
Skin and Subcutaneous Tissue Disorders	203 (56.4)	149 (42.5)	253 (57.1)
Musculoskeletal and Connective Tissue Disorders	86 (23.9)	101 (28.8)	104 (23.5)
Renal and Urinary Disorders	21 (5.8)	21 (6.0)	24 (5.4)
Reproductive System and Breast Disorders	14 (3.9)	11 (3.1)	18 (4.1)
Congenital, Familial and Genetic Disorders	3 (0.8)	0	3 (0.7)
General Disorders and Administration Site Conditions	200 (55.6)	177 (50.4)	251 (56.7)
Investigations	134 (37.2)	166 (47.3)	182 (41.1)
Injury, Poisoning and Procedural Complications	36 (10.0)	18 (5.1)	55 (12.4)
Product Issues	2 (0.6)	0	3 (0.7)

The table includes adverse events with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy.
Patients with multiple occurrences are counted once per System Organ Class and Preferred Term regardless of the number of occurrences. Table is sorted by international order for System Organ Class.
N, number of patients per treatment group.
Note: data from IA.

Common adverse events

Table 69 Most Common Treatment Emergent Adverse Events (Frequency of ≥ 5% in Any Treatment Arm) by Decreasing Frequency and Preferred Term in Pivotal Study and BC Pool (SAS FA)

Preferred Term	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Patients with any TEAE	350 (97.2)	337 (96.0)	353 (98.1)	339 (96.6)	433 (97.7)	436 (98.4)
Nausea	201 (55.8)	95 (27.1) [b]	204 (56.7)	95 (27.1) [b]	252 (56.9)	255 (57.6)
Stomatitis	184 (51.1)	50 (14.2) [b]	189 (52.5)	50 (14.2) [b]	249 (56.2)	254 (57.3)
Alopecia	136 (37.8)	78 (22.2) [b]	136 (37.8)	80 (22.8) [b]	165 (37.2)	165 (37.2)
Constipation	121 (33.6)	60 (17.1) [b]	126 (35.0)	60 (17.1) [b]	141 (31.8)	146 (33.0)
Fatigue	99 (27.5)	71 (20.2)	103 (28.6)	71 (20.2)	133 (30.0)	137 (30.9)
Vomiting	86 (23.9)	41 (11.7) [b]	88 (24.4)	42 (12.0) [b]	113 (25.5)	115 (26.0)
Dry eye	87 (24.2)	46 (13.1) [b]	97 (26.9)	46 (13.1) [b]	103 (23.3)	113 (25.5)
Anaemia	56 (15.6)	86 (24.5)	62 (17.2)	87 (24.8)	70 (15.8)	76 (17.2)
COVID-19	55 (15.3)	47 (13.4)	74 (20.6)	53 (15.1)	57 (12.9)	76 (17.2)
Decreased appetite	57 (15.8)	56 (16.0)	58 (16.1)	56 (16.0)	71 (16.0)	72 (16.3)
AST increased	55 (15.3)	59 (16.8)	61 (16.9)	60 (17.1)	65 (14.7)	71 (16.0)
Cough	48 (13.3)	32 (9.1)	49 (13.6)	33 (9.4)	62 (14.0)	63 (14.2)
Asthenia	55 (15.3)	59 (16.8)	56 (15.6)	61 (17.4)	56 (12.6)	57 (12.9)
Diarrhoea	38 (10.6)	66 (18.8)	43 (11.9)	68 (19.4)	52 (11.7)	57 (12.9)
Headache	26 (7.2)	38 (10.8)	30 (8.3)	38 (10.8)	49 (11.1)	53 (12.0)
Rash	32 (8.9)	10 (2.8)	34 (9.4)	10 (2.8)	46 (10.4)	48 (10.8)
ALT increased	37 (10.3)	50 (14.2)	38 (10.6)	50 (14.2)	45 (10.2)	46 (10.4)
Punctate keratitis	38 (10.6)	23 (6.6)	44 (12.2)	23 (6.6)	40 (9.0)	46 (10.4)
Pyrexia	29 (8.1)	39 (11.1)	30 (8.3)	40 (11.4)	41 (9.3)	42 (9.5)
Pruritus	32 (8.9)	6 (1.7)	32 (8.9)	7 (2.0)	38 (8.6)	38 (8.6)
Neutrophil count decreased	23 (6.4)	77 (21.9) [b]	25 (6.9)	77 (21.9) [b]	34 (7.7)	36 (8.1)
Weight decreased	25 (6.9)	15 (4.3)	31 (8.6)	17 (4.8)	30 (6.8)	36 (8.1)
Keratitis	30 (8.3)	9 (2.6)	30 (8.3)	10 (2.8)	35 (7.9)	35 (7.9)
Lacrimation increased	26 (7.2)	3 (0.9)	28 (7.8)	3 (0.9)	33 (7.4)	35 (7.9)
Abdominal pain	23 (6.4)	29 (8.3)	25 (6.9)	30 (8.5)	29 (6.5)	31 (7.0)
Blood ALP increased	19 (5.3)	14 (4.0)	22 (6.1)	16 (4.6)	28 (6.3)	31 (7.0)
Oropharyngeal pain	20 (5.6)	6 (1.7)	22 (6.1)	6 (1.7)	29 (6.5)	31 (7.0)
Urinary tract infection	23 (6.4)	20 (5.7)	27 (7.5)	21 (6.0)	27 (6.1)	31 (7.0)
Dry mouth	19 (5.3)	6 (1.7)	21 (5.8)	6 (1.7)	28 (6.3)	30 (6.8)
Dry skin	22 (6.1)	6 (1.7)	23 (6.4)	6 (1.7)	29 (6.5)	30 (6.8)

Blepharitis	27 (7.5)	6 (1.7)	28 (7.8)	6 (1.7)	27 (6.1)	28 (6.3)
Hypokalaemia	15 (4.2)	12 (3.4)	16 (4.4)	13 (3.7)	27 (6.1)	28 (6.3)
White blood cell count decreased	17 (4.7)	41 (11.7)	18 (5.0)	41 (11.7)	27 (6.1)	28 (6.3)
Arthralgia	19 (5.3)	25 (7.1)	21 (5.8)	25 (7.1)	24 (5.4)	26 (5.9)
Dysgeusia	18 (5.0)	14 (4.0)	19 (5.3)	14 (4.0)	25 (5.6)	26 (5.9)
Dyspnoea	12 (3.3)	21 (6.0)	15 (4.2)	22 (6.3)	23 (5.2)	26 (5.9)
Hypoalbuminaemia	14 (3.9)	10 (2.8)	18 (5.0)	10 (2.8)	21 (4.7)	25 (5.6)
Meibomian gland dysfunction	24 (6.7)	6 (1.7)	25 (6.9)	6 (1.7)	24 (5.4)	25 (5.6)
Dizziness	14 (3.9)	14 (4.0)	15 (4.2)	15 (4.3)	23 (5.2)	24 (5.4)
Conjunctivitis	15 (4.2)	3 (0.9)	17 (4.7)	4 (1.1)	21 (4.7)	23 (5.2)
Vision blurred	13 (3.6)	3 (0.9)	18 (5.0)	3 (0.9)	18 (4.1)	23 (5.2)
Pain in extremity	21 (5.8)	22 (6.3)	20 (5.6)	21 (6.0)	23 (5.2)	22 (5.0)
Rash maculo-papular	15 (4.2)	5 (1.4)	15 (4.2)	6 (1.7)	22 (5.0)	22 (5.0)
Upper respiratory tract infection	17 (4.7)	19 (5.4)	21 (5.8)	19 (5.4)	18 (4.1)	22 (5.0)
Neutropenia	18 (5.0)	88 (25.1) [b]	21 (5.8)	91 (25.9) [b]	18 (4.1)	21 (4.7)
Abdominal pain upper	15 (4.2)	17 (4.8)	18 (5.0)	17 (4.8)	15 (3.4)	18 (4.1)
Back pain	7 (1.9)	23 (6.6)	9 (2.5)	23 (6.6)	13 (2.9)	15 (3.4)
Leukopenia	13 (3.6)	28 (8.0)	13 (3.6)	29 (8.3)	14 (3.2)	14 (3.2)
Myalgia	7 (1.9)	23 (6.6)	9 (2.5)	23 (6.6)	9 (2.0)	11 (2.5)
Neuropathy peripheral	5 (1.4)	24 (6.8)	6 (1.7)	24 (6.8)	10 (2.3)	11 (2.5)
Paraesthesia	8 (2.2)	18 (5.1)	10 (2.8)	21 (6.0)	9 (2.0)	11 (2.5)
Platelet count decreased	7 (1.9)	20 (5.7)	9 (2.5)	20 (5.7)	8 (1.8)	10 (2.3)
Palmar-plantar erythrodysaesthesia syndrome	8 (2.2)	43 (12.3) [b]	9 (2.5)	45 (12.8) [b]	8 (1.8)	9 (2.0)

[a] TB01 (n=360) + TP01 BC (n=83).

[b] Difference of ≥ 10% between the Dato-DXd arm and the ICC arm in TB01 study.

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarisation, a subject is counted once if the subject reported one or more AEs.

Table is sorted by decreasing frequency of preferred terms within SOC based on the BC 6 mg/kg pool (TB01, TP01) column.

Adverse events by SOC

Table 70 AEs by SOC and PT (SAS FA)

System Organ Class Preferred Term (MedDRA version 26.0)	Dato-DXd N=360 n (%)	ICC N=351 n (%)
Any AE	353 (98.1)	339 (96.6)
INFECTIONS AND INFESTATIONS	200 (55.6)	133 (37.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	127 (35.3)	71 (20.2)
Aphonia	1 (0.3)	0
Aspiration	1 (0.3)	0
Asthma	3 (0.8)	1 (0.3)
Atelectasis	0	1 (0.3)
Bronchospasm	1 (0.3)	1 (0.3)
Chronic obstructive pulmonary disease	1 (0.3)	0
Cough	49 (13.6)	33 (9.4)
Dry throat	1 (0.3)	0
Dysphonia	4 (1.1)	7 (2.0)
Dyspnoea	15 (4.2)	22 (6.3)
Dyspnoea exertional	0	3 (0.9)
Epistaxis	4 (1.1)	1 (0.3)
Hiccups	4 (1.1)	0
Hypoxia	1 (0.3)	1 (0.3)
Interstitial lung disease	9 (2.5)	0
Laryngeal haemorrhage	2 (0.6)	0
Laryngeal pain	1 (0.3)	0
Nasal congestion	6 (1.7)	0
Nasal dryness	1 (0.3)	1 (0.3)
Oropharyngeal discomfort	3 (0.8)	1 (0.3)
Oropharyngeal pain	22 (6.1)	6 (1.7)
Pharyngeal inflammation	4 (1.1)	0
Pharyngeal paraesthesia	1 (0.3)	0
Pharyngeal swelling	0	1 (0.3)
Pleural effusion	3 (0.8)	4 (1.1)
Pleuritic pain	1 (0.3)	0
Pneumonitis	9 (2.5)	1 (0.3)
Productive cough	11 (3.1)	5 (1.4)
Pulmonary artery thrombosis	1 (0.3)	0
Pulmonary embolism	7 (1.9)	4 (1.1)
Pulmonary mass	0	1 (0.3)
Respiratory distress	0	1 (0.3)
Rhinitis allergic	1 (0.3)	1 (0.3)
Rhinorrhoea	5 (1.4)	2 (0.6)
Sinus disorder	1 (0.3)	0
Sneezing	1 (0.3)	1 (0.3)
Throat irritation	1 (0.3)	0
Throat tightness	1 (0.3)	0
Tonsillar inflammation	1 (0.3)	0
Upper respiratory tract inflammation	1 (0.3)	0

Adverse events by grade

Table 71 Patients with TEAEs by Maximum CTCAE Grade in Pivotal Study and BC Pool (SAS)

Maximum reported CTCAE Grade	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Total	350 (97.2)	337 (96.0)	353 (98.1)	339 (96.6)	433 (97.7)	436 (98.4)
Grade 1	56 (15.6)	44 (12.5)	49 (13.6)	45 (12.8)	65 (14.7)	58 (13.1)
Grade 2	177 (49.2)	103 (29.3)	178 (49.4)	99 (28.2)	213 (48.1)	214 (48.3)
Grade 3	112 (31.1)	134 (38.2)	119 (33.1)	137 (39.0)	143 (32.3)	150 (33.9)
Grade 4	5 (1.4)	53 (15.1)	6 (1.7)	55 (15.7)	11 (2.5)	12 (2.7)
Grade 5	0	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.2)	2 (0.5)

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Grade ≥3 adverse events

Table 72. TEAEs of CTCAE Grade ≥ 3 by Decreasing Frequency and Preferred Term Reported in ≥ 1% of Patients in Any Treatment Arm in Pivotal Study and BC Pool (Safety Analysis Set)

