European Union Risk Management Plan for Poherdy (Pertuzumab)

RMP version to be assessed as part of this application:

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Summary of significant changes in this RMP: Not applicable.

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QPPV name: Fernanda Tavares

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

Table of content

List of Tables

Abbreviations

Term/Abbreviation	Explanation
ADA	Anti-drug Antibody
ADCC	Antibody-dependent cell-mediated Cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CHF	Congestive Heart Failure
CI	Confidence Interval
Cr	Creatinine
DLP	Data Lock Point
EBC	Early Breast Cancer
EDC	Electronic Data Capture
EEA	European Economic Area
EFD	Ejection Fraction Decreased
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GD	Gestation Day
H	Trastuzumab (Herceptin)
HALT	Hormone Ablation Therapy
HFI	Hereditary Fructose Intolerance
HIV	Human Immunodeficiency Virus
INN	International Nonproprietary Name
IRR	Infusion-related Reaction
ITT	Intent-to-treat
IV	Intravenous
LVD	Left Ventricular Dysfunction
LVEF	Left Ventricular Ejection Fraction
MAH	Marketing Authorization Holder
MAP	Mitogen-activated Protein
MBC	Metastatic Breast Cancer

Term/Abbreviation	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
ORR	Overall Response Rate
PBRER	Periodic Benefit Risk Evaluation Report
PFS	Progression-free Survival
PK	Pharmacokinetic
PI3K	Phosphoinositide 3-kinase
PL	Package Leaflet
Pla	Placebo
PSUR	Periodic Safety Update Report
Ptz	Pertuzumab
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
TBIL	Total Bilirubin
ULN	Upper Limit Normal

Part I: Product Overview

Table 1 Product Overview

Active substance (INN or common name)	Pertuzumab
Pharmacotherapeutic group (ATC Code)	L01FD02
Marketing Authorisation Applicant or Marketing Authorization Holder (MAH)	N.V. Organon
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Poherdy
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Recombinant anti-human epidermal growth factor receptor 2 (HER2) domain II humanized monoclonal antibody
	Summary of mode of action: Poherdy is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including epidermal growth factor receptor (EGFR), HER3 and HER4. As a result, Poherdy inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, Poherdy mediates antibody-dependent cell-mediated cytotoxicity (ADCC). While Poherdy alone inhibited the proliferation of human tumour cells, the combination of Poherdy and trastuzumab significantly augmented antitumour activity in HER2-overexpressing xenograft models.
	Important information about its composition: Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.
Hyperlink to the Product Information	Poherdy Product Information (Module 1.3.1)
Indications in the EEA	Current: **Early breast cancer** Poherdy is indicated for use in combination with trastuzumab and chemotherapy in:

	• the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence **Metastatic breast cancer** Poherdy is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: The recommended initial loading dose of Poherdy is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. Poherdy and trastuzumab should be administered sequentially and not mixed in the same infusion bag. Poherdy and trastuzumab can be given in any order. When administered with Poherdy the recommendation is to follow a 3 weekly schedule for trastuzumab administered as either: • an intravenous (IV) infusion with an initial loading dose of trastuzumab 8 mg/kg body weight followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight or • a fixed subcutaneous dose of trastuzumab by injection (600 mg) every 3 weeks irrespective of the patient's body weight. In patients receiving a taxane, Poherdy and trastuzumab should be administered prior to the taxane. When administered with Poherdy, docetaxel can be started at 75 mg/m^2, and subsequently escalated to 100 mg/m^2 depending on the chosen regimen and tolerability of the initial dose. Alternatively, docetaxel can be given at 100 mg/m^2 on a 3 weekly schedule from the start, again depending on the chosen regimen. If a carboplatin-based regimen is used, the recommended dose for docetaxel is 75 mg/m^2 throughout (no dose escalation). When administered with Poherdy in the adjuvant setting, the recommended dose of paclitaxel is 80 mg/m^2 once weekly for 12 weekly cycles. In patients receiving an anthracycline-based regimen, Poherdy and trastuzumab should be administered following completion of the entire anthracycline regimen. **Metastatic breast cancer** Poherdy should be administered in combination with trastuzumab and docetaxel. Treatment with Poherdy and trastuzumab may continue until

	disease progression or unmanageable toxicity even if treatment with docetaxel is discontinued. **Early breast cancer** In the neoadjuvant setting, Poherdy should be administered for 3 to 6 cycles in combination with trastuzumab and chemotherapy, as part of a complete treatment regimen for early breast cancer. In the adjuvant setting, Poherdy should be administered in combination with trastuzumab for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline- and/or taxane-based chemotherapy. Poherdy and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: Pharmaceutical form: Concentrate for solution for infusion. Clear to slightly opalescent, colourless to pale yellow, liquid. Strengths: One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/mL.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

HLX11 is being developed as a biosimilar product to the reference medicinal product pertuzumab (Trade name: Perjeta®). This section is not applicable for biosimilar products.

Part II: Module SII - Non-clinical part of the safety specification

As a biosimilar, the non-clinical development of HLX11 has primarily focussed on the in vitro comparison of HLX11 to Perjeta® for biosimilarity.

Based on the outcome of the analytical similarity exercise and the in vitro functional/biological assays, the similarity between HLX11 (420 mg/14 mL/vial) and Perjeta® has been established. As such, the non-clinical data generated for Perjeta® can be referenced for HLX11, and there are no additional non-clinical safety findings which could constitute an important potential risk to the target population.

In conclusion, there are no additional safety concerns, as a result of non-clinical studies, that require inclusion in the RMP for HLX11.

Part II: Module SIII - Clinical trial exposure

As HLX11 is a biosimilar, the safety data collected from studies conducted with pertuzumab licenced in the European Union (EU) as Perjeta® provide the main data used to support a safety assessment of HLX11. Thus, the data in the RMP and the summary of product characteristics (SmPC) of Perjeta® provides the basis of the known safety profile for pertuzumab.

The clinical development programs for HLX11 (pertuzumab biosimilar) consisted of one Phase I pharmacokinetic (PK) study (HLX11-001) conducted in healthy Chinese male volunteers, and one Phase III study (HLX11-BC301) conducted in female patients with HER2-positive and HR-negative early-stage or locally advanced breast cancer.

- HLX11-001: A Randomized, Double-blind, Parallel, Four-arm, Single-dose, Phase I Clinical Study to Compare Pharmacokinetics, Safety, and Immunogenicity of HLX11 vs. Perjeta® (US, EU, and CN-sourced) via Intravenous Infusion in Healthy Chinese Male Subjects
- HLX11-BC-301: A Multicenter, Randomized, Double-Blind, Parallel-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Pertuzumab Biosimilar HLX11 vs. EU-Perjeta® in the Neoadjuvant Therapy of HER2-Positive and HR-Negative Early-Stage or Locally Advanced Breast Cancer

Table 2 provides the overview of the clinical trials of HLX11 in safety evaluations. The cumulative subject exposure to HLX11 and Perjeta® was provided in Table 3, Table 4, Table 5 and Table 6. Further details on cumulative subject exposure categorized by age, gender, dose and ethnic origin are provided in the Tables below (from Table 7 to Table 16) respectively.

