TABLE OF CONTENTS

SUMMARY OF RISK MANAGEMENT PLAN FOR ENHERTU.................................................................3

I THE MEDICINE AND WHAT IT IS USED FOR..............................................................................3

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO
MINIMISE OR FURTHER CHARACTERIZE THE RISKS ..............................................................3

II.A List of Important Risks and Missing Information.................................................................4

II.B Summary of Important Risks..............................................................................................5

II.C Post-Authorisation Development Plan .................................................................................8

II.C.1 Studies Which Are Conditions of the Marketing Authorisation .......................................8

II.C.2 Other Studies in Post-Authorisation Development Plan ...................................................9
LIST OF TABLES

Table Part VI Module II.1: Lists of Important Risks and Missing Information ..................................4
SUMMARY OF RISK MANAGEMENT PLAN FOR ENHERTU

This is a summary of the RMP for T-DXd. The RMP details important risks of T-DXd, how these risks can be minimised, and how more information will be obtained about T-DXd’s risks and uncertainties (missing information).

The SmPC and package leaflet for T-DXd give essential information to HCPs and patients on how T-DXd should be used.

This summary of the RMP for T-DXd should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which will be part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of T-DXd’s RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Trastuzumab deruxtecan is indicated:

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


II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of T-DXd, together with measures to minimise such risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be the following:
  - Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
  - Important advice on the medicine’s packaging.
  - The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
  - The medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of T-DXd, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.
In addition to these measures, information about adverse reactions is continuously collected and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of is not yet available for T-DXd, it is listed under “missing information” below.

II.A List of Important Risks and Missing Information

Important risks of T-DXd are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of T-DXd. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI Module II.1: Lists of Important Risks and Missing Information

<table>
<thead>
<tr>
<th>List of Important Risks and Missing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>• Interstitial Lung Disease/Pneumonitis</td>
</tr>
<tr>
<td>• Left Ventricular Dysfunction</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>• Embryo-foetal Toxicity</td>
</tr>
<tr>
<td>• Product confusion-related medication errors</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
<tr>
<td>• Use in Patients with Moderate or Severe Hepatic Impairment</td>
</tr>
<tr>
<td>• Long-term safety</td>
</tr>
</tbody>
</table>
## II.B Summary of Important Risks

Important identified risks with T-DXd include ILD/pneumonitis and left ventricular dysfunction as outlined below.

<table>
<thead>
<tr>
<th>Important Identified Risk 1: Interstitial Lung Disease/Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence for linking the risk to the medicine</strong></td>
</tr>
<tr>
<td><strong>Risk factors and risk groups</strong></td>
</tr>
<tr>
<td><strong>Risk minimisation measures</strong></td>
</tr>
<tr>
<td><strong>Additional pharmacovigilance activities</strong></td>
</tr>
</tbody>
</table>

ILD = interstitial lung disease; SmPC = Summary of Product Characteristics
### Important Identified Risk 2: Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Cardiotoxicity has been observed with anti-HER2 drugs, including single-agent trastuzumab, which has a warning for cardiomyopathy. LVEF decreases have been observed infrequently in clinical studies with T-DXd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>None</td>
</tr>
</tbody>
</table>
| Risk minimisation measures                    | **Routine risk communication:**
|                                               | SmPC Section 4.2
|                                               | SmPC Section 4.4
|                                               | SmPC Section 4.8
|                                               | **Routine risk minimisation activities recommending specific clinical measures to address the risk:**
|                                               | Recommendations for monitoring of LVEF decrease are included in SmPC Section 4.4.
|                                               | Dose modification guidance for managing the risk of LVEF decrease is included in SmPC Section 4.2.
|                                               | **Additional risk minimisation measures:**
|                                               | None                                                                                                                                                                                            |

**HER2** = human epidermal growth factor receptor 2; **LVEF** = left ventricular ejection fraction; **SmPC** = Summary of Product Characteristics; **T-DXd** = trastuzumab deruxtecan

Important potential risks considered important for inclusion in the list of safety concerns include embryo-foetal toxicity and product confusion-related medication errors, as outlined below.

### Important Potential Risk 1: Embryo-foetal Toxicity

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Findings from nonclinical data, the potential mechanism of the released drug of T-DXd and known effects of anti-HER2 agents on embryo-foetal toxicity suggest that T-DXd may potentially cause foetal harm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>None</td>
</tr>
</tbody>
</table>
| Risk minimisation measures                    | **Routine risk communication:**
|                                               | SmPC Section 4.4
|                                               | SmPC Section 4.6
|                                               | **Routine risk minimisation activities recommending specific clinical measures to address the risk:**
|                                               | Recommendations for pregnancy monitoring and contraception usage are included in SmPC Section 4.4 and SmPC Section 4.6.
|                                               | **Additional risk minimisation measures:**
|                                               | None                                                                                                                                                                                            |

**HER2** = human epidermal growth factor receptor 2; **LVEF** = left ventricular ejection fraction; **SmPC** = Summary of Product Characteristics
### Important Potential Risk 2: Product confusion-related medication errors