	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
Preferred Term	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Patients with any CTCAE Grade ≥ 3	117 (32.5)	190 (54.1) [b]	126 (35.0)	195 (55.6) [b]	155 (35.0)	164 (37.0)
Stomatitis	23 (6.4)	9 (2.6)	23 (6.4)	9 (2.6)	32 (7.2)	32 (7.2)
Anaemia	9 (2.5)	12 (3.4)	10 (2.8)	14 (4.0)	13 (2.9)	14 (3.2)
Fatigue	8 (2.2)	8 (2.3)	9 (2.5)	8 (2.3)	12 (2.7)	13 (2.9)
AST increased	9 (2.5)	4 (1.1)	10 (2.8)	4 (1.1)	11 (2.5)	12 (2.7)
Lymphocyte count decreased	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)	11 (2.5)	11 (2.5)
ALT increased	5 (1.4)	1 (0.3)	5 (1.4)	1 (0.3)	7 (1.6)	7 (1.6)
Vomiting	4 (1.1)	4 (1.1)	5 (1.4)	4 (1.1)	6 (1.4)	7 (1.6)
Asthenia	5 (1.4)	5 (1.4)	6 (1.7)	5 (1.4)	5 (1.1)	6 (1.4)
Blood bilirubin increased	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)	6 (1.4)	6 (1.4)
Nausea	5 (1.4)	2 (0.6)	5 (1.4)	2 (0.6)	6 (1.4)	6 (1.4)
Urinary tract infection	6 (1.7)	2 (0.6)	6 (1.7)	3 (0.9)	6 (1.4)	6 (1.4)
Blood ALP increased	4 (1.1)	0	4 (1.1)	0	5 (1.1)	5 (1.1)
Decreased appetite	5 (1.4)	3 (0.9)	5 (1.4)	3 (0.9)	5 (1.1)	5 (1.1)
Hypertension	5 (1.4)	2 (0.6)	5 (1.4)	2 (0.6)	5 (1.1)	5 (1.1)
Hyponatraemia	3 (0.8)	0	3 (0.8)	0	5 (1.1)	5 (1.1)
Pneumonia	2 (0.6)	3 (0.9)	4 (1.1)	3 (0.9)	3 (0.7)	5 (1.1)
Pulmonary embolism	4 (1.1)	4 (1.1)	4 (1.1)	4 (1.1)	5 (1.1)	5 (1.1)
Sepsis	2 (0.6)	1(0.3)	4 (1.1)	1 (0.3)	3 (0.7)	5 (1.1)
Abdominal pain	1 (0.3)	4 (1.1)	2 (0.6)	4 (1.1)	3 (0.7)	4 (0.9)

Gamma-glutamyltransferase increased	2 (0.6)	5 (1.4)	3 (0.8)	5 (1.4)	3 (0.7)	4 (0.9)
Neutrophil count decreased	3 (0.8)	54 (15.4) [b]	3 (0.8)	54 (15.4) [b]	4 (0.9)	4 (0.9)
Syncope	4 (1.1)	1 (0.3)	4 (1.1)	1 (0.3)	4 (0.9)	4 (0.9)
Diarrhoea	2 (0.6)	5 (1.4)	2 (0.6)	6 (1.7)	2 (0.5)	2 (0.5)
Platelet count decreased	0	6 (1.7)	1 (0.3)	6 (1.7)	1 (0.2)	2 (0.5)
WBC count decreased	2 (0.6)	16 (4.6)	2 (0.6)	17 (4.8)	2 (0.5)	2 (0.5)
Femur fracture	1 (0.3)	4 (1.1)	1 (0.3)	4 (1.1)	1 (0.2)	1 (0.2)
Neutropenia	1 (0.3)	62 (17.7) [b]	1 (0.3)	64 (18.2) [b]	1 (0.2)	1 (0.2)
Febrile neutropenia	0	8 (2.3)	0	8 (2.3)	0	0
Leukopenia	0	12 (3.4)	0	12 (3.4)	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	7 (2.0)	0	7 (2.0)	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

[b] Difference of ≥ 10% between the Dato-DXd arm and the ICC arm in TB01 study.

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarisation, a subject is counted once if the subject reported one or more AEs.

Source: SCS updated (results from final analysis highlighted in title).

Table 73 Treatment-emergent Adverse Events of CTCAE Grade ≥ 3 by SOC in TB01 Study and BC Pool (Safety Analysis Set) (IA)

System Organ Class	Number (%) of patients [a]		
	Individual Study		BC Pool
	Dato-DXd (6 mg/kg) N = 360	ICC N = 351	Dato-DXd (6 mg/kg) (N=443)
Patients with AE of CTCAE Grade 3 Or Higher	**124 (34.4)**	**195 (55.6)**	**162 (36.6)**
Infections and Infestations	21 (5.8)	21 (6.0)	25 (5.6)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2 (0.6)	1 (0.3)	2 (0.5)
Blood and Lymphatic System Disorders	13 (3.6)	86 (24.5)	19 (4.3)
Endocrine Disorders	1 (0.3)	1 (0.3)	1 (0.2)
Metabolism and Nutrition Disorders	11 (3.1)	12 (3.4)	16 (3.6)
Psychiatric Disorders	1 (0.3)	0	2 (0.5)
Nervous System Disorders	11 (3.1)	7 (2.0)	11 (2.5)
Eye Disorders	10 (2.8)	4 (1.1)	11 (2.5)
Cardiac Disorders	1 (0.3)	3 (0.9)	3 (0.7)
Vascular Disorders	7 (1.9)	3 (0.9)	7 (1.6)
Respiratory, Thoracic and Mediastinal Disorders	15 (4.2)	8 (2.3)	20 (4.5)
Gastrointestinal Disorders	45 (12.5)	26 (7.4)	58 (13.1)
Hepatobiliary Disorders	2 (0.6)	3 (0.9)	3 (0.7)
Skin and Subcutaneous Tissue Disorders	2 (0.6)	10 (2.8)	2 (0.5)
Musculoskeletal and Connective Tissue Disorders	2 (0.6)	5 (1.4)	3 (0.7)
Renal and Urinary Disorders	4 (1.1)	5 (1.4)	5 (1.1)
General Disorders and Administration Site Conditions	18 (5.0)	14 (4.0)	22 (5.0)
Investigations	28 (7.8)	78 (22.2)	48 (10.8)
Injury, Poisoning and Procedural Complications	3 (0.8)	4 (1.1)	4 (0.9)

[a] Patients with multiple AEs of CTCAE grade 3 or higher are counted once for each Preferred Term.
Number (%) of patients with AEs of CTCAE grade 3 or higher, sorted by international SOC order. Includes adverse events with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy. Patients who have a maximum CTCAE grade 5 post the data cut-off (DCO) date, have been reset to unknown at the DCO date. This affects 0 patients in Dato-DXd treatment group and 0 patients in ICC treatment group. MedDRA version 26.0.
N, number of patients per treatment group.
Note: results from IA.

Table 74 Treatment-emergent Adverse Events of CTCAE Grade ≥ 3, Infections and Infestations SOC, TB01 Study and BC Pool (Safety Analysis Set) (IA)

System Organ Class Preferred Term	Number (%) of patients [a]		
	Individual Study		BC Pool
	Dato-DXd N = 360	ICC N = 351	Dato-DXd (6 mg/kg) (N=443)
Patients with AE of CTCAE grade 3 or higher	**124 (34.4)**	**195 (55.6)**	**162 (36.6)**
INFECTIONS AND INFESTATIONS	21 (5.8)	21 (6.0)	25 (5.6)
Abdominal infection	0	1 (0.3)	0
Bacteriuria	0	1 (0.3)	0

System Organ Class Preferred Term	Number (%) of patients [a]		
	Individual Study		BC Pool
	Dato-DXd N = 360	ICC N = 351	Dato-DXd (6 mg/kg) (N=443)
Bronchitis	1 (0.3)	0	2 (0.5)
COVID-19	3 (0.8)	3 (0.9)	3 (0.7)
COVID-19 pneumonia	2 (0.6)	0	2 (0.5)
Cellulitis	1 (0.3)	1 (0.3)	1 (0.2)
Clostridium difficile colitis	0	1 (0.3)	0
Coronavirus pneumonia	0	1 (0.3)	0
Device related infection	0	1 (0.3)	0
Device related sepsis	1 (0.3)	0	1 (0.2)
Erysipelas	1 (0.3)	0	1 (0.2)
Herpes zoster	1 (0.3)	0	1 (0.2)
Meningitis tuberculous	0	1 (0.3)	0
Pneumonia	4 (1.1)	3 (0.9)	5 (1.1)
Pneumonia bacterial	0	2 (0.6)	0
Postoperative wound infection	1 (0.3)	0	1 (0.2)
Pulmonary sepsis	0	1 (0.3)	0
Sepsis	3 (0.8)	1 (0.3)	4 (0.9)
Septic shock	0	2 (0.6)	0
Skin infection	0	0	1 (0.2)
Spinal cord infection	1 (0.3)	0	1 (0.2)
Upper respiratory tract infection	0	1 (0.3)	0
Urinary tract infection	6 (1.7)	3 (0.9)	6 (1.4)
Urosepsis	3 (0.8)	0	3 (0.7)

[a] Patients with multiple AEs of CTCAE grade 3 or higher are counted once for each Preferred Term.

Number (%) of patients with AEs of CTCAE grade 3 or higher, sorted by alphabetical PT. Includes adverse events with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy. Patients who have a maximum CTCAE grade 5 post the data cut-off (DCO) date, have been reset to unknown at the DCO date. This affects 0 patients in Dato-DXd treatment group and 0 patients in ICC treatment group. MedDRA version 26.0.

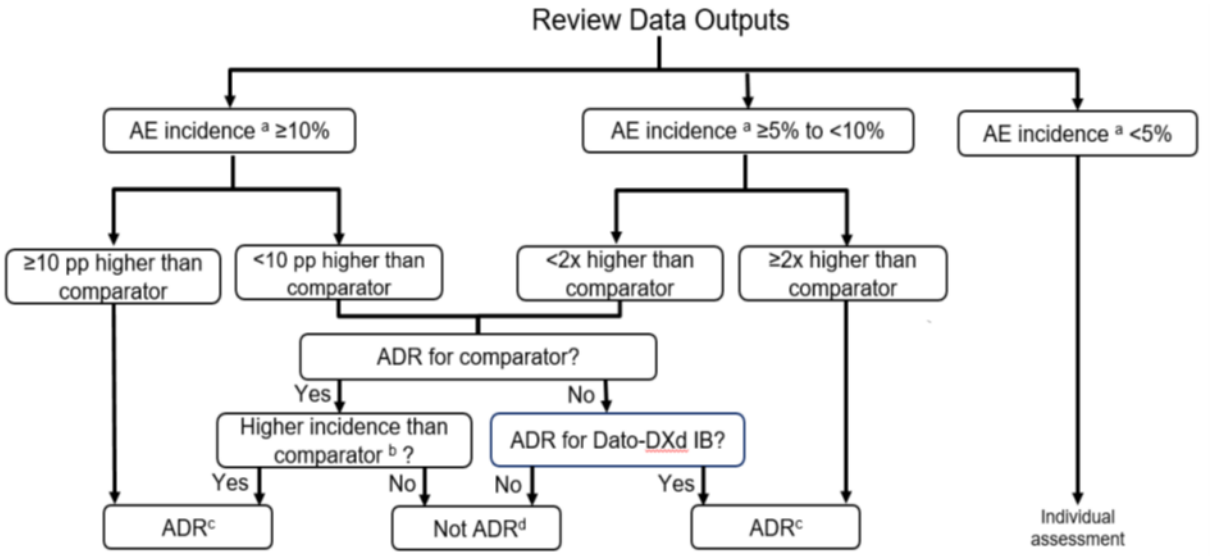
CTCAE Common terminology criteria for adverse events (version 5.0).

N, number of patients per treatment group.

Note: results from IA.

Adverse drug reactions

Figure 36 Methodology of Adverse Drug Reaction Determination in Study TB01



[a] AE incidence in the Dato-DXd arm.

[b] Individual assessments may be required if the TEAE is not listed as an ADR in all comparator labels.

[c] If evidence suggest that the event is due to the underlying disease / alternative etiology, it may be determined as **not** an ADR.

[d] If there is a casual relationship between the event and the study drug, it may be determined as an ADR.

The term "pp" denotes percentage points.