Table 2 Overview of Two Clinical Trials of HLX11 in Safety Evaluations

Study Number	Population	Study Design	Dosing Regimen and Duration	Route of Administration	Planned Number of Subjects	Objectives	Status
HLX11-001	Healthy Chinese male subjects	A randomized, double-blind, parallel, 4-arm, single-dose, Phase I clinical study to compare the PK of HLX11 vs. Perjeta® (US-Perjeta®, EU-Perjeta®, and CN-Perjeta®) via IV infusion in healthy Chinese male subjects, and to evaluate the safety, tolerability, and immunogenicity of the study drugs	A single dose of 420 mg of HLX11, US-Perjeta®, EU-Perjeta®, or CN-Perjeta® over 60 ± 10 minutes	IV infusion	160 (40 each in the HLX11, US-Perjeta®, EU-Perjeta®, and CN-Perjeta® groups)	Primary Objective: To compare the PK similarity of HLX11 and Perjeta® (US-Perjeta®, EU-Perjeta®, and CN-Perjeta®) after a single IV infusion in healthy Chinese male subjects. Secondary Objectives: To compare the safety, tolerability, and immunogenicity of HLX11 and Perjeta® (US-Perjeta®, EU-Perjeta®, and CN-Perjeta®) after a single IV infusion in healthy Chinese male subjects and to further describe its PK profiles.	Completed
HLX11-BC301	Patients with early-stage or locally advanced, HER2-positive and HR-negative breast cancer	A Phase III, double-blind, randomized, parallel-controlled, multicenter, equivalence study to compare the similarity of efficacy	**Dosing regimen of HLX11/EU-Perjeta®:** **Neoadjuvant therapy period:** HLX11 or EU-Perjeta®: 840 mg over 60 minutes on Cycle 1 Day 1, followed by 420 mg over 30 to 60 minutes on Day	IV infusion	900 (450 each in the HLX11 and EU-Perjeta® groups)	Primary objective: To demonstrate that HLX11 and EU-Perjeta® have similar clinical efficacy on HER2-positive and HR-negative early-stage	Completed (data cut-off date for this submission: 15May2024)

Study Number	Population	Study Design	Dosing Regimen and Duration	Route of Administration	Planned Number of Subjects	Objectives	Status
	with a primary tumor diameter > 2 cm	and safety between HLX11 and EU-Perjeta® in combination with docetaxel and trastuzumab in the neoadjuvant therapy period, and in combination with trastuzumab in the adjuvant therapy period	1 of Cycle 2 to Cycle 4, every 3 weeks as a cycle. **Adjuvant therapy period:** HLX11 or EU-Perjeta®: 840 mg over 60 minutes on Cycle 9 Day 1, followed by 420 mg over 30 to 60 minutes on Day 1 of Cycles 10 to 21, every 3 weeks as a cycle. **Dosing regimens of other study drugs:** **Neoadjuvant therapy period:** Trastuzumab: loading dose of 8 mg/kg IV on Cycle1 Day 1, followed by 6 mg/kg IV on D1 in Cycle 2 to Cycle 4. Docetaxel: 75 mg/m^2 IV on Day 1 in Cycle 1 to Cycle 4. **Adjuvant chemotherapy period:** Doxorubicin: 60 mg/m^2 IV on D1 in Cycle 5 to Cycle 8. Cyclophosphamide: 600 mg/m^2 IV on D1 in Cycle 5 to Cycle 8. **Adjuvant HER2-targeted treatment period:** Trastuzumab: loading dose of 8 mg/kg IV on Cycle 9 Day 1, followed by 6 mg/kg IV on D1 in Cycle 10 to Cycle 21.			or locally advanced breast cancer. Secondary objectives: To compare the safety, PK, and immunogenicity of HLX11 vs. EU-Perjeta®.	

Table 3 Duration of Exposure to HLX11/Perjeta® in HLX11-001 study

	HLX11 (N=40)		EU-Perjeta® (N=40)		US-Perjeta® (N=40)		CN-Perjeta® (N=40)	
Duration of exposure	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
1 dose	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06
Total	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06
Total exposure min, (min)								
n	40		40		40		40	
Mean (SD)	71.0 (0.00)		71.0 (0.16)		71.0 (0.16)		71.0 (0.00)	
Median	71.0		71.0		71.0		71.0	
Range	71, 71		70, 71		71, 72		71, 71	

Note: The indication of HLX11-001 study is not applicable as the study is conducted in healthy male subjects.

Table 4 Duration of Exposure to HLX11/Perjeta® in HLX11-BC301 study - Neoadjuvant Therapy Period

	HLX11 (N=453)		EU-Perjeta® (N=454)	
	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Study Drug Administered at the Stage	453 (100)	979.68	454 (100)	980.53
Total Patient cycles of exposure				
n	453		454	
Mean (SD)	4.0 (0.20)		4.0 (0.28)	
Median	4.0		4.0	
Range	2, 4		1, 4	
Duration of Exposure				
n	453	979.68	454	980.53
< 1months	4 (0.9)	2.89	6 (1.3)	3.06
1 - < 3months	444 (98.0)	960.49	442 (97.4)	957.47
3 - < 6months	5 (1.1)	16.30	6 (1.3)	20.01
6 - < 12months	0	0	0	0
12 - < 24months	0	0	0	0
≥ 24months	0	0	0	0
Patient exposure duration (months per patient)				
n	453		454	
Mean (SD)	2.163 (0.2420)		2.160 (0.2855)	
Median	2.103		2.103	
Range	0.72, 3.88		0.03, 4.01	

Note: The indication of HLX11-BC301 is early breast cancer (EBC).

Table 5 Duration of Exposure to HLX11/Perjeta® in HLX11-BC301 study - Adjuvant HER2-Targeted Therapy Period

	HLX11-HLX11 (N=154)		EU-Perjeta®- EU-Perjeta® (N=79)		EU-Perjeta®- HLX11 (N=79)	
	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Study Drug Administered at the Stage	154 (100)	866.69	79 (100)	441.69	78 (98.7)	462.06
Total Patient cycles of exposure						
n	154		79		78	
Mean (SD)	8.9 (4.25)		8.9 (4.47)		9.3 (4.19)	
Median	10.0		11.0		11.0	
Range	1, 13		1, 13		1, 13	
Duration of Exposure						
n	154	866.69	79	441.69	78	462.06
< 1months	14 (9.1)	5.98	10 (12.7)	2.96	7 (8.9)	2.92
1 - < 3months	28 (18.2)	52.37	12 (15.2)	22.67	11 (13.9)	19.35
3 - < 6months	30 (19.5)	141.86	14 (17.7)	64.56	13 (16.5)	61.93
6 - < 12months	82 (53.2)	666.48	43 (54.4)	351.51	47 (59.5)	377.86
12 - < 24months	0	0	0	0	0	0
≥ 24months	0	0	0	0	0	0
Patient exposure duration (months per patient)						
n	154		79		78	
Mean (SD)	5.628 (3.0027)		5.591 (3.1607)		5.924 (2.9533)	
Median	6.439		6.899		7.179	
Range	0.03, 9.72		0.03, 9.23		0.03, 9.86	

Note: The indication of HLX11-BC301 is early breast cancer (EBC).