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>Medication errors between trastuzumab (ie, Herceptin) and trastuzumab emtansine (ie, KADCYLA) have been reported. Potential for medication errors due to product confusion of T-DXd with trastuzumab and trastuzumab emtansine indicated for breast cancer treatment is considered.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>None</td>
</tr>
</tbody>
</table>
| Risk minimisation measures                 | **Routine risk communication:**  
SmPC Section 4.2  
SmPC Section 4.4  
SmPC Section 6.6  
**Routine risk minimisation activities recommending specific clinical measures to address the risk:**  
None  
**Additional risk minimisation measures:**  
Healthcare Professional Guide |

SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan

Missing information with T-DXd includes use in patients with moderate or severe hepatic impairment, as outlined below.

### Missing Information 1: Use in Patients With Moderate or Severe Hepatic Impairment

<table>
<thead>
<tr>
<th>Evidence for linking the risk to the medicine</th>
<th>T-DXd has not been studied in subjects with severe hepatic impairment. A maximum of 10 subjects with moderate hepatic impairment were eligible for inclusion in Study U201; however, only 2 subjects in the All Tumour Types ≥5.4 mg/kg Pool had moderate hepatic impairment at baseline. Based on a population PK analysis, the clearance of the released drug of T-DXd decreases with increasing AST and increasing total bilirubin.</th>
</tr>
</thead>
</table>
| Risk minimisation measures                 | **Routine risk communication:**  
SmPC Section 4.2  
SmPC Section 4.4  
SmPC Section 5.2  
**Routine risk minimisation activities recommending specific clinical measures to address the risk:**  
None  
**Additional risk minimisation activities:**  
None |
| Additional pharmacovigilance activities   | Analysis of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies. |

AST = aspartate aminotransaminase; BC = breast cancer; HER2 = human epidermal growth factor receptor 2; PK = pharmacokinetic; SmPC = Summary of Product Characteristics; T-DXd = trastuzumab deruxtecan
### Missing Information 2: Long-term Safety

| Evidence for linking the risk to the medicine | The median treatment duration, defined as ([date of last dose − date of first dose + 21]/30.44) in the All Tumour Types ≥5.4 mg/kg Pool (N = 1219) was 7.72 months (range: 0.7 to 41.0). A total of 194 (15.9%) subjects had been treated for >6 to ≤9 months, 118 (9.7%) for >9 to ≤12 months, 223 (18.3%) for >12 to ≤18 months, 126 (10.3%) for >18 to ≤24 months, and 62 (5.1%) for >24 months. |

| Risk minimisation measures | Routine risk minimisation communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation activities: None |

### II.C Post-Authorisation Development Plan

#### II.C.1 Studies Which Are Conditions of the Marketing Authorisation

The Phase 3 clinical trial (DS8201-A-U301) serves as the confirmatory trial (see also RMP Part IV). Details are provided in the table below.
### DS8201-A-U301

**Short title**
A Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a, an anti-HER2-antibody drug conjugate, versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pretreated with prior standard of care HER2 therapies, including T-DM1.

**Purpose of the study**

**Primary objective:**
To compare the progression-free survival (PFS) benefit of T-DXd to investigator’s choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1.

**Key secondary objective:**
To compare overall survival (OS) benefit of T-DXd to investigator’s choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1.

**Other secondary Objectives:**
To evaluate efficacy of T-DXd compared to investigator’s choice on:
- Confirmed objective response rate (ORR);
- Duration of response (DoR);
- To further determine pharmacokinetics (PK) of T-DXd.
- To further evaluate safety of T-DXd compared to investigator’s choice.
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints for T-DXd compared to investigator’s choice.

Safety concern addressed: overall safety, long-term safety.

T-DXd = trastuzumab deruxtecan

### II.C.2 Other Studies in Post-Authorisation Development Plan

**Prescriber survey**

**Short title**
EU survey of relevant healthcare professionals on understanding of key risk minimization measures pertaining to ILD/pneumonitis

**Purpose of the study**
The primary objective is to evaluate the effectiveness of proposed educational material as risk minimization measures by:
- Evaluating the level of knowledge of educational materials by HCPs of risks, early recognition, diagnosis and management of ILD/pneumonitis.
- Evaluating the extent to which HCPs receive the HCP guide and distribute the PC to patients.

Safety concern addressed: risk minimization for ILD/pneumonitis.

EU = European Union; HCP = healthcare professional; ILD = interstitial lung disease; PC = Patient Card
### PK and safety data analysis in patients with moderate hepatic impairment

<table>
<thead>
<tr>
<th>Short title</th>
<th>Collection and analysis of PK and safety data in subjects with moderate hepatic impairment from ongoing clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose of the study</td>
<td>Overall assessment of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies. Safety concern addressed: Missing information: Use in patients with moderate or severe hepatic impairment.</td>
</tr>
</tbody>
</table>

PK = pharmacokinetic