Table 75 All Adverse Drug Reactions in Pooled Data of TB01 and TP01(6mg/kg), by Grouped/MedDRA SOC, Grouped Term/PT, and Frequency (SAS)

	Number (%) of Subjects			
	Dato-DXd (N=443)			
	CTCAE Grade			
MedDRA System Organ Class Preferred Term or Grouped Term [a]	Frequency [b]	All Grades	Grade 3 or 4	Serious ADR
Subjects with any adverse drug reaction		432 (97.5)	110 (24.8)	33 (7.4)
Blood and lymphatic system disorders				
Anaemia	Very Common	76 (17.2)	14 (3.2)	2 (0.5)
Neutropenia [a]	Very Common	53 (12.0)	5 (1.1)	0
Leukopenia	Common	14 (3.2)	0	0
Eye disorders				
Dry eye	Very Common	113 (25.5)	3 (0.7)	0
Keratitis [a]	Very Common	79 (17.8)	4 (0.9)	1 (0.2)
Conjunctivitis [a]	Common	43 (9.7)	1 (0.2)	0
Lacrimation increased	Common	35 (7.9)	0	0
Blepharitis	Common	28 (6.3)	0	0
Meibomian gland dysfunction	Common	25 (5.6)	0	0
Vision blurred	Common	23 (5.2)	1 (0.2)	0
Photophobia	Common	6 (1.4)	0	0

Visual impairment	Uncommon	4 (0.9)	0	0
Gastrointestinal disorders				
Stomatitis [a]	Very Common	287 (64.8)	35 (7.9)	1 (0.2)
Nausea	Very Common	255 (57.6)	6 (1.4)	1 (0.2)
Constipation	Very Common	146 (33.0)	1 (0.2)	0
Vomiting	Very Common	115 (26.0)	7 (1.6)	3 (0.7)
Diarrhoea	Very Common	57 (12.9)	2 (0.5)	2 (0.5)
Dry mouth	Common	30 (6.8)	1 (0.2)	0
General disorders and administration site conditions				
Fatigue [a]	Very Common	189 (42.7)	19 (4.3)	1 (0.2)
Infections and infestations				
COVID-19 [a]	Very Common	79 (17.8)	5 (1.1)	6 (1.4)
Urinary tract infection	Common	31 (7.0)	6 (1.4)	5 (1.1)
Pneumonia [a]	Common	19 (4.3)	5 (1.1)	3 (0.7)
Sepsis	Common	5 (1.1)	4 (0.9)	4 (0.9)
Injury, poisoning and procedural complications				
Infusion-related reaction [a]	Common	35 (7.9)	0	0
Investigations				
Aspartate aminotransferase increased	Very Common	71 (16.0)	12 (2.7)	0
Alanine aminotransferase increased	Very Common	46 (10.4)	7 (1.6)	0
Metabolism and nutrition disorders				
Decreased appetite	Very Common	72 (16.3)	5 (1.1)	0
Nervous system disorders				
Dysgeusia	Common	26 (5.9)	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	Common	26 (5.9)	1 (0.2)	2 (0.5)
Interstitial lung disease [a]	Common	21 (4.7)	4 (0.9)	5 (1.1)
Skin and subcutaneous tissue disorders				
Alopecia	Very Common	165 (37.2)	0	0
Rash [a]	Very Common	68 (15.3)	0	0
Dry skin	Common	30 (6.8)	0	0
Pruritus	Common	28 (6.3)	1 (0.2)	0
Skin hyperpigmentation [a]	Common	24 (5.4)	0	0
Madarosis	Common	7 (1.6)	0	0

ADR = adverse drug reaction; CTCAE = Common Terminology Criteria for Adverse Events, version 5.0; MedDRA = Medical Dictionary for Regulatory Activities, version 26.0.
N = total number of treated subjects; NA = not applicable; PT = preferred term; SAE = serious adverse event; SOC = system organ class; Source: adam.adaeadr; Percentages were calculated by using the number of subjects in the Safety Analysis Set as the denominator. SOCs were sorted by alphabetic order. PTs/grouped terms were sorted by descending frequency in the "All Grades" column.
If a subject had multiple occurrences of the same ADR, the subject was counted once for that specific ADR.
[a] The PTs included in each of the grouped terms in this table are defined in Table 2.7.4.8.1 [b] Frequency: (1) very common (1/10 subjects); (2) common (> =1/100 to < 1/10 subjects); (3) uncommon (1/1,000 to < 1/100 subjects); (4) rare (1/10,000 to < 1/1,000 subjects); (5) very rare (< 1/10,000 subjects); and (6) NK (not known -cannot be estimated from available data)

2.6.8.3. Serious adverse event/deaths/other significant events

Adverse Events of Special Interest

The following five AESIs have been identified for Dato-DXd, based on clinical development program experience, nonclinical data, epidemiologic information, and literature review for products of a similar class.

- ILD/pneumonitis
- Infusion-related reactions

- Oral mucositis/stomatitis
- Mucosal inflammation other than oral mucositis/stomatitis
- Ocular surface toxicity.

Interstitial lung disease/pneumonitis is an important identified risk for Dato-DXd based on nonclinical data, clinical data, and literature review of in-class products.

An independent, external ILD Adjudication Committee was established for the clinical development program and adjudicated all events of potential ILD reported by investigators on an ongoing basis, to ensure a comprehensive assessment of ILD. Data for all patients with a reported preferred term listed among the preferred terms of the AESI of ILD/pneumonitis that would trigger adjudication for a potential ILD event were submitted to the ILD Adjudication Committee. The ILD Adjudication Committee adjudicated each potential ILD/pneumonitis event with regard to whether it was ILD and whether it was related to study treatment (regardless of the assessment of the investigator). The ILD Adjudication Committee also determined the onset dates and adjudicated severity grades for events that the Adjudication Committee considered to be ILD. Protocol-defined on-treatment death for any patient who experienced a potential ILD/pneumonitis event was also adjudicated as to whether the death was due to ILD.

Table 76 Adjudicated Drug-related ILD by Category in Pivotal Study and BC Pool (Safety Analysis Set)

AESI Category	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any adjudicated drug related ILD	12 (3.3)	0	15 (4.2) [c]	0	13 (2.9)	16 (3.6) [c]
CTCAE Grade 1	5 (1.4)	0	7 (1.9) [c]	0	5 (1.1)	7 (1.6) [c]
CTCAE Grade 2	4 (1.1)	0	5 (1.4)	0	4 (0.9)	5 (1.1)
CTCAE Grade 3	2 (0.6)	0	2 (0.6)	0	3 (0.7)	3 (0.7)
CTCAE Grade 4	0	0	0	0	0	0
CTCAE Grade 5	1 (0.3) [b]	0	1 (0.3) [b]	0	1 (0.2)	1 (0.2)
CTCAE Grade Missing	0	0	0	0	0	0
Any Grade ≥ 2 adjudicated drug-related ILD	7 (1.9)	0	8 (2.2)	0	8 (1.8)	9 (2.0)
Any Grade ≥ 3 adjudicated drug-related ILD	3 (0.8)	0	3 (0.8)	0	4 (0.9)	4 (0.9)
Any serious adjudicated drug-related ILD	4 (1.1)	0	4 (1.1)	0	5 (1.1)	5 (1.1)
Action taken [d]						
Any adjudicated drug-related ILD associated with dose reduction	1 (0.3)	0	2 (0.6)	0	1 (0.2)	2 (0.5)
Any adjudicated drug-related ILD associated with drug interrupted	3 (0.8)	0	3 (0.8)	0	3 (0.7)	3 (0.7)
Any adjudicated drug-related ILD associated with drug withdrawn	5 (1.4)	0	6 (1.7)	0	6 (1.4)	7 (1.6)
Any adjudicated drug-related ILD associated with death	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Outcome of worst NCI CTCAE drug-related adjudicated ILD	12 (3.3)	0	14 (3.9)	0	13 (2.9)	15 (3.4)
Fatal	0 [c]	0	0 [c]	0	0 [c]	0 [c]
Not recovered/not resolved	7 (1.9)	0	8 (2.2)	0	8 (1.8)	9 (2.0)
Recovering/Resolving	0	0	0	0	0	0

Recovered/Resolved with sequelae	0	0	0	0	0	0
Recovered/Resolved	5 (1.4)	0	6 (1.7)	0	5 (1.1)	6 (1.4)
Missing/Unknown	0	0	0	0	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

[b] Subject had an event of pneumonitis and died (assessed by the investigator as Grade 3 and death due to disease progression) that was subsequently assessed by the ILD Adjudication Committee as fatal drug-related ILD.

[c] Including one subject who had Grade 1 adjudicated drug-related ILD, with an investigator-reported preferred term of 'interstitial lung disease', which was subsequently inactivated in the database by the investigator (see Listing 2.7.4.4.8.3, ISS Final Analysis, Module 5.3.5.3).

[d] Action taken is per the investigator.

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

If a subject has more than one event per AESI category (or preferred term) level, the subject is counted once at each level of summation. If a subject has both missing and non-missing CTCAE grades for a TEAE, the missing CTCAE grade is treated as the lowest severity grade. Grades for adjudicated drug-related ILDs are from the adjudication committee.

Drug interrupted includes both infusion interruption and dose delay.

Source: SCS updated (results from final analysis highlighted in title).

Infusion-related Reaction is an identified risk for Dato-DXd based on the available clinical and nonclinical experience with Dato-DXd. To be considered an infusion-related reaction, events from a list of pre-defined infusion-related reaction preferred terms were required to start on the same day of an infusion. Risk mitigation guidelines are currently in place in all study protocols in the Dato-DXd clinical program, with risk information provided in the informed consent forms. Clinical study protocols contained guidance on prophylaxis to prevent the development of infusion-related reaction, and the effective management if an event were to occur. Patients were monitored during and for a specified time period after the infusion for the development of a potential infusion-related reaction.

Table 77 Infusion-related Reaction AESI by Category in Pivotal Study and BC Pool Studies (Safety Analysis Set)

AESI Category	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any AESI of IRR	32 (8.9)	12 (3.4)	34 (9.4)	13 (3.7)	45 (10.2)	47 (10.6)
Grade 1	22 (6.1)	9 (2.6)	23 (6.4)	10 (2.8)	32 (7.2)	33 (7.4)
Grade 2	9 (2.5)	3 (0.9)	10 (2.8)	3 (0.9)	12 (2.7)	13 (2.9)
Grade 3	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Any Grade ≥ 2 IRR	10 (2.8)	3 (0.9)	11 (3.1)	3 (0.9)	13 (2.9)	14 (3.2)
Any Grade ≥ 3 IRR	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Any treatment-related IRR	26 (7.2)	9 (2.6)	26 (7.2)	10 (2.8)	38 (8.6)	38 (8.6)
Any treatment-related and Grade ≥ 3 IRR	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Any serious IRR	0	0	0	0	0	0
Any serious and treatment-related IRR	0	0	0	0	0	0
Action taken						
Any IRR associated with dose reduction	0	0	0	0	0	0
Any IRR associated with drug interrupted	5 (1.4)	0	5 (1.4)	0	5 (1.1)	5 (1.1)
Any IRR associated with drug withdrawn	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Outcome of worst NCI CTCAE IRR	32 (8.9)	12 (3.4)	34 (9.4)	13 (3.7)	45 (10.2)	47 (10.6)
Fatal	0	0	0	0	0	0
Not recovered/not resolved	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.7)	3 (0.7)
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved with sequelae	0	0	0	0	0	0
Recovered/Resolved	31 (8.6)	11 (3.1)	33 (9.2)	12 (3.4)	42 (9.5)	44 (9.9)

Missing/Unknown	0	0	0	0	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

If a subject has multiple IRR events, the CTCAE grade is for the event with the worst grade.

IRR terms were defined by the occurrence of the relevant preferred terms up to 24 hours after dosing in TB01.

Where events occurred the day after an infusion and onset time is not provided for 10 subjects, these subjects are excluded from this table.

Source: SCS updated (results from final analysis highlighted in the title of the table).

Oral mucositis/stomatitis is an identified risk for Dato-DXd and AESI based on the available clinical and nonclinical experience with Dato-DXd.

Risk mitigation guidelines are currently in place in all study protocols in the Dato-DXd clinical program, with risk information provided in the informed consent form. As noted in the study protocols, patients were advised to initiate a daily oral care protocol to prevent oral mucositis/stomatitis.

Table 78 Oral Mucositis/Stomatitis AESI by Category in Pivotal Study and BC Pool (Safety Analysis Set)

AESI Category	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any AESI of oral mucositis/stomatitis	211 (58.6)	61 (17.4)	216 (60.0)	61 (17.4)	282 (63.7)	287 (64.8)
Grade 1	96 (26.7)	37 (10.5)	96 (26.7)	36 (10.3)	130 (29.3)	130 (29.3)
Grade 2	90 (25.0)	15 (4.3)	94 (26.1)	16 (4.6)	118 (26.6)	122 (27.5)
Grade 3	25 (6.9)	9 (2.6)	26 (7.2)	9 (2.6)	34 (7.7)	35 (7.9)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Any Grade ≥ 2 oral mucositis/stomatitis	115 (31.9)	24 (6.8)	120 (33.3)	25 (7.1)	152 (34.3)	157 (35.4)
Any Grade ≥ 3 oral mucositis/stomatitis	25 (6.9)	9 (2.6)	26 (7.2)	9 (2.6)	34 (7.7)	35 (7.9)
Any treatment related oral mucositis/stomatitis	200 (55.6)	52 (14.8)	206 (57.2)	52 (14.8)	267 (60.3)	273 (61.6)
Any treatment-related and Grade ≥ 3 oral mucositis/stomatitis	25 (6.9)	9 (2.6)	26 (7.2)	9 (2.6)	34 (7.7)	35 (7.9)
Any serious oral mucositis/stomatitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)
Any serious and treatment-related oral mucositis/stomatitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)
Action taken						
Any oral mucositis/stomatitis associated with dose reduction	48 (13.3)	5 (1.4)	51 (14.2)	5 (1.4)	54 (12.2)	57 (12.9)
Any oral mucositis/stomatitis associated with drug interrupted	7 (1.9)	3 (0.9)	10 (2.8)	3 (0.9)	21 (4.7)	24 (5.4)
Any oral mucositis/stomatitis associated with drug withdrawn	1 (0.3)	0	1 (0.3)	0	2 (0.5)	2 (0.5)

Outcome of worst NCI CTCAE oral mucositis/stomatitis	211 (58.6)	61 (17.4)	216 (60.0)	61 (17.4)	282 (63.7)	287 (64.8)
Fatal	0	0	0	0	0	0
Not recovered/not resolved	76 (21.1)	15 (4.3)	29 (8.1)	8 (2.3)	106 (23.9)	59 (13.3)
Recovering/Resolving	26 (7.2)	1 (0.3)	15 (4.2)	0	27 (6.1)	16 (3.6)
Recovered/Resolved with sequelae	0	0	2 (0.6)	0	0	2 (0.5)
Recovered/Resolved	109 (30.3)	45 (12.8)	170 (47.2)	53 (15.1)	149 (33.6)	210 (47.4)
Missing/Unknown	0	0	0	0	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

If a subject has multiple AESI events, the CTCAE grade is for the event with the worst grade.

Source: SCS updated (results from final analysis highlighted in the title of the table).

Mucosal inflammation other than oral mucositis/stomatitis is an identified risk for Dato-DXd and AESI based on the available clinical and nonclinical experience with Dato-DXd. Mucosal inflammation other than oral mucositis/stomatitis AESIs are defined by the single preferred term of mucosal inflammation.