Table 6 Duration of Exposure to HLX11/Perjeta® in HLX11-BC301 study – Entire Study

	HLX11-HLX11 (N=154)		EU-Perjeta®- EU-Perjeta® (N=79)		EU-Perjeta®- HLX11 (N=79)	
	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Study Drug Administered at the Stage	154 (100)	1202.30	79 (100)	614.41	79 (100)	637.14
Total Patient cycles of exposure						
n	154		79		79	
Mean (SD)	12.9 (4.25)		12.9 (4.47)		13.2 (4.30)	
Median	14.0		15.0		15.0	
Range	5, 17		5, 17		4, 17	
Duration of Exposure						
n	154	1202.30	79	614.41	79	637.14
< 1months	0	0	0	0	0	0
1 - < 3months	14 (9.1)	36.07	10 (12.7)	25.03	7 (8.9)	16.95
3 - < 6months	35 (22.7)	152.44	15 (19.0)	67.35	15 (19.0)	63.44
6 - < 12months	105 (68.2)	1013.78	54 (68.4)	522.02	55 (69.6)	531.71
12 - < 24months	0	0	0	0	2 (2.5)	25.03
≥ 24months	0	0	0	0	0	0
Patient exposure duration (months per patient)						
n	154		79		79	
Mean (SD)	7.807 (3.0356)		7.777 (3.1492)		8.065 (3.0814)	
Median	8.657		9.133		9.232	
Range	2.10, 11.83		2.10, 11.93		2.10, 12.62	

Note: The indication of HLX11-BC301 is early breast cancer (EBC).

Table 7 Exposure to HLX11/Perjeta® by Age and Gender in HLX11-001 study

Age group	HLX11 (N=40)		EU-Perjeta® (N=40)		US-Perjeta® (N=40)		CN-Perjeta® (N=40)	
	Number of subjects Male n (%)	Person time (months) Male	Number of subjects Male n (%)	Person time (months) Male	Number of subjects Male n (%)	Person time (months) Male	Number of subjects Male n (%)	Person time (months) Male
Age (years)								
<18	0	0	0	0	0	0	0	0
18-64	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06
65-74	0	0	0	0	0	0	0	0
≥75	0	0	0	0	0	0	0	0
Total	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06

Table 8 Exposure to HLX11/Perjeta® by Age and Gender in HLX11-BC301 study - Neoadjuvant Therapy Period

Age group	HLX11 (N=453)				EU-Perjeta® (N=454)				Total (N=907)			
	Number of subjects		Person time (months)		Number of subjects		Person time (months)		Number of subjects		Person time (months)	
	Male n (%)	Female n (%)	Male	Female	Male n (%)	Female n (%)	Male	Female	Male n (%)	Female n (%)	Male	Female
Age (years)												
<18	0	0	0	0	0	0	0	0	0	0	0	0
18-64	0	408 (90.1)	0	882.46	0	416 (91.6)	0	896.69	0	824 (90.8)	0	1779.15
65-74	0	43 (9.5)	0	91.99	0	37 (8.1)	0	81.71	0	80 (8.8)	0	173.70
≥75	0	2 (0.4)	0	5.22	0	1 (0.2)	0	2.14	0	3 (0.3)	0	7.36
Total	0	453 (100)	0	979.68	0	454 (100)	0	980.53	0	907 (100)	0	1960.21

Table 9 Exposure to HLX11/Perjeta® by Age and Gender in HLX11-BC301 study - Adjuvant HER2-Targeted Therapy Period

Age group	HLX11-HLX11 (N=154)				EU-Perjeta®- EU-Perjeta® (N=79)				EU-Perjeta®- HLX11 (N=79)				Total (N=312)			
	Number of subjects		Person time (months)		Number of subjects		Person time (months)		Number of subjects		Person time (months)		Number of subjects		Person time (months)	
	Male n (%)	Female n (%)	Male	Female	Male n (%)	Female n (%)	Male	Female	Male n (%)	Female n (%)	Male	Female	Male n (%)	Female n (%)	Male	Female
Age (years)																
<18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-64	0	136 (88.3)	0	770.60	0	67 (84.8)	0	376.77	0	76 (96.2)	0	446.62	0	279 (89.4)	0	1593.99
65-74	0	18 (11.7)	0	96.10	0	12 (15.2)	0	64.92	0	3 (3.8)	0	15.44	0	33 (10.6)	0	176.46
≥75	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	154 (100)	0	866.69	0	79 (100)	0	441.69	0	79 (100)	0	462.06	0	312 (100)	0	1770.45

Table 10 Exposure to HLX11/Perjeta® by Dose in HLX11-001 study

	HLX11 (N=40)		EU-Perjeta® (N=40)		US-Perjeta® (N=40)		CN-Perjeta® (N=40)	
Dose	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
420 mg	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06
Total	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06

Table 11 Exposure to HLX11/Perjeta® by Dose in HLX11-BC301 study – Neoadjuvant Therapy Period

	HLX11 (N=453)		EU-Perjeta® (N=454)	
	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Actual Cumulative Total Dose (mg)				
Mean (SD)	2089.70 (85.518)		2085.82 (116.061)	
Median	2100.00		2100.00	
Range	1260.0, 2100.0		840.0, 2100.0	
Study Drug Administrated at the Stage	453 (100)	979.68	454 (100)	980.53

Table 12 Exposure to HLX11/Perjeta® by Dose in HLX11-BC301 study – Adjuvant HER2-Targeted Therapy Period

	HLX11-HLX11 (N=154)		EU-Perjeta®- EU-Perjeta® (N=79)		EU-Perjeta®- HLX11 (N=79)	
	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Actual Cumulative Total Dose (mg)						
Mean (SD)	4175.5 (1782.71)		4157.5 (1876.60)		4338.1 (1756.55)	
Median	4620.0		5040.0		5040.0	
Range	840, 5880		840, 5880		840, 5880	
Study Drug Administrated at the Stage	154 (100)	866.69	79 (100)	441.69	78 (98.7)	462.06

Table 13 Exposure to HLX11/Perjeta® by Dose in HLX11-BC301 study – Entire Study

	HLX11-HLX11 (N=154)		EU-Perjeta®- EU-Perjeta® (N=79)		EU-Perjeta®- HLX11 (N=79)	
	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Actual Cumulative Total Dose (mg)						
Mean (SD)	6275.16 (1782.430)		6255.71 (1875.033)		6383.15 (1812.211)	
Median	6720.00		7140.00		7140.00	
Range	2940.0, 7980.0		2940.0, 7980.0		2100.0, 7980.0	
Study Drug Administrated at the Stage	154 (100)	1202.30	79 (100)	614.41	79 (100)	637.14

Table 14 Exposure to HLX11/Perjeta® by Race in HLX11-001 study

	HLX11 (N=40)		EU-Perjeta® (N=40)		US-Perjeta® (N=40)		CN-Perjeta® (N=40)	
Ethnic Origin	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Asian	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06
Total	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06	40 (100)	0.06

Table 15 Exposure to HLX11/Perjeta® by Race in HLX11-BC301 study – Neoadjuvant Therapy Period

	HLX11 (N=453)		EU-Perjeta® (N=454)		Total (N=907)	
Race	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Asian	453 (100)	979.68	454 (100)	980.53	907 (100)	1960.21
Total	453 (100)	979.68	454 (100)	980.53	907 (100)	1960.21

Table 16 Exposure to HLX11/Perjeta® by Race in HLX11-BC301 study – Adjuvant HER2-Targeted Therapy Period

	HLX11-HLX11 (N=154)		EU-Perjeta®-EU-Perjeta® (N=79)		EU-Perjeta®-HLX11 (N=79)		Total (N=312)	
Race	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)	Number of subjects n (%)	Person time (months)
Asian	154 (100)	866.69	79 (100)	441.69	79 (100)	462.06	312 (100)	1770.45
Total	154 (100)	866.69	79 (100)	441.69	79 (100)	462.06	312 (100)	1770.45

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion 1: Hypersensitivity

Reason for exclusion: Patients with known hypersensitivity to pertuzumab or to any of its excipients were excluded from clinical trials to avoid risk of anaphylactic shock/reaction.

Is it considered to be included as missing information?: No

Rationale: Patient with hypersensitivity to the active substance or to any of the excipients is contraindicated as per EU SmPC. A statement regarding severe hypersensitivity, including anaphylaxis and events with a fatal outcome, have been observed with pertuzumab has been added in Section 4.4 of the EU SmPC. In addition, a statement regarding permanent discontinuation of pertuzumab for any patient who experiences a NCI CTCAE Grade 4 reaction, will remain in Section 4.4 of the EU SmPC.

Criterion 2: Pregnant or lactating patient

Reason for exclusion: Pregnant or lactating patients were excluded in clinical trials as studies of Perjeta® in animals have shown reproductive related toxicity. Human IgG is secreted in human milk and the potential for absorption and harm to the infant is unknown.

Is it considered to be included as missing information?: Yes. Please refer to section SVII.3 for additional details on the missing information 'Use during pregnancy and lactation'.

Rationale: Not applicable.

Criterion 3: Patients exposed to cumulative doses of doxorubicin > 360 mg/m^2 (or equivalent cumulative doses of other anthracyclines)

Reason for exclusion: Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents.

Is it considered to be included as missing information?: No

Rationale: Included in Section 4.4, Special Warnings and Precautions for Use, in the EU SmPC for pertuzumab.

Criterion 4: Patients with uncontrolled hypertension, high risk uncontrolled arrhythmias, unstable angina or angina requiring anti-angina medication, clinically significant valvular heart disease, or a history of transmural myocardial infarction

Reason for exclusion: Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents.

Is it considered to be included as missing information?: No

Rationale: Not applicable.

Criterion 5: Patients with a history of cardiac failure or systolic dysfunction

Reason for exclusion: Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents.

Is it considered to be included as missing information?: No

Rationale: Not applicable.

Criterion 6: Patients with inadequate renal or hepatic function or with impaired bone marrow reserve (manifest as anemia, neutropenia or thrombocytopenia)

Reason for exclusion: Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy.

Is it considered to be included as missing information?: No

Rationale: EU SmPC for pertuzumab indicates that there is no information on patients with severe renal impairment. EU SmPC for pertuzumab indicates that pertuzumab has not been studied in patients with hepatic impairment. EU SmPCs for docetaxel and doxorubicin indicate that clearance may be reduced and/or toxicity increased in patients with hepatic impairment. EU SmPC for docetaxel do not include information on patients with severe renal impairment; for doxorubicin, SmPC indicate that dose reductions may be required for renal impairment. The SmPCs for these agents also clearly indicate the high risk of myelosuppression and the need to monitor blood counts before and during therapy.

Criterion 7: Patients known to be infected with HIV, HBV or HCV

Reason for exclusion: Such patients may not be able to tolerate taxane- or anthracycline based therapy and are at increased risk of infectious complications associated with myelosuppression.

Is it considered to be included as missing information? No.

Rationale: No specific warning or exclusion included in the EU SmPC for pertuzumab since assessment of a patient's fitness for chemotherapy is part of routine oncology practice. This concern is not considered by the MAH to be a sufficient reason to limit physician options in treatment of patients with active infections with pertuzumab. However, Section 4.4 of the pertuzumab SmPC indicates that patients treated with pertuzumab, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel. The SmPCs of cytotoxic agents commonly used in patients with breast cancer (e.g., docetaxel, paclitaxel, doxorubicin and epirubicin) provide extensive warnings about the risks of neutropenia and its complications.

Criterion 8: Patients who have had recent major surgical procedures

Reason for exclusion: Such patients may not be able to tolerate taxane- or anthracycline based therapy and are at increased risk of infectious complications associated with myelosuppression.

Is it considered to be included as missing information? No.

Rationale: No specific warning or exclusion included in the EU SmPC for pertuzumab since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice).

Criterion 9: Patients with other malignancies in the last 5 years (other than curatively treated skin cancer or in situ carcinomas treated with curative intent)

Reason for exclusion: Such patients were excluded from clinical trials because relapse or progression of the other malignancy could confound interpretation of trial efficacy data.

Is it considered to be included as missing information? No.

Rationale: Such patients should still benefit from treatment with pertuzumab, trastuzumab, and chemotherapy. No warning or exclusion included in the EU SmPC.

Criterion 10: Patients receiving other investigational treatments

Reason for exclusion: Such patients were excluded from clinical trials because the other investigational agent could confound interpretation of trial safety and efficacy data.

Is it considered to be included as missing information? No.

Rationale: No warning or exclusion included in the EU SmPC. Co-administration of investigational agents is beyond the scope of the EU SmPC.

Criterion 11: Other serious concurrent medical conditions that could interfere with the treatment plan, including severe pulmonary status/disease

Reason for exclusion: Such patients may not be able to tolerate taxane- or anthracycline based therapy and may not be able to tolerate the infusion reactions associated with pertuzumab, trastuzumab, and docetaxel, clinical symptoms of which may manifest as pulmonary adverse reactions such as dyspnea and hypoxia, etc.

Is it considered to be included as missing information? No.