Table 79 Mucosal Inflammation Other Than Oral Mucositis/Stomatitis AESI by Category in Pivotal Study and BC Pool (Safety Analysis Set)

	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
AESI Category	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any AESI of mucosal inflammation other than stomatitis/oral mucositis	5 (1.4)	1 (0.3)	4 (1.1)	1 (0.3)	5 (1.1)	4 (0.9)
Grade 1	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.2)	0
Grade 2	4 (1.1)	0	4 (1.1)	0	4 (0.9)	4 (0.9)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0

Any Grade ≥ 2 mucosal inflammation other than stomatitis/oral mucositis	4 (1.1)	0	4 (1.1)	0	4 (0.9)	4 (0.9)
Any Grade ≥ 3 mucosal inflammation other than stomatitis/oral mucositis	0	0	0	0	0	0
Any treatment related mucosal inflammation other than stomatitis/oral mucositis	5 (1.4)	1 (0.3)	4 (1.1)	1 (0.3)	5 (1.1)	4 (0.9)
Any treatment-related and Grade ≥ 3 mucosal inflammation other than stomatitis/oral mucositis	0	0	0	0	0	0
Any serious mucosal inflammation other than stomatitis/oral mucositis	0	0	0	0	0	0
Any serious and treatment-related mucosal inflammation other than stomatitis/oral mucositis	0	0	0	0	0	0
Action taken						
Any mucosal inflammation other than stomatitis/oral mucositis associated with dose reduction	0	0	0	0	0	0
Any mucosal inflammation other than stomatitis/oral mucositis associated with drug interrupted	0	0	0	0	0	0

Any mucosal inflammation other than stomatitis/oral mucositis associated with drug withdrawn	0	0	0	0	0	0
Outcome of worst NCI CTCAE mucosal inflammation other than stomatitis/oral mucositis	5 (1.4)	1 (0.3)	4 (1.1)	1 (0.3)	5 (1.1)	4 (0.9)
Fatal	0	0	0	0	0	0
Not recovered/not resolved	2 (0.6)	0	0	0	2 (0.5)	0
Recovering/Resolving	0	0	0	0	0	0
Recovered/Resolved with sequelae	0	0	0	0	0	0
Recovered/Resolved	3 (0.8)	1 (0.3)	4 (1.1)	1 (0.3)	3 (0.7)	4 (0.9)
Missing/Unknown	0	0	0	0	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

If a subject has multiple AESI events, the CTCAE grade is for the event with the worst grade

Source: SCS updated (results from final analysis highlighted in title).

Ocular surface toxicity is an AESI that is monitored in the Dato-DXd clinical development program. This AESI is based on the emerging clinical safety data as well as nonclinical data including the expression of the TROP2 protein in the corneal tissues, detection of the topoisomerase I warhead in ocular surface tissues, and ocular findings in the non-human primates.

Current risk mitigation strategies include mandatory ophthalmologic assessments and preventative measures such as use of artificial tears. Management guidelines were provided in all protocols for clinical studies, with information in the informed consent form about the risk of ocular surface toxicity. To comply with an FDA requirement, the TB01 protocol included the collection of a specified series of ocular assessments by an eyecare specialist at baseline, every 3 cycles, as clinically indicated and at end of study treatment. Clinically significant ocular events as assessed by investigator were reported as TEAEs.

In compliance with an FDA commitment, ophthalmological assessments were performed more often in Study TB01 (ie, at baseline, every third cycle regardless of any clinical symptoms, as clinically indicated, and at the end of study treatment) than in the other pooled studies (ie, at baseline, as clinically indicated, and at the end of study treatment) which may have contributed to the higher detection rates of ocular events in the TB01 Dato-DXd arm. Furthermore, it was noted that a higher number of patients in the Dato-DXd arm compared with the ICC arm underwent ophthalmologic assessments.

Table 80 Ocular Surface Toxicity AESI by Category in Pivotal Study and BC Pool (Safety Analysis Set)

AESI Category	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any AESI of ocular surface toxicity	175 (48.6)	81 (23.1)	185 (51.4)	80 (22.8)	207 (46.7)	217 (49.0)
Grade 1	139 (38.6)	67 (19.1)	136 (37.8)	66 (18.8)	158 (35.7)	155 (35.0)
Grade 2	33 (9.2)	14 (4.0)	42 (11.7)	14 (4.0)	45 (10.2)	54 (12.2)
Grade 3	3 (0.8)	0	7 (1.9)	0	4 (0.9)	8 (1.8)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Any Grade ≥ 2 ocular surface toxicity	36 (10.0)	14 (4.0)	49 (13.6)	14 (4.0)	49 (11.1)	62 (14.0)
Any Grade ≥ 3 ocular surface toxicity	3 (0.8)	0	7 (1.9)	0	4 (0.9)	8 (1.8)
Any treatment related ocular surface toxicity	144 (40.0)	41 (11.7)	158 (43.9)	42 (12.0)	172 (38.8)	186 (42.0)
Any treatment-related and Grade ≥ 3 ocular surface toxicity	3 (0.8)	0	7 (1.9)	0	4 (0.9)	8 (1.8)

Any serious ocular surface toxicity	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Any serious and treatment-related ocular surface toxicity	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Action taken						
Any ocular surface toxicity associated with dose reduction	4 (1.1)	1 (0.3)	10 (2.8)	1 (0.3)	6 (1.4)	12 (2.7)
Any ocular surface toxicity associated with drug interrupted	9 (2.5)	0	14 (3.9)	1 (0.3)	11 (2.5)	16 (3.6)
Any ocular surface toxicity associated with drug withdrawn	1 (0.3)	0	3 (0.8)	0	3 (0.7)	5 (1.1)
Outcome of worst NCI CTCAE ocular surface toxicity	175 (48.6)	81 (23.1)	185 (51.4)	80 (22.8)	207 (46.7)	217 (49.0)
Fatal	0	0	0	0	0	0
Not recovered/not resolved	109 (30.3)	53 (15.1)	91 (25.3)	42 (12.0)	134 (30.2)	116 (26.2)
Recovering/Resolving	17 (4.7)	8 (2.3)	10 (2.8)	4 (1.1)	18 (4.1)	11 (2.5)
Recovered/Resolved with sequelae	0	0	0	0	0	0
Recovered/Resolved	49 (13.6)	20 (5.7)	84 (23.3)	34 (9.7)	55 (12.4)	90 (20.3)
Missing/Unknown	0	0	0	0	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

If a subject has multiple AESI events, the CTCAE grade is for the event with the worst grade.

Source: SCS updated (results from final analysis highlighted in title).

Table 81 Serious Adverse Events Reported in ≥ 1% of Patients in Either Treatment Group, by Preferred Term (Safety Analysis Set)

Preferred Term	**Number (%) of patients**	
	Dato-DXd N = 360	**ICC N = 351**
Any SAE	62 (17.2)	67 (19.1)
Urinary tract infection	5 (1.4)	3 (0.9)
COVID-19	4 (1.1)	3 (0.9)
Sepsis [a]	4 (1.1)	1 (0.3)
Pneumonia	2 (0.6)	4 (1.1)
Femur fracture	1 (0.3)	4 (1.1)

Febrile neutropenia	0	5 (1.4)

[a] Source Table 14.3.2.1.FA and Table 14.3.4.1.2.FA reflects the data from the database which includes 3 (0.8%) patients in the Dato-DXd arm with a serious adverse event of sepsis as assessed by the investigator. An additional event of sepsis in the Dato-DXd arm was reviewed after database lock and was deemed serious, so has been manually included in this table.
This table includes AEs with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy.
Patients with multiple occurrences are counted once per PT regardless of the number of occurrences. Table is sorted by decreasing number of patients based on the total number of AEs for the Dato-DXd arm.

Table 82 Serious Adverse Events ≥ Grade 3 in > 1 Patient in Either Treatment Arm, by Preferred Term (Safety Analysis Set)

Preferred Term	**Number (%) of patients**	
	Dato-DXd N = 360	**ICC N = 351**
Any SAE ≥ Grade 3	51 (14.2)	63 (17.9)
Urinary tract infection	5 (1.4)	3 (0.9)
Sepsis [a]	4 (1.1)	1 (0.3)
COVID-19	3 (0.8)	3 (0.9)
Pneumonitis	3 (0.8)	0
Urosepsis	3 (0.8)	0
Acute kidney injury	2 (0.6)	0
Anaemia	2 (0.6)	1 (0.3)
COVID-19 pneumonia	2 (0.6)	0
Pneumonia	2 (0.6)	3 (0.9)
Pulmonary embolism	2 (0.6)	2 (0.6)
Femur fracture	1 (0.3)	4 (1.1)
Pleural effusion	1 (0.3)	3 (0.9)
Cardiac failure	0	2 (0.6)
Febrile neutropenia	0	5 (1.4)
Neutrophil count decreased	0	2 (0.6)
Pneumonia bacterial	0	2 (0.6)
Septic shock	0	2 (0.6)

[a] Source Table 14.3.4.1.6.FA reflects the data from the database which includes 3 (0.8%) patients in the Dato-DXd arm with a serious adverse event of sepsis ≥ Grade 3 as assessed by the investigator. An additional event of sepsis in the Dato-DXd arm was reviewed after database lock and was deemed serious, so has been manually included in this table. The table includes AEs with an onset date or that worsen on or after the date of first dose of IP up to and including date of last IP + 35 days and prior to start of any subsequent cancer therapy. Patients with multiple occurrences are counted once per PT regardless of the number of

occurrences. Table is sorted by decreasing number of patients based on the total number of AEs for Dato-DXd arm. Grade 3: severe, Grade 4: life-threatening, Grade 5: fatal. CTCAE Version 5.0

Serious TEAEs

Table 83 Serious Treatment-emergent Adverse Events by Decreasing Frequency and Preferred Term Reported in ≥ 1% of Patients in Any Treatment Arm in Pivotal Study and BC Pool (Safety Analysis Set)

	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
Preferred Term	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Patients with any serious TEAE	54 (15.0)	64 (18.2)	62 (17.2)	67 (19.1)	67 (15.1)	75 (16.9)
Urinary tract infection	5 (1.4)	2 (0.6)	5 (1.4)	3 (0.9)	5 (1.1)	5 (1.1)
COVID-19	4 (1.1)	3 (0.9)	4 (1.1)	3 (0.9)	4 (0.9)	4 (0.9)
Pneumonia	1 (0.3)	4 (1.1)	2 (0.6)	4 (1.1)	2 (0.5)	3 (0.7)
Femur fracture	1 (0.3)	4 (1.1)	1 (0.3)	4 (1.1)	1 (0.2)	1 (0.2)
Febrile neutropenia	0	5 (1.4)	0	5 (1.4)	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarization, a subject is counted once if the subject reported one or more AEs.

Source: SCS updated (results from final analysis highlighted in the title)

Deaths

Table 84. Deaths by Primary Cause Reported in Pivotal Study and BC Pool (Safety Analysis Set)

Category	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any Deaths	77 (21.4)	87 (24.8)	220 (61.1)	206 (58.7)	121 (27.3)	264 (59.6)
Primary Cause of Death						
Adverse Event	0	4 (1.1)	1 (0.3)	4 (1.1)	1 (0.2)	2 (0.5)
Death Related to Disease Under Investigation	68 (18.9)	71 (20.2)	190 (52.8)	177 (50.4)	68 (15.3)	190 (42.9)
Disease Progression	NA [b]	NA [b]	NA [b]	NA [b]	30 (6.8)	30 (6.8)
Unknown	2 (0.6)	3 (0.9)	8 (2.2)	11 (3.1)	13 (2.9)	19 (4.3)
Other	7 (1.9)	9 (2.6)	21 (5.8)	14 (4.0)	9 (2.0)	23 (5.2)
On-Treatment Deaths [c]	5 (1.4)	14 (4.0)	6 (1.7)	14 (4.0)	7 (1.6)	8 (1.8)
Primary Cause of Death						
Adverse Event	0	3 (0.9)	0	3 (0.9)	1 (0.2)	1 (0.2)
Death Related to Disease Under Investigation	5 (1.4)	11 (3.1)	6 (1.7)	11 (3.1)	5 (1.1)	6 (1.4)
Disease Progression	NA [b]	NA [b]	NA [b]	NA [b]	1 (0.2)	1 (0.2)
Unknown	0	0	0	0	0	0
Other	0	0	0	0	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

[b] Category not applicable for individual study on the case report form field.

[c] On-Treatment Death is defined as death occurred from the start date of study treatment (inclusive) until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the first subsequent therapy (TB01)

Percentages are based on the number of subjects in the Safety Analysis Set.

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

Source: SCS updated (results from final analysis highlighted in title).

Table 85 Treatment-emergent Adverse Events Associated with Death by Preferred Term in Pivotal Study and BC Pool (Safety Analysis Set)

Preferred Term	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any Preferred Term	0 [b]	3 (0.9)	1 (0.3) [b]	3 (0.9)	1 (0.2) [b]	2 (0.5) [b]
Dyspnoea	0	0	0	0	1 (0.2)	1 (0.2)
Febrile neutropenia	0	1 (0.3)	0	1 (0.3)	0	0
Respiratory distress	0	1 (0.3)	0	1 (0.3)	0	0
Sepsis	0	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.2)

[a] TB01 (n=360) + TP01 BC (n=83).

[b] One additional subject (not included) had an event of pneumonitis and died (initially assessed by the investigator as Grade 3 and death due to disease progression) that was subsequently assessed by the ILD Adjudication Committee as fatal drug-related ILD (see section 2.1.8.1.1). If this subject were to be included, the events would increase by 1.

Source: SCS updated (results from final analysis highlighted in title).