Rationale: No specific warning or exclusion included in the EU SmPC for pertuzumab since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development program is specific to that for biosimilars and is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 17 Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities	
Patients with hepatic impairment	In HLX11-001 study, healthy subjects were enrolled and those with any serious clinical disease were excluded. In HLX11-BC301 study, the subjects should have adequate liver function and the subjects who didn't meet the defined liver functions criteria were excluded. The subjects with viral hepatitis (Hepatitis B, Hepatitis C, co-infection of Hepatitis B and Hepatitis C) were excluded. (Note: Hepatitis B subjects whose disease status are stable after antiviral treatment (HBV-DNA ≤ 2500 copies/mL or 500 IU/mL) during the screening period can be enrolled in the study.) Defined liver function criteria:

Type of special population	Exposure
	• Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), for patients with Gilbert's syndrome, ≤ 2 × ULN; • Aspartate aminotransferase (AST) ≤ 2.5 × ULN; • Alanine aminotransferase (ALT) ≤ 2.5 × ULN; • Alkaline phosphatase (ALP) ≤ 2.5 × ULN.
Patients with renal impairment	In HLX11-001 study, healthy subjects were enrolled and those with any serious clinical disease were excluded. In HLX11-BC301 study, the subjects should have adequate renal function and the subjects who didn't meet the defined renal function criteria were excluded. Defined renal function criteria: Serum creatinine (Cr) ≤ 1.5 × ULN; In case of > 1.5 × ULN, creatinine clearance must be ≥ 50 mL/min (Calculated by Cockcroft-Gault formula)
Patients with cardiovascular impairment	In HLX11-001 study, the healthy subjects were enrolled and those with any serious clinical disease were excluded. In HLX11-BC301 study, the subjects' left ventricular ejection fraction (LVEF) at baseline should be ≥ 55% and the subjects with serious heart disease were excluded.
Immunocompromised patients	In HLX11-001 study, the healthy subjects were enrolled and those with positive anti-human immunodeficiency virus (HIV) antibody were excluded. In HLX11-BC301 study, the subjects with HIV infection, and positive anti-HIV antibody were excluded.
Population with relevant different ethnic origin	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Children	Children and adolescents below the age of 18 years were not included in the clinical development plan.
Elderly aged ≥ 75 years	These subjects were not excluded from the clinical trial program for HLX11. The number of subjects aged > 75 years exposed via participation in clinical trials remains small.
Male breast cancer patients	Male breast cancer patients were not excluded from the clinical trial program for HLX11. However, there was no male breast cancer patient enrolled.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable, to be completed when updating this RMP after authorisation.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of hemoglobin levels. There is no evidence that Poherdy has such effects which makes it highly unlikely that Poherdy will be misused for illegal purposes.

Part II: Module SVII - Identified and potential risks

As a biosimilar product to the reference medicinal product Perjeta®, the safety concerns of Poherdy are aligned with that of the reference medicinal product, no discrepancies of safety concerns were found in the clinical development. In addition, Poherdy is a sorbitol-containing product. Therefore, serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI) was added as an important potential risk of Poherdy.

The important identified risks of Poherdy include infusion-related reactions, hypersensitivity reactions/ anaphylaxis; congestive heart failure/ left ventricular dysfunction.

The important potential risks of Poherdy include oligohydramnios, risk in fertility in humans, risk in patients aged 75 years or older, lack of efficacy due to immunogenicity, serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI).

The missing information includes risk in pregnant or lactating women.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

As HLX11 is a biosimilar product, the safety concerns mirror those of the reference medicinal product. No new risks were identified from the clinical trials involving HLX11.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

As HLX11 is a biosimilar product, the safety concerns mirror those of the reference medicinal product. No new risks were identified as a result of the HLX11 clinical trials.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Based on the European Medicines Agency (EMA) guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The risk of sorbitol exposure in patients with HFI is also included. The following risks are the safety concerns of HLX11.

Important Identified Risk:

- Infusion-related reactions, Hypersensitivity reactions/ anaphylaxis

- Congestive heart failure/ Left ventricular dysfunction

Important Potential Risk:

- Oligohydramnios
- Risk in fertility in humans
- Risk in patients aged 75 years or older
- Lack of efficacy due to immunogenicity
- Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)

Missing Information:

- Risk in pregnant or lactating women

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, as this is the initial RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Based on the EMA guide on similar biological medicinal products, the RMP should take into account identified and potential risks associated with the use of the reference product. So, this section will contain all the important identified risks and important potential risks described in the European Public Assessment Report (EPAR) - Risk Management Plan for the reference product, Perjeta®.

Details of Important Identified Risk 1: Infusion-related reactions, Hypersensitivity reactions/ Anaphylaxis

Potential mechanisms:

IRRs are thought to be due to release of cytokines and/or other chemical mediators. Anaphylactic or hypersensitivity reactions to the IV administration of protein, for example monoclonal antibodies, may also play a part in some patients. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms of these reactions overlap.

Evidence source(s) and strength of evidence:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

Characterisation of the risk:

In general, antibody infusion-associated AEs are more frequent and severe with the first infusion, and decrease in number and severity over time, and the majority of AEs resolve fully.

Infusion-associated reactions typically occur during or shortly after infusions of monoclonal antibodies but may also show a delayed onset. The true relation of an event to infusion of study treatment is therefore difficult to ascertain, particularly when treatment regimens involve

combination therapy. Other monoclonal antibodies (e.g. trastuzumab) and chemotherapies (e.g. docetaxel) are also associated with infusion-related reactions, hypersensitivity reactions and anaphylaxis.

- The data of the reference product:

The frequency of infusion-related reactions in early breast cancer (EBC) and metastatic breast cancer (MBC) patients (N=3830) was 6.3% (95% confidence interval [CI]: 5.6; 7.1). The great majority of patients included received pertuzumab + Herceptin + chemotherapy (Ptz + H + chemo).

There have been no infusion reactions and/or hypersensitivity reactions/ anaphylaxis with a fatal outcome in the reference product's clinical trials (CLEOPATRA, NEOSPHERE, TRYPHAENA, APHINITY and PERUSE).

Infusion-related reactions (IRRs): The reference product has been associated with IRRs, including events with fatal outcomes. Overall, the incidence and severity of IRRs was similar across treatment arms and studies. Less than 5% of patients in any treatment arm experienced Grade ≥ 3 reactions. The incidence of IRRs was generally highest in the first cycle of therapy and declined thereafter, as is typical of infusion reactions with monoclonal antibodies.

Hypersensitivity and Anaphylaxis: The incidence and severity of events was similar across different clinical trials, with the majority of events being Grade 1-2 in severity. Hypersensitivity reactions would be expected to worsen with repeated doses.

- The data of HLX11 clinical studies:

Infusion-related reactions (IRRs)

According to the protocols of HLX11 studies, if an AE is considered as an IRR by the investigator, the individual signs and symptoms should be reported as the AE terms and be recorded accordingly.

a) HLX11-001: There were no reports of IRR.

b) HLX11-BC301:

In the neoadjuvant therapy period, a total of 71 (7.8%) subjects (HLX11 group: 35 [7.7%] subjects; EU-Perjeta® group: 36 [7.9%] subjects) experienced IRRs, all of which were non-serious Grade 1-2 events and have resolved. A total of 36 (4.0%) subjects (HLX11 group: 18 [4.0%] subjects; EU-Perjeta® group: 18 [4.0%] subjects) experienced IRRs related to HLX11/EU-Perjeta®. (Table 18)

In the adjuvant chemotherapy period, a total of 8 (2.1%) subjects (HLX11 group: 5 [2.7%] subjects; EU-Perjeta® group: 3 [1.5%] subjects) experienced IRRs. (Table 19)

In the adjuvant HER2-targeted therapy period, a total of 11 (3.5%) subjects (HLX11-HLX11 group: 4 [2.6%] subjects; EU-Perjeta®-EU-Perjeta® group: 3 [3.8%] subjects; EU-Perjeta®-HLX11 group: 4 [5.1%] subjects) experienced IRRs, all of which were non-serious Grade 1-2 events and have resolved. A total of 9 (2.9%) subjects (HLX11-HLX11 group: 3 [1.9%] subjects; EU-Perjeta®-EU-Perjeta® group: 3 [3.8%] subjects; EU-Perjeta®-HLX11 group: 3 [3.8%] subjects) experienced IRRs related to HLX11/EU-Perjeta®. (Table 20)

In the overall treatment period, a total of 84 (9.3%) subjects (HLX11 (not re-randomized) group: 22 [7.4%] subjects; EU-Perjeta® (not re-randomized) group: 18 [6.1%] subjects; HLX11-HLX11 group: 20 [13.0%] subjects; EU-Perjeta®-EU-Perjeta® group: 11 [13.9%] subjects; EU-Perjeta®-HLX11 group: 13 [16.5%] subjects) experienced IRRs. (Table 21)

Hypersensitivity reactions/ Anaphylaxis

Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms of these reactions overlap. Due to the clinical difficulty in distinguishing between IRRs and hypersensitivity reactions/anaphylaxis, the investigators in the HLX11 clinical trials typically categorized and recorded the symptoms and signs of these reactions as IRRs (as above results). Excluding IRRs, the occurrence of other identified adverse events of hypersensitivity reactions/anaphylaxis is as follows:

a) HLX11-001: There were no reports of hypersensitivity reactions/anaphylaxis.

b) HLX11-BC301:

In the neoadjuvant therapy period, a total of 4 (0.4%) subjects (HLX11 group: 0 subjects; EU-Perjeta® group: 4 [0.9%] subjects) experienced hypersensitivity reactions/anaphylaxis, all of which were non-serious events, unrelated to HLX11/EU-Perjeta® and have resolved. (Table 22)

In the adjuvant chemotherapy period, no subjects experienced hypersensitivity reaction/ anaphylaxis.

In the adjuvant HER2-targeted therapy period, a total of 1 (0.3%) subject (HLX11-HLX11 group: 0 subjects; EU-Perjeta®-EU-Perjeta® group: 0 subjects; EU-Perjeta®-HLX11 group: 1 [1.3%] subject) experienced hypersensitivity reaction/anaphylaxis, which was a non-serious event related to HLX11/EU-Perjeta® and has resolved. (Table 23)

In the overall treatment period, a total of 5 (0.6%) subjects (HLX11 (not re-randomized) group: 0 subjects; EU-Perjeta® (not re-randomized) group: 3 [1.0%] subjects; HLX11-HLX11 group: 0 subjects; EU-Perjeta®-EU-Perjeta® group: 0 subjects; EU-Perjeta®-HLX11 group: 2 [2.5%] subjects) experienced hypersensitivity reactions/anaphylaxis. (Table 24)

Impact on quality of life:

Patients may experience considerable discomfort during a reaction (e.g., chills, rigors, flushing, breathing difficulty, vomiting, itching, headache), although symptoms are likely to resolve completely following the infusion. Hence, such reactions are likely to have no long-term impact on quality of life.

On the other hand, although severe infusion reactions, hypersensitivity and anaphylactic reactions to pertuzumab are rare events, such reactions would prevent the patient from continuing treatment.

Table 18 Summary of IRRs in HLX11-BC301 study – Neoadjuvant Therapy Period

	HLX11 (N=453)	EU-Perjeta® (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant Therapy Period	453	454	907
Infusion-related reactions (IRRs)			
Non-serious	35 (7.7) 94	36 (7.9) 82	71 (7.8) 176
Serious	0	0	0
Grade 1-2	35 (7.7) 94	36 (7.9) 82	71 (7.8) 176
Grade ≥3	0	0	0
Resolved	35 (7.7) 94	36 (7.9) 82	71 (7.8) 176
Not Resolved	0	0	0
Related to HLX11/Perjeta®	18 (4.0) 65	18 (4.0) 45	36 (4.0) 110
Unrelated to HLX11/Perjeta®	17 (3.8) 29	18 (4.0) 37	35 (3.9) 66

Table 19 Summary of IRRs in HLX11-BC301 study – Adjuvant Chemotherapy Period

	HLX11 (N=453)	EU-Perjeta® (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Adjuvant Chemotherapy Period	186	197	383
Infusion-related reactions (IRRs)			
Non-serious	5 (2.7) 13	3 (1.5) 17	8 (2.1) 30
Serious	0	0	0
Grade 1-2	5 (2.7) 13	3 (1.5) 17	8 (2.1) 30
Grade ≥3	0	0	0
Resolved	5 (2.7) 13	2 (1.0) 16	7 (1.8) 29
Not Resolved	0	1 (0.5) 1	1 (0.3) 1
Related to HLX11/Perjeta®	0	0	0
Unrelated to HLX11/Perjeta®	5 (2.7) 13	3 (1.5) 17	8 (2.1) 30

Table 20 Summary of IRRs in HLX11-BC301 study – Adjuvant HER2-Targeted Therapy Period

	HLX11-HLX11 (N=154)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)	Total (N=907)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-Targeted Therapy Period	154	79	79	312
Infusion-related reactions (IRRs)				
Non-serious	4 (2.6) 4	3 (3.8) 5	4 (5.1) 11	11 (3.5) 20
Serious	0	0	0	0
Grade 1-2	4 (2.6) 4	3 (3.8) 5	4 (5.1) 11	11 (3.5) 20
Grade ≥3	0	0	0	0
Resolved	4 (2.6) 4	3 (3.8) 5	4 (5.1) 11	11 (3.5) 20
Not Resolved	0	0	0	0
Related to HLX11/Perjeta®	3 (1.9) 3	3 (3.8) 5	3 (3.8) 8	9 (2.9) 16
Unrelated to HLX11/Perjeta®	1 (0.6) 1	0	1 (1.3) 3	2 (0.6) 4