2.6.8.4. Laboratory findings

Table 86 Haematology and clinical chemistry, maximum worsening CTCAE grade shift from baseline during treatment (safety analysis set) (FA)

Parameter	Group	Subjects at baseline [b]	Number (%) of subjects with CTCAE grade shift [a]				
			Any grade shift	1-grade shift	2-grade shift	3-grade shift	4-grade shift
Hemoglobin (g/L)	Dato-DXd (N=360)	359 (100)	133 (37.0)	114 (31.8)	17 (4.7)	2 (0.6)	0
	ICC (N=351)	340 (100)	177 (52.1)	143 (42.1)	28 (8.2)	6 (1.8)	0
Leukocytes (10^9/L)	Dato-DXd (N=360)	359 (100)	152 (42.3)	103 (28.7)	47 (13.1)	1 (0.3)	1 (0.3)
	ICC (N=351)	341 (100)	217 (63.6)	76 (22.3)	87 (25.5)	45 (13.2)	9 (2.6)
Lymphocytes (10^9/L)	Dato-DXd (N=360)	289 (100)	111 (38.4)	66 (22.8)	30 (10.4)	14 (4.8)	1 (0.3)
	ICC (N=351)	264 (100)	117 (44.3)	73 (27.7)	36 (13.6)	7 (2.7)	1 (0.4)
Neutrophils (10^9/L)	Dato-DXd (N=360)	313 (100)	101 (32.3)	42 (13.4)	54 (17.3)	5 (1.6)	0
	ICC (N=351)	288 (100)	178 (61.8)	23 (8.0)	58 (20.1)	63 (21.9)	34 (11.8)
Platelets (10^9/L)	Dato-DXd (N=360)	359 (100)	36 (10.0)	33 (9.2)	1 (0.3)	0	2 (0.6)
	ICC (N=351)	340 (100)	71 (20.9)	60 (17.6)	7 (2.1)	4 (1.2)	0
Alanine Aminotransferase (ukat/L)	Dato-DXd (N=360)	359 (100)	94 (26.2)	78 (21.7)	11 (3.1)	5 (1.4)	0
	ICC (N=351)	337 (100)	107 (31.8)	98 (29.1)	7 (2.1)	1 (0.3)	1 (0.3)

Albumin (g/L)	Dato-DXd (N=360)	358 (100)	103 (28.8)	84 (23.5)	18 (5.0)	1 (0.3)	0
	ICC (N=351)	335 (100)	79 (23.6)	66 (19.7)	13 (3.9)	0	0
Alkaline Phosphatase (ukat/L)	Dato-DXd (N=360)	359 (100)	91 (25.3)	77 (21.4)	12 (3.3)	2 (0.6)	0
	ICC (N=351)	336 (100)	73 (21.7)	63 (18.8)	8 (2.4)	2 (0.6)	0
Aspartate Aminotransferase(ukat/L)	Dato-DXd (N=360)	359 (100)	97 (27.0)	87 (24.2)	4 (1.1)	6 (1.7)	0
	ICC (N=351)	336 (100)	99 (29.5)	89 (26.5)	7 (2.1)	2 (0.6)	1 (0.3)
Calcium Corrected for Albumin (mmol/L) - Hyper	Dato-DXd (N=360)	352 (100)	20 (5.7)	9 (2.6)	9 (2.6)	2 (0.6)	0
	ICC (N=351)	332 (100)	11 (3.3)	2 (0.6)	3 (0.9)	3 (0.9)	3 (0.9)
Calcium Corrected for Albumin (mmol/L) - Hypo	Dato-DXd (N=360)	352 (100)	151 (42.9)	139 (39.5)	9 (2.6)	2 (0.6)	1 (0.3)
	ICC (N=351)	332 (100)	154 (46.4)	149 (44.9)	2 (0.6)	3 (0.9)	0
Creatinine (umol/L)	Dato-DXd (N=360)	359 (100)	50 (13.9)	21 (5.8)	21 (5.8)	2 (0.6)	6 (1.7)
	ICC (N=351)	337 (100)	43 (12.8)	24 (7.1)	16 (4.7)	3 (0.9)	0
Magnesium (mmol/L) - Hyper	Dato-DXd (N=360)	356 (100)	27 (7.6)	24 (6.7)	1 (0.3)	2 (0.6)	0
	ICC (N=351)	335 (100)	22 (6.6)	19 (5.7)	0	3 (0.9)	0
Magnesium (mmol/L) - Hypo	Dato-DXd (N=360)	356 (100)	58 (16.3)	54 (15.2)	4 (1.1)	0	0
	ICC (N=351)	335 (100)	50 (14.9)	46 (13.7)	4 (1.2)	0	0
Potassium (mmol/L) - Hyper	Dato-DXd (N=360)	359 (100)	44 (12.3)	34 (9.5)	8 (2.2)	2 (0.6)	0
	ICC (N=351)	336 (100)	26 (7.7)	19 (5.7)	7 (2.1)	0	0
Potassium (mmol/L) - Hypo	Dato-DXd (N=360)	359 (100)	48 (13.4)	43 (12.0)	2 (0.6)	3 (0.8)	0
	ICC (N=351)	336 (100)	48 (14.3)	35 (10.4)	1 (0.3)	12 (3.6)	0
Sodium (mmol/L) - Hyper	Dato-DXd (N=360)	359 (100)	28 (7.8)	28 (7.8)	0	0	0
	ICC (N=351)	336 (100)	14 (4.2)	13 (3.9)	0	0	1 (0.3)
Sodium (mmol/L) - Hypo	Dato-DXd (N=360)	359 (100)	65 (18.1)	57 (15.9)	3 (0.8)	5 (1.4)	0
	ICC (N=351)	336 (100)	68 (20.2)	60 (17.9)	3 (0.9)	4 (1.2)	1 (0.3)
Total Bilirubin (umol/L)	Dato-DXd (N=360)	359 (100)	22 (6.1)	12 (3.3)	7 (1.9)	3 (0.8)	0
	ICC (N=351)	337 (100)	44 (13.1)	25 (7.4)	15 (4.5)	4 (1.2)	0

[a] Derived from Lab assessments between the start of treatment and last dose of study medication + 35 days and prior to start of any subsequent cancer therapy, and is the maximum CTCAE grade.
[b] Subjects with a baseline value and at least one on-treatment value. Percentages have been calculated using the number of subjects with a baseline value and a post baseline value.
Baseline is the last non-missing value prior to administration of the first dose of investigational product.
CTCAE Common terminology criteria for adverse events version 5.0. ICC Investigator's choice chemotherapy.
N Number of subjects per treatment group.

Table 87 Proportion of subjects with elevated liver test based on measured laboratory values (Safety analysis set) (FA)

	Number (%) of Subjects	
Group	Dato-DXd N=360	ICC N=351
Number of subjects with measurements	359 (100)	338 (100)
Number of subjects with at least one elevated liver test	136 (37.9)	127 (37.6)
Number of subjects with elevated ALT, AST and total bilirubin	0	0
AST elevation		
>=3xULN - <=5xULN	45 (12.5)	45 (13.3)
>5xULN - <=10xULN	20 (5.6)	14 (4.1)
>10xULN - <=20xULN	7 (1.9)	6 (1.8)
>20XULN	1 (0.3)	1 (0.3)
ALT elevation		
>=3xULN - <=5xULN	23 (6.4)	24 (7.1)
>5xULN - <=10xULN	9 (2.5)	6 (1.8)
>10xULN - <=20xULN	2 (0.6)	1 (0.3)
>20XULN	1 (0.3)	1 (0.3)
AST or ALT elevation		
>=3xULN - <=5xULN	54 (15.0)	52 (15.4)
>5xULN - <=10xULN	22 (6.1)	19 (5.6)
>10xULN - <=20xULN	8 (2.2)	6 (1.8)
>20XULN	1 (0.3)	1 (0.3)
Total Bilirubin elevation		
>=1.5xULN - <=2xULN	10 (2.8)	20 (5.9)
>2X ULN	12 (3.3)	10 (3.0)
ALT or Total Bilirubin (BILI) elevation		
((ALT >= 3X ULN or AST >= 3X ULN) or (ALT >= 5X ULN or AST >= 5X ULN)) and (BILI >=2X ULN concomitantly or subsequently) [a]	7 (1.9)	6 (1.8)
ALP elevation		
>=1.5xULN - <=3xULN	115 (32.0)	91 (26.9)
>3X ULN	58 (16.2)	39 (11.5)

[a] Includes all subjects who have ALT or AST>=3xULN and total bilirubin (BILI) >=2xULN, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in BILI. The abnormalities occurring within a 28-day window. Exceptions include subjects with elevated liver enzymes (ALT or AST >=5x ULN) that have liver metastases at baseline.
Percent is calculated based on the number of subjects with measurements.
Includes measurements taken between the start of treatment and up to date of last dose + 35 days and prior to start of any subsequent cancer therapy.
ALP Alkaline phosphatase. ALT Alanine aminotransferase. AST Aspartate aminotransferase. BILI Bilirubin.
ICC Investigator's choice chemotherapy. N Number of subjects in treatment group. ULN Upper limit of normal.

In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.5. Safety in special populations

Effect of age

Overall, no notable differences were observed between the TB01 Dato-DXd arm and the BC + NSCLC 6 mg/kg pool by TEAE category across the age subgroups, except for the following (with ≥ 10% difference):

The proportion of patients with CTCAE Grade ≥ 3 TEAEs was higher in patients ≥ 65 years in study TB01 Dato-DXd arm and in the BC + NSCLC 6 mg/kg pool compared with < 65 years (40.7% and 47.7% versus 29.7% and 37.6%, respectively)

Effect of race

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined race subgroups (Caucasian/White [n = 179] and Asian [n = 142]; 97.2% and 97.9%, respectively). The number of patients in the Black/African American [n = 4] and other subgroups [n = 3] were small.

In the BC + NSCLC 6 mg/kg pool, the proportion of Caucasian/White (n = 421) and Asian (n = 378) patients with TEAEs was similar to the TB01 Dato-DXd arm (97.6% and 98.1%, respectively). The number of patients in the Black/African American subgroup [n = 16] was small, hence no meaningful inference could be drawn. A total of 72 patients were included in the Other subgroup for the BC + NSCLC 6 mg/kg pool, but no meaningful comparison could be made with the TB01 Dato-DXd arm.

Overall, no notable differences were observed between the TB01 Dato-DXd arm and the BC + NSCLC 6 mg/kg pool by TEAE category across the predefined race subgroups (i.e. Caucasian/White and Asian), except for the following (with ≥ 10% difference):

The proportion of Caucasian/White patients in the TB01 Dato-DXd arm with CTCAE Grade ≥ 3 TEAEs was lower compared with the BC + NSCLC 6 mg/kg pool (34.6% versus 46.1%, respectively) and driven by the NSCLC 6 mg/kg pool (53.9%).

However, the proportion of patients with treatment related CTCAE Grade ≥ 3 TEAEs was similar between the TB01 Dato-DXd arm and BC + NSCLC 6 mg/kg pool.

No further data on persons of Black/African American and Other race are presented due to low numbers.

Effect of Ethnicity

Overall, the data suggest that the safety profile of Dato-DXd was not affected by ethnicity.

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined ethnicity subgroups (Hispanic/Latino [n = 39] and Other [n = 321]; 97.4% and 97.2%, respectively). In the BC + NSCLC 6 mg/kg pool, the proportion of patients with TEAEs in the Hispanic/Latino (n = 70) and Other (n = 857) subgroups was similar with the TB01 Dato-DXd arm (97.1% and 98.0%, respectively).

Overall, no notable differences (ie, with ≥ 10% difference) were observed between the TB01 Dato-DXd arm and the BC + NSCLC 6 mg/kg pool by TEAE category or AESI category across the ethnicity subgroups.

Effect of ECOG Performance Status

Overall, the data suggest that the safety profile of Dato-DXd was not affected by ECOG PS.

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined ECOG subgroups (PS 0 [n = 196] and PS 1 [n = 161]; 96.9% and 97.5%, respectively. In the BC + NSCLC 6 mg/kg pool, the proportion of patients with TEAEs in the ECOG PS 0 (n = 376) and PS 1 (n = 546) subgroups was similar with the TB01 Dato-DXd arm (97.9% and 98.0%, respectively).

Overall, no notable difference was observed between the TB01 Dato-DXd arm and the BC + NSCLC 6 mg/kg pool by TEAE and AESI category. Exceptions were as follows (with ≥ 10% difference):

Lower proportions of patients with ECOG PS 1 in the TB01 Dato-DXd arm compared with the BC + NSCLC 6 mg/kg pool experienced SAEs (13.0% versus 27.1%, respectively). This difference was driven by higher SAE rates in the NSCLC 6 mg/kg pool (n = 339; 34.5%).

Effect of Baseline Brain Metastases

Overall, the data suggest that the safety profile of Dato-DXd was not affected by baseline brain metastases.

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined baseline brain metastases subgroups (Yes [n = 35] and No [n = 325]; 91.4% and 97.8%, respectively). In the BC + NSCLC 6 mg/kg pool, the proportion of patients with TEAEs in the Yes (n = 143) and No (n = 784) subgroups were similar with the TB01 Dato-DXd arm (95.8% and 98.3%, respectively).

Overall, no notable differences were observed between the TB01 Dato-DXd arm and the BC + NSCLC 6 mg/kg pool by TEAE category or AESI category across the baseline brain metastases subgroups, except for the following (with ≥ 10% difference):

In the TB01 Dato-DXd arm, a lower proportion of patients with baseline brain metastases compared with patients without metastases had treatment-related TEAEs (82.9% versus 94.8%, respectively).