Table 21 Summary of IRRs in HLX11-BC301 study – Overall Treatment Period

	HLX11			EU-Perjeta®				Total
	Not Re-randomized (N=299)	HLX11-HLX11 (N=154)	Total (N=453)	Not Re-randomized (N=296)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)	Total (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Overall Treatment Period	299	154	453	296	79	79	454	907
Infusion-related reactions (IRRs)								
Non-serious	22 (7.4) 62	20 (13.0) 49	42 (9.3) 111	18 (6.1) 39	11 (13.9) 19	13 (16.5) 57	42 (9.3)115	84 (9.3) 226
Serious	0	0	0	0	0	0	0	0
Grade 1-2	22 (7.4) 62	20 (13.0) 49	42 (9.3) 111	18 (6.1) 39	11 (13.9) 19	13 (16.5) 57	42 (9.3)115	84 (9.3) 226
Grade ≥3	0	0	0	0	0	0	0	0
Resolved	22 (7.4) 62	20 (13.0) 49	42 (9.3) 111	18 (6.1) 39	11 (13.9) 19	12 (15.2) 56	41 (9.0)114	83 (9.2) 225
Not Resolved	0	0	0	0	0	1 (1.3) 1	1 (0.2) 1	1 (0.1) 1
Related to HLX11/Perjeta®	13 (4.3) 50	8 (5.2) 18	21 (4.6) 68	10 (3.4) 27	8 (10.1) 13	5 (6.3) 18	23 (5.1) 58	44 (4.9) 126
Unrelated to HLX11/Perjeta®	9 (3.0) 12	12 (7.8) 31	21 (4.6) 43	8 (2.7) 12	3 (3.8) 6	8 (10.1) 39	19 (4.2) 57	40 (4.4) 100

Table 22 Summary of Hypersensitivity reactions/ Anaphylaxis in HLX11-BC301 study – Neoadjuvant Therapy Period

	HLX11 (N=453)	EU-Perjeta® (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant Therapy Period	453	454	907
Hypersensitivity reactions/ Anaphylaxis			
Non-serious	0	4 (0.9) 4	4 (0.4) 4
Serious	0	0	0
Grade 1-2	0	2 (0.4) 2	2 (0.2) 2
Grade ≥3	0	2 (0.4) 2	2 (0.2) 2
Resolved	0	4 (0.9) 4	4 (0.4) 4
Not Resolved	0	0	0
Related to HLX11/Perjeta®	0	0	0
Unrelated to HLX11/Perjeta®	0	4 (0.9) 4	4 (0.4) 4

Table 23 Summary of Hypersensitivity reactions/ Anaphylaxis in HLX11-BC301 study – Adjuvant HER2-Targeted Therapy Period

	HLX11-HLX11 (N=154)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)	Total (N=907)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-Targeted Therapy Period	154	79	79	312
Hypersensitivity reactions/ Anaphylaxis				
Non-serious	0	0	1 (1.3) 1	1 (0.3) 1
Serious	0	0	0	0
Grade 1-2	0	0	1 (1.3) 1	1 (0.3) 1
Grade ≥3	0	0	0	0
Resolved	0	0	1 (1.3) 1	1 (0.3) 1
Not Resolved	0	0	0	0
Related to HLX11/Perjeta®	0	0	1 (1.3) 1	1 (0.3) 1
Unrelated to HLX11/Perjeta®	0	0	0	0

Table 24 Summary of Hypersensitivity reactions/ Anaphylaxis in HLX11-BC301 study – Overall Treatment Period

	HLX11			EU-Perjeta®				Total
	Not Re-randomized (N=299)	HLX11-HLX11 (N=154)	Total (N=453)	Not Re-randomized (N=296)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)	Total (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Overall Treatment Period	299	154	453	296	79	79	454	907
Hypersensitivity reactions/ Anaphylaxis								
Non-serious	0	0	0	3 (1.0) 3	0	2 (2.5) 2	5 (1.1) 5	5 (0.6) 5
Serious	0	0	0	0	0	0	0	0
Grade 1-2	0	0	0	2 (0.7) 2	0	1 (1.3) 1	3 (0.7) 3	3 (0.3) 3
Grade ≥3	0	0	0	1 (0.3) 1	0	1 (1.3) 1	2 (0.4) 2	2 (0.2) 2
Resolved	0	0	0	3 (1.0) 3	0	2 (2.5) 2	5 (1.1) 5	5 (0.6) 5
Not Resolved	0	0	0	0	0	0	0	0
Related to HLX11/Perjeta®	0	0	0	0	0	1 (1.3) 1	1 (0.2) 1	1 (0.1) 1
Unrelated to HLX11/Perjeta®	0	0	0	3 (1.0) 3	0	1 (1.3) 1	4 (0.9) 4	4 (0.4) 4

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not be susceptible to infusion-associated reactions, hypersensitivity or anaphylaxis to pertuzumab.

History of asthma, eczema, hay fever (atopy) or hypersensitivity to any of the excipients may slightly increase the risk of developing an IRR (on the day of or the day after a pertuzumab infusion), but it's without any firm conclusion due to small number of patients with a history of atopy. Moreover, patients with a history of atopy did not appear to be at increased risk of anaphylaxis or hypersensitivity reactions.

Prior and concomitant trastuzumab exposure did not appear to reduce or exacerbate the infusion-associated events seen with pertuzumab.

Preventability:

Infusion reactions, hypersensitivity and anaphylactic reactions to pertuzumab cannot be reliably predicted or prevented. However, the incidence and severity of infusion reactions may be reduced by premedication and appropriate monitoring of the patient during infusions, with slowing or discontinuation of the infusion if needed.

Impact on the risk-benefit balance of the product:

The impact of infusion- associated reactions to the benefit-risk balance of HLX11 is considered to be low since the symptoms generally resolve completely once the infusion has been discontinued, slowed or completed. IRRs are commonplace in oncology practice and patients are already at higher risk of reactions due to the concomitant administration of taxanes and trastuzumab. Due to this increased risk, oncology patients are routinely monitored for the typical symptoms of an infusion related event.

Current pharmacovigilance plans and product labels include guidance for patient management in the event of a hypersensitivity or infusion related reaction and these measures are considered adequate to manage the risk.

Public health impact:

The potential public health impact of pertuzumab-related IRRs is considered low. Patients receiving trastuzumab or taxanes are already at risk of IRRs and monitoring and treatment of IRRs is a routine part of oncology clinical practice.

Considering the incidence of anaphylaxis and hypersensitivity events with Grade ≥3 was low, the potential public health impact associated with this safety concern is considered to be low.

Important Identified Risk 2: Congestive heart failure/ Left ventricular dysfunction

Potential mechanisms:

Since pertuzumab targets HER2, like trastuzumab, there is a potential risk of cardiac dysfunction, particularly in patients who have received prior anthracycline treatment. HER2 signaling is required for the growth, repair and survival of cardiomyocytes. These repair mechanisms involve HER2-HER4 heterodimeric receptors which trigger the myocyte survival pathways required during the activation of acute stress signals mainly by anthracyclines. Available clinical evidence to date from studies in MBC and EBC of pertuzumab suggests a similar or only slightly increased risk of cardiotoxicity with the addition of pertuzumab to trastuzumab. It is possible that the maximum

effect on cardiomyocytes is already exerted by trastuzumab and that the addition of pertuzumab does not add to this.