Effect of Renal Function at Baseline

Overall, the data suggest that the safety profile of Dato-DXd was not affected by renal function status at baseline (normal, mild, moderate, and severe impairment). The comparison was done only between the normal, mild, and moderate renal function status at baseline subgroups due to small sample size in the severe renal impairment subgroup.

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined baseline renal function subgroups (normal [n = 178], mild [n = 142], and moderate [n = 40]; 96.6%, 97.9%, and 97.5%, respectively). In the BC + NSCLC 6 mg/kg pool, the proportion of patients with TEAEs in the normal (n = 403), mild (n = 382), and moderate (n = 141) subgroups was similar with the TB01 Dato-DXd arm (97.8%, 98.2%, and 97.9%, respectively).

Effect of Hepatic Function at Baseline

Overall, the data suggest that the safety profile of Dato-DXd was not affected by hepatic function status at baseline. The comparison was done only between the normal and mild hepatic function status at baseline subgroups due to small sample size in the moderate (n ≤ 6) and severe (n = 1) hepatic impairment subgroup.

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined baseline hepatic function subgroups (normal [n = 184] and mild [n = 170]; 96.7% and 97.6%, respectively). In the BC + NSCLC 6 mg/kg pool, the proportion of patients with TEAEs in the normal and mild baseline hepatic function subgroups was similar with the TB01 Dato-DXd arm (97.8% and 98.2%, respectively).

Effect of Region

Overall, the data suggest that the safety profile of Dato-DXd was not affected by region.

In the TB01 Dato-DXd arm, the proportion of patients with TEAEs was similar between the predefined region subgroups (US/Canada/Europe [n = 185] and RoW [n = 175]; 96.2% and 98.3%, respectively). In the BC + NSCLC 6 mg/kg pool, the proportion of patients with TEAEs in the US/Canada/Europe (n = 522) and RoW (n = 405) subgroups was similar with the TB01 Dato-DXd arm (97.9% and 98.0%, respectively).

2.6.8.6. Immunological events

For information on immunological events, please see sections Clinical pharmacology.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies with Dato-DXd were conducted.

2.6.8.8. Discontinuation due to adverse events

Dose Reductions

Table 88 Treatment-emergent Adverse Events Leading to a Dose Reduction by Preferred Term Reported in ≥ 1% of Patients in Any Treatment Arm in Pivotal Study and BC Pool (Safety Analysis Set)

	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
Preferred Term	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Patients with any TEAE leading to dose reduction	83 (23.1)	113 (32.2)	95 (26.4)	113 (32.2)	94 (21.2)	106 (23.9)
Stomatitis	44 (12.2)	5 (1.4)	45 (12.5)	5 (1.4)	50 (11.3)	51 (11.5)
Fatigue	6 (1.7)	6 (1.7)	6 (1.7)	6 (1.7)	9 (2.0)	9 (2.0)
Nausea	9 (2.5)	4 (1.1)	8 (2.2)	4 (1.1)	9 (2.0)	8 (1.8)
Weight decreased	7 (1.9)	2 (0.6)	8 (2.2)	2 (0.6)	7 (1.6)	8 (1.8)
Asthenia	5 (1.4)	2 (0.6)	5 (1.4)	2 (0.6)	5 (1.1)	5 (1.1)
Anaemia	1 (0.3)	4 (1.1)	1 (0.3)	4 (1.1)	1 (0.2)	1 (0.2)
Diarrhoea	1 (0.3)	8 (2.3)	1 (0.3)	8 (2.3)	1 (0.2)	1 (0.2)
Neutropenia	1 (0.3)	23 (6.6)	1 (0.3)	24 (6.8)	1 (0.2)	1 (0.2)
Neuropathy peripheral	0	4 (1.1)	0	4 (1.1)	0	0
Neutrophil count decreased	0	23 (6.6)	0	24 (6.8)	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	12 (3.4)	0	12 (3.4)	0	0
White blood cell count decreased	0	5 (1.4)	0	5 (1.4)	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarization, a subject is counted once if the subject reported one or more AEs.

Treatment interruptions

Table 89 Adverse Events Leading to Study Treatment Interruption by Preferred Term Reported in ≥ 1% Patients in Any Treatment Arm in Pivotal Study and BC Pool (Safety Analysis Set) (includes dose delay and infusion interruption):

	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
Preferred Term	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any AE leading to drug interruption	78 (21.7)	120 (34.2)	95 (26.4)	119 (33.9)	104 (23.5)	121 (27.3)
Stomatitis	6 (1.7)	3 (0.9)	8 (2.2)	3 (0.9)	20 (4.5)	22 (5.0)
COVID-19	12 (3.3)	14 (4.0)	16 (4.4)	15 (4.3)	13 (2.9)	17 (3.8)
Fatigue	5 (1.4)	2 (0.6)	6 (1.7)	2 (0.6)	7 (1.6)	8 (1.8)
Infusion related reaction	5 (1.4)	0	5 (1.4)	0	5 (1.1)	5 (1.1)
Interstitial lung disease	5 (1.4)	0	5 (1.4)	0	5 (1.1)	5 (1.1)
Pneumonia	3 (0.8)	1 (0.3)	5 (1.4)	1 (0.3)	3 (0.7)	5 (1.1)
Anaemia	3 (0.8)	4 (1.1)	4 (1.1)	3 (0.9)	3 (0.7)	4 (0.9)
Decreased appetite	3 (0.8)	5 (1.4)	4 (1.1)	1 (0.3)	3 (0.7)	4 (0.9)
Upper respiratory tract infection	3 (0.8)	5 (1.4)	4 (1.1)	5 (1.4)	3 (0.7)	4 (0.9)
Asthenia	1 (0.3)	4 (1.1)	2 (0.6)	3 (0.9)	1 (0.2)	2 (0.5)
Diarrhoea	2 (0.6)	4 (1.1)	2 (0.6)	4 (1.1)	2 (0.5)	2 (0.5)
Pyrexia	2 (0.6)	5 (1.4)	2 (0.6)	5 (1.4)	2 (0.5)	2 (0.5)
Leukopenia	0	6 (1.7)	0	6 (1.7)	0	0
Neutropenia	0	38 (10.8)	0	38 (10.8)	0	0
Neutrophil count decreased	0	27 (7.7)	0	27 (7.7)	0	0
Thrombocytopenia	0	4 (1.1)	0	4 (1.1)	0	0
White blood cell count decreased	0	4 (1.1)	0	4 (1.1)	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarization, a subject is counted once if the subject reported one or more AEs.

Drug interrupted includes both infusion interruption and dose delay.

Source: SCS updated (results from final analysis highlighted in the title).

Discontinuations Due to Adverse Events

Table 90 Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment by Preferred Term in Pivotal Study and BC Pool Studies (Safety Analysis Set)

	Number (%) of Patients					
	Pivotal Study TB01				BC Pool [a]	
	IA1		FA		IA1	FA
Preferred Term	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 360	ICC N = 351	Dato-DXd 6 mg/kg N = 443	Dato-DXd 6 mg/kg N = 443
Any TEAE leading to discontinuation of study treatment	11 (3.1)	10 (2.8)	15 (4.2)	11 (3.1)	17 (3.8)	21 (4.7)
Pneumonitis	2 (0.6)	0	3 (0.8)	0	5 (1.1)	6 (1.4)
Interstitial lung disease	3 (0.8)	0	3 (0.8)	0	3 (0.7)	3 (0.7)
Dry eye	1 (0.3)	0	2 (0.6)	0	1 (0.2)	2 (0.5)
Stomatitis	1 (0.3)	0	1 (0.3)	0	2 (0.5)	2 (0.5)
Anal inflammation	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Brain oedema	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Bronchospasm	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Fatigue	2 (0.6)	0	1 (0.3)	0	2 (0.5)	1 (0.2)
Keratitis	0	0	0	0	1 (0.2)	1 (0.2)
Keratopathy	0	0	0	0	1 (0.2)	1 (0.2)
Muscular weakness	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Punctate keratitis	0	0	1 (0.3)	0	0	1 (0.2)
Radiation necrosis	0	0	1 (0.3)	0	0	1 (0.2)
Rash	0	0	1 (0.3)	0	0	1 (0.2)
Angina pectoris	0	1 (0.3)	0	1 (0.3)	0	0
COVID-19	0	1 (0.3)	0	1 (0.3)	0	0
Gastrointestinal haemorrhage	0	0	0	1 (0.3)	0	0
Hepatic function abnormal	0	1 (0.3)	0	1 (0.3)	0	0
Meningitis tuberculous	0	1 (0.3)	0	1 (0.3)	0	0
Neuropathy peripheral	0	1 (0.3)	0	1 (0.3)	0	0
Neutropenia	0	1 (0.3)	0	1 (0.3)	0	0
Neutropenic colitis	0	1 (0.3)	0	1 (0.3)	0	0
Paraesthesia	0	1 (0.3)	0	1 (0.3)	0	0
Peripheral sensory neuropathy	0	1 (0.3)	0	1 (0.3)	0	0
Thrombocytopenia	0	1 (0.3)	0	1 (0.3)	0	0

[a] TB01 (n=360) + TP01 BC (n=83).

Percentages are based on the number of subjects in the Safety Analysis Set. TEAEs were coded using the MedDRA Version 26.0 and graded using the NCI CTCAE (NCI CTCAE version 5.0 for TB01 and NCI CTCAE version 4.03 before protocol amendment version 5.0 and NCI CTCAE version 5.0 afterwards for TP01).

A TEAE is defined as an AE with a start or worsening date on or after the start of study treatment until 35 days since the last dose of study treatment (TP01), or earliest date between 35 days since the last dose of treatment and the start date of the 1st subsequent therapy (TB01).

Radiotherapy is not considered as a subsequent anti-cancer therapy in TB01.

At each level of summarization, a subject is counted once if the subject reported one or more AEs.

2.6.8.9. Post marketing experience

No post-marketing data are available, as Dato-DXd is not yet approved in any country.

2.6.9. Discussion on clinical safety

Safety data collection: Data for the evaluation of the safety of Dato-DXd treatment in HR-pos/HER2- breast cancer are derived from the pivotal randomised, open-label phase III trial TB01 with supportive data contributed by breast cancer patients from the TP01 study. The Applicant defines the primary safety population for the Dato-DXd in BC application as N=443 patients (360 and 41 HR+ HER2-from TB01 and TP01, respectively, and 42 TNBC from TP01). The frequency of ADRs in the SmPC was estimated based on this defined primary safety population and using all-causality frequency. This approach is considered acceptable.

Patient exposure: During the procedure, the applicant provided updated safety based on the final analysis (FA) (DCO 24 JULY 2024). Compared to IA2 (DCO 17 JULY 2023) the median treatment duration was unchanged at 6.8 months.

Summary safety profile: At FA, most subjects had at least 1 TEAE, and 35% subjects treated with Dato-DXd had TEAEs of Grade ≥3, compared to 55% for the ICC arm. SAEs were reported in 17.2% of subjects treated with Dato-DXd vs. 19.1% for ICC and TEAEs associated with death by the investigator were reported in one instance in the Dato-DXd arm (0.3%) vs three the ICC arm (0.9%). In addition to the one event in the Dato-DXd arm above, one event of pneumonitis in the Dato-DXd arm was adjudicated as a fatal drug- related ILD. Most AEs were also considered drug-related in both treatment arms. Drug-related TEAEs of Grade ≥3 were reported at a lower frequency in the Dato-DXd arm compared to ICC (22.2% vs. 45.6%), and drug-related SAEs were also reported at a lower frequency (6.1% vs. 9.1%). TEAEs associated with drug discontinuation occurred at low and comparable rates (4.2% in Dato-DXd arm vs 3.1%). TEAEs associated with dose reduction and dose delay occurred at a lower incidence with Dato-DXd compared to ICC; 26.4% vs. 32.2%, and 26.4% vs. 33.9%, respectively.

Overall, the summary of safety profile indicates that treatment with Dato-DXd at the recommended dose has a different and at least in some respects, improved, safety profile compared to ICC based on TEAEs of Grade ≥3 and SAEs.

Adverse events: At the FA (DCO 24 JULY 2024), similar proportions of patients experienced any TEAE in the Dato-DXd (98.1%) and control-arm (96.6%) while Grade ≥3 TEAEs (Dato-DXd = 35% vs. 55.6% among controls), SAEs (17.2% vs. 19.1%), dose reductions (26.4% vs. 32.2%) and drug interruptions (26.4% vs. 33.9%) were lower in the Dato-DXd arm. The system organ classes with the most frequently reported TEAEs (>50%) in both treatment arms were Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders (note data from IA2). The most commonly reported TEAEs for Dato-DXd were nausea (56.7%), stomatitis (52.5%), alopecia (37.8%), constipation (35%), fatigue (28.6%), dry eye (26.9%), and vomiting (24.4%). All were reported in a higher proportion of patients in the Dato-DXd arm than in the ICC arm (≥10% difference, except for fatigue). Other frequently reported TEAEs were decreased appetite (16.1%), anaemia (17.2%), AST increased (16.9%), asthenia (15.6%), and COVID-19 (20.6%). TEAEs reported in at least 5% of subjects in either treatment arm at ≥2-fold higher incidences in the Dato-DXd arm included pruritis, keratitis, rash, dry mouth, and blephatitis. Conversely, the most frequently reported TEAEs in the chemotherapy arm included nausea (but at a lower frequency than with Dato-DXd), neutropenia, anaemia, alopecia (again, lower frequency than in Dato-DXd arm), neutrophil count decreased, and fatigue (lower frequency than Dato-DXd). These were in line with the known safety profile of the ICC. There were no data provided per type of ICC, the most

commonly used drugs in the comparator arm being eribulin (60%) and capecitabine (21%). The safety profile of Dato-DXd is clinically different from these drugs where safety is more dominated by haematological toxicity (especially eribulin) and hand-foot syndrome (capecitabine). Use of symptomatic management was in general higher in the Dato-DXd arm and related to the prevention/occurrence of nausea and the adverse events of interests like stomatitis and ocular toxicities. Use of G-CSF was more prevalent in the comparator arm.

Despite the greater risk of neutropenia and febrile neutropenia in the chemotherapy arm, it appears that infections and infestations in general are much more common in the Dato-DXd arm than in the chemotherapy arm (55.6% vs 37.9%). Eye and oral infections (e.g., oropharyngeal candidiasis, periodontitis, pharyngitis) account for the majority of infections that prevailed in the Dato-DXd datasets in comparison to ICC. To note, upper respiratory tract infections, COVID and urinary tract infections had similar incidence regardless of arm. Grade ≥3 infections and infestations were balanced between the two arms.

Overall, most TEAEs with Dato-DXd were grade 1 or 2 and the most commonly reported Grade ≥3 TEAE were stomatitis (6.4%), anaemia and AST increased (each 2.8%), and fatigue (2.5%). This is in line with the known safety profile of topoisomerase inhibitors (e.g. gastrointestinal toxicity) and the nonclinical findings (e.g. corneal and skin toxicity).

≥G3 adverse events: The overall incidence of ≥G3 AEs was higher in the ICC arm (55.6%) in comparison to Dato-DXd (35%). It seems that the driver for this difference was haematological toxicity from chemotherapy and this is confirmed in the investigations SOC. It is to note, however, that ≥G3 GI disorders occurred in twice as many patients in the Dato-DXd datasets in comparison to ICC. A similar pattern emerges in respiratory disorders.

Adverse drug reactions: Treatment-related TEAEs were more common in the Dato-DXd arm (94.7% vs. 86.3%) while treatment-related TEAE of Grade ≥3 were lower in the Dato-DXd arm compared to chemotherapy (22.2% vs. 45.6%). The most commonly observed ADRs associated with Dato-DXd treatment included: stomatitis, nausea, alopecia, fatigue and dry eye. Prophylactic treatment with antiemetics was recommended during the study and a recommendation is included in section 4.2 of the SmPC.

Adverse events of special interest: Five AESIs have been identified for Dato-DXd: ILD/pneumonitis, infusion-related reactions, oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis and ocular surface toxicity.

ILD/pneumonitis:

Cases of interstitial lung disease (ILD), including pneumonitis, have been reported in patients treated with Datroway. Fatal outcomes have been observed.

Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. ≥ 0.5 mg/kg/day prednisolone or equivalent). Datroway should be delayed until recovery to Grade 0 and may be resumed according to instructions in Table 2. For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g. ≥ 1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Datroway should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis. Patients with a history of

ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis and should be monitored carefully (see sections 4.2, 4.4 and 4.8 of the SmPC).

Ocular surface toxicity: Ocular surface toxicity including keratitis was reported in a higher proportion of subjects in the Dato-DXd arm than in the ICC arm (51.4% vs. 22.8%). The most common PTs in the AESI of ocular surface toxicity in the Dato-DXd arm were dry eye (26.9%), punctuate keratitis (12.2%), keratitis (8.3%), blepharitis (7.8%), and lacrimation increased (7.8%). Most of these corresponded to dry eye, keratitis and punctate keratitis, with 1 case of ulcerative keratitis. The majority of events were mild or moderate. Seven subjects (1.9%) reported ocular surface toxicity events of grade ≥3 in the Dato-DXd arm and no grade 4 or 5 events were observed. Events resulted in dose delay (n=14, 3.9%), or dose reduction (n=10, 2.8%), and three subjects (0.8%) discontinued from study treatment. Dose modifications have been included in the SmPC section 4.2 for keratitis.

The following precautionary measures have been reflected in section 4.4 of the SmPC and are in line with the study protocol. Patients should be advised to use preservative-free lubricant eye drops several times daily for prophylaxis. Patients should be advised to avoid use of contact lenses unless directed by an eye care professional. Patients should be promptly referred for appropriate ophthalmologic assessments for any new or worsening ocular signs and symptoms that could suggest keratitis. Keratitis should be monitored and if diagnosis is confirmed, Datroway should be dose delayed, dose reduced, or permanently discontinued (see sections 4.2, 4.4 and 4.8 of the SmPC).

Oral mucositis/stomatitis: A significantly higher proportion of patients in the Dato-DXd arm had an AESI of oral mucositis/stomatitis in the Dato-DXd arm compared with in the ICC arm (60% versus 17.4%, respectively). The most commonly reported preferred term contributing to oral mucositis/stomatitis AESIs in the Dato-DXd arm was stomatitis (52.5%). Most events were grade 1 or 2, while grade 3 events occurred in 7.2% of subjects in the Dato-DXD arm. Events were predominantly managed by dose reduction (14.2%) and dose interruption and discontinuation were observed at low rates (2.8% and 0.3%, respectively). Section 4.4 of the SmPC reflects that , in addition to practicing good oral hygiene, when starting Datroway and throughout treatment, daily use of a steroid-containing mouthwash (e.g. dexamethasone oral solution 0.1 mg/mL 4 times daily or a similar steroid-containing mouthwash regimen) is recommended for prophylaxis and treatment. Where clinically indicated, antifungal agents may be considered in accordance with local guidelines. In the absence of a prophylactic steroid-containing mouthwash, use of bland mouth rinses (e.g. a non-alcoholic and/or bicarbonate-containing mouthwash) per local guidelines is recommended. Ice chips or ice water held in the mouth throughout the infusion may also be considered. If stomatitis does occur, frequency of mouthwashes may be increased and/or other topical treatments may be used. Based on the severity of the adverse reaction, the administration of Datroway should be delayed, the dose reduced, or permanently discontinued (see sections 4.2, 4.4 and 4.8 of the SmPC).

Mucosal inflammation other than oral mucositis/stomatitis is an identified risk for Dato-DXd and an AESI based on the available clinical and non-clinical experience with Dato-DXd. However, the reported frequency was low with four subjects (1.1%) reporting an event in the Dato-DXd arm and no additional risks minimisation measures are planned or needed.

Infusion-related reaction (IRR): As per FA, IRRs occurred in 9.4% of subjects in the Dato-DXd arm and the frequency was higher than observed in the ICC arm (3.7%). Most common IRR by PT in the Dato-DXd arm were infusion-related reaction and pruritus. Most events were grade 1 or 2, and only 1 grade 3 event was reported. Only a few patients required dose interruption (1.4%) and one patient discontinued study treatment.

Section 4.2 adequately states the recommended use of premedication in line with the study protocol, stating that prior to each infusion of Datroway, a premedication regimen for the prevention of infusion-related reactions that consists of an antihistamine and paracetamol (with or without glucocorticoids)

should be considered (see SmPC section 4.8). It is also recommended that patients receive prophylactic antiemetic agents (dexamethasone with 5-HT3 antagonists as well as other medicinal products, such as NK1 receptor antagonists) prior to infusion of Datroway and on subsequent days as needed.

Serious AEs: A total of 17.2% subjects in the Dato-DXd arm and 19.1% of subjects in the ICC arm had at least 1 serious TEAE. Urinary tract infection (1.4%), COVID-19 (1.1%) and pneumonia (0.6%) were the most frequently reported SAEs in the Dato-DXd arm. Drug-related SAEs were reported in 6.1% of subjects in the Dato-DXd arm and 9.1% in the ICC arm. Pneumonitis (0.8%) (plus 1 case of ILD (0.3%)), hemiparesis and urinary tract infections (each 0.6%) were the most frequently reported drug-related SAEs.

Deaths: On-treatment deaths were reported in 1.7% of subjects in the Dato-DXd arm and 4.0% of subjects in the ICC arm, with the primary cause being death related to disease under investigation in both arms. One fatal TEAE was reported in the Dato-DXd arm by the investigator vs 4 fatal AEs in the ICC arm. However, one patient in the Dato-DXd arm had an event of pneumonitis that was adjudicated as fatal drug-related ILD in addition to the one sepsis event classified as fatal TEAE in the Dato-DXd arm.

Dose modifications: Dose reductions were less frequent in the Dato-DXd arm (26.4%) compared to the control arm (32.2%). In the Dato-DXd arm, the most frequently reported TEAE leading to dose reduction was stomatitis (12.5% vs 1.4% in the control arm). Treatment interruptions/dose delays were less frequent in the Dato-DXd arm (26.4%) compared to the control arm (33.9%). In the Dato-DXd arm, the most frequently reported TEAE leading to treatment interruptions/dose delays was COVID-19 (4.4% vs 4.3% in the control arm). Discontinuations due to AEs were seen at similar frequency in the Dato-DXd and control arms (4.2% vs 3.1%).

Most subjects had one delay of treatment, mostly due to AEs. Most patients with a dose delay of Dato-DXD had a dose delay ≤21 days and <10 patients had a maximum dose delay between 40-62 days. Dose delay did not negatively impact mPFS based on the provided post-hoc analyses (data not shown).

Immunogenicity: The prevalence and incidence of ADA to Dato-DXd were 19.6% and 15.3%, respectively. The ADA response appears to be transient (disappear after cycle 2). The incidence of treatment-emergent NAb was 2%. There was no apparent effect of immunogenicity on safety of Dato-DXd, except for a higher rate of IRR among treatment-emergent ADA positive patients (18.5% versus 7.4% in ADA-negative patients).

Safety in special populations:

Age: Of the 443 patients with breast cancer treated with Datroway 6 mg/kg, 23.3% were 65 years or older and 4.7% were 75 years or older. Data are limited to establish the safety in patients 85 years or older.aThere was a numerically higher proportion of Grade 3/4 adverse reactions (23.3% vs 22.6%), serious adverse reactions (6.8% vs 3.5%) and adverse reactions leading to discontinuation (3.9% vs 3.5%) observed in patients aged 65 years or older compared to patients younger than 65 years old (see section 4.8 of the SmPC).

The overall frequency of any study treatment-related TEAEs was similar regardless of Ethnicity.

In patients with moderate renal impairment at baseline who received datopotamab deruxtecan 6 mg/kg, a higher incidence of serious adverse reactions was observed compared to those with normal renal function. In terms of race (Caucasian vs Asian), Caucasian/white patients had a higher risk of dose reductions, SAEs and ≥G3 SAEs. Patients with brain metastasis suffered more SAEs compared to those without. Patients with moderately impaired renal function (no assessment of persons with severe impairment) suffered more ≥G3 AEs and SAEs (including ≥G3 SAEs) but fewer treatment-related AEs,

compared to those with normal or mildly impaired renal function. PS (ECOG 0 vs 1) did not seem to correlate with any particular signal of risk.

Relevant safety information in patients with renal or hepatic impairment and in elderly is included in various sections in the SmPC. More specifically, section 4.4 states that there are limited data in patients with moderate hepatic impairment and severe hepatic impairment. As metabolism and biliary excretion are the primary routes of elimination of the topoisomerase I inhibitor, DXd, Datroway should be administered with caution in patients with moderate and severe hepatic impairment (see sections 4.2 and 5.2).

Laboratory and other findings:

Haematology: Most subjects had normal or CTCAE grade 1 for haematology tests at baseline and post-baseline worst grade of Grade 3 or 4 was reported in a limited number of subjects (<5%), except for lymphocytes (9 %). The majority of shifts from baseline were 1-grade or 2-grade. Haematological toxicities are well- known with ADCs due to their payload, however, except for anaemia this appears less frequent with Dato-DXd. Though observed at relatively low frequencies, TEAEs of leukopenia (3.6%), white blood cell decreased (5.0%), neutropenia (5.8%), neutrophil count decreased (6.9%), and platelet count decreased (2.5%) were reported.

Clinical chemistry: In both treatment arms, clinical chemistry values remained generally consistent over time, with no clinically relevant changes in median values of clinical chemistry parameters observed during treatment in the majority of patients. The majority of CTCAE grade shifts were 1-grade shifts, with only a small proportion of patients (about 2%) in the Dato-DXd developing a 3-grade or 4-grade shift.

Liver function tests: At baseline, 47.2% subjects in the Dato-DXd arm had mild liver impairment. Overall, no subjects in the Dato-DXd arm had postbaseline LFT values that met the biochemical criteria for potential Hy's Law. There were 6 potential cases which were being assessed as being due to disease progression or underlying disease. The proportion of patients with concurrent ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN was 3.3%. Increases in AST and ALT were reported in 16.9% and 10.6% of subjects respectively, and over half of these were considered drug-related by the investigator.

Renal function tests: A total of 142 (39.4%) subjects had mild renal impairment and 40 (11.1%) had moderate renal impairment at baseline.

The majority of patients had a shift from normal renal function at baseline to mild renal impairment postbaseline (39.4%) or normal renal function at baseline to moderate renal function postbaseline (11.1%). No patients in the Dato-DXd arm had a shift from normal renal function at baseline to severe renal function postbaseline.

Vital signs: No safety signals were identified.

Electrocardiogram: A total of 13.6% of subjects had an increase in QTcF from baseline of >30 ms and 6.1% had an increase from baseline >60 ms. Four subjects (3.0%) had a new QTcF interval > 500 ms. Cardiac disorders were reported for 19 (5.3%) patients in the Dato-DXd arm and 9 (2.6%) in the ICC. There was one subject with ejection fraction decreased. Individual cardiac disorder preferred terms were reported in few patients in either treatment arm. There is no signal for cardiotoxicity.

Interactions – extrinsic/intrinsic factors: These subgroup analyses for safety were performed for the pooled studies only. According to the Applicant, the data suggest that the safety profile of Dato-DXd was not affected by age. However, the proportion of patients with CTCAE Grade ≥3 TEAEs was higher in patients ≥65 years in the BC + NSCLC 6 mg/kg pool compared with < 65 years (47.7% versus 37.6%, respectively).

In the pivotal study lower proportions of patients with normal and mild baseline renal function had a grade ≥3 TEAEs compared with patients with moderate renal function (31.5%, 28.9%, and 50.0%, respectively). No notable difference was reported in the incidence of AESIs between the subgroups in the TB01 Dato-DXd arm or in the BC + NSCLC 6 mg/kg pool.

A total of 47.2% of subjects had mild hepatic impairment at baseline, few patients had moderate or severe hepatic impairment. Overall, the data suggest that the safety profile of Dato-DXd was not affected by hepatic function status at baseline.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of Dato-DXd in the proposed indication of patients diagnosed with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer, who have received prior endocrine therapy and at least one additional systemic therapy, is non-negligible but overall acceptable and most events are clinically manageable by dose modifications and supportive treatments. The overall safety profile is different to but likely slightly improved compared to the current standard of care (chemotherapy) based on TEAEs of Grade ≥3 and SAEs. The safety profile is mainly characterized by GI events, skin toxicities and ocular surface toxicity. The main safety issue is ILD/pneumonitis including at least one fatal event, despite adequate risk minimization measures in the SmPC. Furthermore, one death due to sepsis was seen.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 91 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Interstitial lung disease / pneumonitis Keratitis
Important potential risks	Embryo-foetal toxicity

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 92 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 Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Keratitis	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 • Legal status: Prescription-only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 • Legal status: Prescription-only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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 27.12.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Datroway (datopotamab 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 assessment

3.1. Therapeutic context

3.1.1. Disease or condition

Datroway as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer, who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

3.1.2. Available therapies and unmet medical need

In the targeted patient population, which is patients with unresectable or metastatic HR-positive, HER2-negative breast cancer, who have received endocrine therapy, single-agent chemotherapy is considered the standard of care (SOC), such as anthracyclines (if no prior use), eribulin, capecitabine, gemcitabine, vinorelbine, taxanes (Cardoso et al 2018, ESMO 2023, NCCN 2023). Recently, ADCs have also been approved for the treatment of advanced breast cancer, so current treatment guidelines now include sacituzumab govitecan and trastuzumab deruxtecan as systemic therapy options for the targeted patient population with HR-positive and HER2 negative/HER2-low breast cancer, respectively (ESMO 2023, Moy et al 2022, NCCN 2023).

Despite these advances, there remains a high unmet medical need for new therapeutic options that would provide a clinically meaningful delay in time to progression and improved survival.

3.1.3. Main clinical studies

Pivotal evidence was submitted from the pivotal study TROPION-Breast01, which is a phase 3, open-label, randomised study of Dato-DXd versus single-agent chemotherapy of Investigator's choice (ICC) in patients with unresectable or metastatic HR-positive, HER2-negative breast cancer, who have been treated with one or 2 prior lines of systemic therapy.

3.2. Favourable effects

The presented data is from the primary and final analysis of PFS, DCO 29 April 2024 and final analysis of OS, DCO 24 July 2024.

The dual endpoint of **PFS by BICR** was met and showed a statistically significant improvement of 2 months from 4.9 months for ICC to 6.9 months with Dato-DXd, HR 0.63 (95%CI: 0.52, 0.76). The PFS data is mature at the time of the primary and final analysis of PFS as 58.1% events in the Dato-DXd arm and 64.0% events in the ICC arm were observed, respectively.

The other dual primary endpoint was **OS** and there were 61.1% and 58.0% of events in the Dato-DXd and the ICC arm, respectively. Hence, the OS data is now mature after a median follow-up of ~22months for OS. The median OS in the Dato-DXd arm was 18.6 months, while the median OS was 18.3 months in the ICC arm, resulting in a final OS HR of 1.01 (95%CI: 0.83-1.22).

Relevant secondary endpoints were: PFS by investigator (INV), ORR, DoR, and PFS2.

PFS by INV at the primary analysis was 6.9 vs 4.9 months in the Dato-DXd arm vs ICC, respectively, HR 0.64 (0.53, 0.76); which is in line with the PFS by BICR results. The updated PFS by INV at IA2 (HR 0.64; 95%CI 0.54, 0.75; median PFS 6.9 months vs 4.5 months for Dato-DXd vs ICC, respectively) is consistent with the results from the primary analysis. No updated PFS by BICR analysis was provided.

The confirmed **ORR by BICR** was 36.44% for Dato-DXd vs 22.89% for ICC.

The median DoR was 1 month longer in the Dato-DXd arm (6.7 months) than in the ICC arm (5.7 months), with a similar median time to onset of response (2.7 months for Dato-DXd and 2.6 months for ICC).

Time from randomisation to second progression (PFS2) was 12.7 months with Dato-DXd vs 10.4 months on ICC, HR 0.71 (95%CI: 0.55, 0.92).

3.3. Uncertainties and limitations about favourable effects

Most of the patients in the control arm received either eribulin (59.9%), followed by capecitabine (20.7%), vinorelbine (10.4%), and gemcitabine (9.0%). In the ICC arm, 43% of patients had not received prior anthracyclines and/or taxanes. For this reason, the performance of the control arm may be hypothesised to be inferior to what could have been expected if inclusion of anthracyclines and taxanes had been allowed. This leads to the uncertainty that the actual PFS benefit of Dato-DXd in clinical practice compared to chemotherapy may be lower.

3.4. Unfavourable effects

At final analysis (DCO 24-JUL-2024), similar proportions of patients experienced **any TEAE** in the Dato-DXd (98.1%) and control-arm (96.6%) while **Grade ≥3 TEAEs** (Dato-DXd = 35% vs. 55.6% among controls), **SAEs** (17.2% vs. 19.1%), **dose reductions** (26.4% vs. 32.2%) and **drug interruptions** (26.4% vs. 33.9%) were lower in the Dato-DXd arm. The most frequently reported TEAEs in the Dato-DXd arm included nausea, stomatitis, alopecia, constipation, fatigue, dry eye, and vomiting. All were reported in a higher proportion of patients in the Dato-DXd arm than in the chemotherapy arm.

Infections and infestations in general are more common in the Dato-DXd arm than in the chemotherapy arm (55.6% vs 37.9%), while grade ≥3 infections and infestations were balanced between the two arms.

Treatment-related TEAEs were more common in the Dato-DXd arm (94.7% vs. 86.3%) while treatment-related TEAE of Grade ≥3 were lower in the Dato-DXd arm compared to chemotherapy (22.2% vs. 45.6%). The most commonly observed ADRs associated with Dato-DXd treatment

included: stomatitis, nausea, alopecia, fatigue and dry eye. There were more Grade ≥3 TEAEs, SAEs and Grade ≥3 SAEs in subjects with moderate renal function impairment.

Adjudicated drug-related ILD occurred in 4.2% (n=15) of subjects, three (0.8%) subjects experienced Grade ≥3 events and one subject (0.3%) experienced a Grade 5 event. Ocular surface toxicity was reported in 48.6% of subjects, the most common AEs by PT were dry eye (26.9%), punctuate keratitis (12.2%), keratitis (8.3%), blepharitis (7.8%), and lacrimation increased (7.2%). Keratitis (Grouped term) was reported in 17.8% of subjects (BC-pool).

Serious AEs and possibly related serious ADRs were more commonly observed in the chemotherapy arm compared to the Dato-DXd arm in study TB01.

Overall, similar proportions of deaths were reported in the Dato-DXd and chemotherapy arms (albeit numerically slightly lower in the Dato-DXd arm (21.4% vs 24.8%). Few subjects (<1%) had TEAEs associated with death in both treatment arms.

Discontinuations due to AEs were seen at similar frequency in the Dato-DXd and control arms (4.2% vs 3.1%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 93 Effects Table for Datopotamab deruxtecan for advanced HR+, HER2-negative breast cancer (data cut-off: 17 July 2023). Updated OS data from IA2 (DCO 29 April 2024). Final analysis safety data cut-off: 24JUL2024 (TB01 safety population n=360)

Effect	Short Description	Unit	Treatment Dato-DXd N=365	Control ICC N=367	Uncertainties/ Strength of evidence
Favourable Effects					
PFS by BICR	Progression-free survival	Months (95% CI)	6.9 (5.7, 7.4)	4.9 (4.2, 5.5)	HR 0.63 (95% CI: 0.52; 0.76) 58.1% vs 64% events Strengths: RCT, blinded review, mature data Uncertainties: Open-label design, performance of control arm
OS	Overall survival	Months (95% CI)	18.6 (17.3, 20.1)	18.3 (17.3, 20.5)	HR 1.01 (95%CI: 0.83-1.22) 61.1% and 58.0% events Strengths: RCT Uncertainties: 95%CI overlaps 1, more patients received subsequent ADC treatment in the ICC arm
Unfavourable Effects					
Grade ≥3		%	35.0	55.6	

Effect	Short Description	Unit	Treatment Dato-DXd N=365	Control ICC N=367	Uncertainties/ Strength of evidence
SAEs		%	17.2	19.1	
AEs leading to disc.		%	4.2	3.1	
AEs associated with death		%	0.6	0.9	One patient (0.3%) died due to Dato-DXd associated ILD/pneumonitis as adjudicated by the ILD AC. Another died from sepsis.
Pneumonitis		%	2.5	0.3	
Interstitial lung disease		%	2.5	0	
Adjudicated drug-related ILD/Pneumonitis		%	4.2	0	
Infections and infestations		%	55.6	37.9	
Keratitis		%	18.6	9.1	Data from IA1 (DCO: 17JUL2023)

Abbreviations: BICR: Blinded independent review; AE: Adverse Event; ILD AC: interstitial lung disease adjudication committee; SAE: Serious Adverse Event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of Dato-DXd compared to single-agent chemotherapy of the Investigator's choice (ICC) in the proposed 2L+ indication after one or two prior lines of systemic therapy is considered to be established.

One of the dual primary endpoints was PFS by BICR, and mature PFS data show a PFS benefit of 2 months (HR 0.63, 95% CI: 0.52; 0.76). The 2-month-difference in median PFS between Dato-DXd and single-agent chemotherapy per Physicians' choice, is statistically significant and clinically relevant.

Most of the patients in the control arm received either eribulin (59.9%), followed by capecitabine (20.7%), vinorelbine (10.4%), and gemcitabine (9.0%). In the ICC arm, 43% of patients had not received prior anthracyclines and/or taxanes, so they would probably have been offered these important standard of care options in the studied treatment setting. For this reason, the performance of the control arm may have been better if inclusion of anthracyclines and taxanes had been allowed. This leads to the uncertainty that PFS benefit of Dato-DXd compared to chemotherapy may be lower in clinical practice. Also, the median PFS for the capecitabine group was comparable with the median PFS on Dato-DXd i.e. 7.2 months.

At the final analysis of OS after 22.8 months of median follow up, mature data show a final OS HR of 1.01 (95%CI: 0.83-1.22), with a median OS of the Dato-DXd arm of 18.6 months vs 18.3 months in the ICC arm, respectively. Despite the lack of observed OS benefit compared to the ICC arm, there is

no apparent detriment. Moreover, it should be noted that for some of the used comparators, OS benefit has been observed and the upper confidence interval overlap above 1 is not in itself considered to be sign of a detriment. Also, the increment in PFS over the ICC arm is not such as to make an increment in OS likely. The shown safety profile of datopotamab deruxtecan is different from the comparators, single-agent chemotherapy, with increased gastrointestinal toxicity, stomatitis, ILD, and eye disorders, while less haematological toxicity and potentially less neurotoxicity. However, the potential for Dato-DXd's toxicity to impact OS seems to be limited, since deaths and discontinuations were similar in both treatment arms.

Relevant secondary endpoints of PFS by investigator, ORR, DoR, and PFS2 are in favour of Dato-DXd and considered supportive of one of the dual primary endpoints, PFS by BIRC.

The shown safety profile of datopotamab deruxtecan is different from the comparators, single-agent chemotherapy, with increased gastrointestinal toxicity, stomatitis, ILD, and eye disorders, while less haematological toxicity and potentially less neurotoxicity. However, the potential for Dato-DXd's toxicity to impact OS seems to be limited, since deaths and discontinuations were similar in both treatment arms.

The safety profile of Dato-DXd is non-negligible and characterised by gastrointestinal toxicities, ocular surface toxicity and skin and subcutaneous tissue toxicities, which were rarely of high grade and mostly manageable by routine clinical practice guidelines. The frequently occurring events are known side effects of topoisomerase inhibitors. In addition, treatment with Dato-DXd is associated with a remarkably high risk of infection despite its apparently modest risk of neutropenia. One patient died due to sepsis.

The main safety issue from Dato-DXd is ILD/pneumonitis, including at least one fatal event.

3.7.2. Balance of benefits and risks

The 2 months gain in PFS is statistically significant and clinically relevant. The PFS benefit is also supported by relevant secondary endpoints of PFS by INV, ORR, DoR and PFS2. The final OS data did not show any apparent detriment. The safety profile, although not negligible can be considered acceptable in this setting. The benefit-risk balance is therefore positive in the final indication.

3.8. Conclusions

The overall benefit/risk balance of Datroway is positive, subject to the conditions stated in section 'Recommendations'.

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 Datroway is favourable in the following indication(s):

Datroway as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine therapy and at least one line of chemotherapy in the advanced setting.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that datopotamab deruxtecan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.