Evidence source(s) and strength of evidence:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

Characterisation of the risk:

- The data of the reference product:

According to the clinical data of the reference product, the incidence of congestive heart failure (CHF) in early and metastatic breast cancer patients (N=3830) is 2.2% (95% CI: 1.7; 2.7). CHF is defined by SAEs in the SMQ (wide) Cardiac Failure.

In the clinical trials of the reference product, there were two fatal CHF events in the APHINITY study: an event of cardiogenic shock in the Ptz + H +Chemo arm, and an event of cardiac failure in the placebo + Herceptin + chemotherapy (Pla + H + Chemo) arm.

In the TRYPHAENA study of the reference product, LVEF declines of at least 10%-points from baseline to below 50% were observed in 15 patients, based on local and central data. At the end of the study, the LVEF measurements had improved to ≥ 50% in all but 4 patients.

In the APHINITY study of the reference product, Grade ≥ 3 events of cardiac failure and ejection fraction decreased (EFD) were observed in 2.3% of patients in the Ptz + H + Chemo arm and in 2.0% of patients the Pla + H + Chemo arm. Note that a primary cardiac event (defined as either Heart Failure [NYHA Class III or IV] and a drop in LVEF of at least 10 EF points from baseline AND to below 50%, or Cardiac Death) was reported in 0.7% of patients in the Ptz + H + Chemo arm and 0.3% of patients in the Pla + H + Chemo arm.

In the BERENICE study of the reference product, the rates of cardiac toxicity during the overall study period were as expected in the two treatment arms. The rates of declines in LVEF (of at least ≥10% points from baseline to a value of < 50%) as measured by echocardiography or MUGA were also as expected (13.6% [n = 27; 95% CI: 9.1; 19.1] of patients in Cohort A and 12.1% [n = 24; 95% CI: 7.9; 17.5] in Cohort B).The rates of asymptomatic LVEF decline (reported as an AE with the term ‘ejection fraction decreased’) were 13.6% (n = 27) of patients in Cohort A and 13.1% [n = 26] in Cohort B.

- The data of HLX11 clinical studies:

a) HLX11-001:

A total of 19 (11.9%) subjects (HLX11 group: 3 [7.5%] subjects; EU-Perjeta® group: 8 [20.0%] subjects; US-Perjeta® group: 7 [17.5%] subjects; CN-Perjeta® group: 1 [2.5%] subject) experienced any cardiac adverse events, all of which were non-serious Grade 1-2 adverse events and have resolved. A total of 8 (5.0%) subjects (HLX11 group: 1 [2.5%] subject; EU-Perjeta® group: 4 [10.0%] subjects; US-Perjeta® group: 2 [5.0%] subjects; CN-Perjeta® group: 1 [2.5%] subject) experienced HLX11/Perjeta®-related any cardiac adverse events. No subjects experienced left ventricular dysfunction (LVD), LVEF decline, or CHF events. (Table 25)

b) HLX11-BC301:

In the neoadjuvant therapy period, a total of 70 (7.7%) subjects (HLX11 group: 31 [6.8%] subjects; EU-Perjeta® group: 39 [8.6%] subjects) experienced any cardiac adverse events. The majority of cardiac adverse events were non-serious Grade 1-2 events, with only 2 (0.4%) subjects from the

EU-Perjeta® group experiencing serious ≥Grade 3 adverse events. Most cardiac adverse events were related to HLX11/EU-Perjeta® and the majority have resolved. A total of 2 (0.2%) subjects experienced LVD events, including 1 (0.2%) subject from the HLX11 group who had a non-serious <Grade 3 LVD (this AE occurred in a 63-year-old elderly patient with a history of left atrial enlargement and mild mitral regurgitation, and echocardiogram after treatment suggesting mild left ventricular diastolic dysfunction without LVEF decline or any symptoms of heart failure), and 1 (0.2%) subject from the EU-Perjeta® group who had a serious ≥Grade 3 acute left ventricular failure. Both events were related to HLX11/EU-Perjeta® and have not resolved. The acute left ventricular failure event was classified as a CHF SAE. No events of LVEF decline were reported. No cases of Grade 5 CHF events leading to death occurred. (Table 26)

In the adjuvant chemotherapy period, a total of 26 (6.8%) subjects (HLX11 group: 9 [4.8%] subjects; EU-Perjeta® group: 17 [8.6%] subjects) experienced any cardiac adverse events. No subjects experienced LVD or CHF events. (Table 27)

In the adjuvant HER2-targeted therapy period, a total of 35 (11.2%) subjects (HLX11-HLX11 group: 18 [11.7%] subjects; EU-Perjeta®-EU-Perjeta® group: 8 [10.1%] subjects; EU-Perjeta®-HLX11 group: 9 [11.4%] subjects) experienced any cardiac adverse events. The majority of cardiac adverse events were non-serious Grade 1-2 events, with only 1 (0.6%) subject in the HLX11-HLX11 group experiencing a ≥Grade 3 serious adverse event (cardiac failure) that was related to HLX11 and has not resolved. This cardiac failure event was classified as a LVD event and a CHF serious adverse event (SAE). Most cardiac adverse events were related to HLX11/EU-Perjeta® and the majority have resolved. No events of LVEF decline were reported. No cases of Grade 5 CHF events leading to death occurred. (Table 28)

In the overall treatment period, a total of 108 (11.9%) subjects (HLX11 (not re-randomized) group: 20 [6.7%] subjects; EU-Perjeta® (not re-randomized) group: 26 [8.8%] subjects; HLX11-HLX11 group: 25 [16.2%] subjects; EU-Perjeta®-EU-Perjeta® group: 17 [21.5%] subjects; EU-Perjeta®-HLX11 group: 20 [25.3%] subjects) experienced any cardiac adverse events. (Table 29)

Note: LVEF decline was LVEF<50% and ≥10% decrease from baseline.

Impact on quality of life:

Cardiac failure may have a significant impact on the quality of life on individual patients and the presence of pre-existing risk factors or co-morbidities need to be taken into account when determining the benefit risk evaluation for individual patients.

Table 25 Summary of Congestive heart failure/ Left ventricular dysfunction events in HLX11-001 study

	HLX11 (N=40)	EU-Perjeta® (N=40)	US-Perjeta (N=40)	CN-Perjeta (N=40)	Total (N=160)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Any Cardiac AEs					
Non-serious	3 (7.5) 3	8 (20.0) 11	7 (17.5) 10	1 (2.5) 1	19 (11.9) 25
Serious	0	0	0	0	0
Grade 1-2	3 (7.5) 3	8 (20.0) 11	7 (17.5) 10	1 (2.5) 1	19 (11.9) 25
Grade ≥3	0	0	0	0	0
Resolved	3 (7.5) 3	8 (20.0) 11	7 (17.5) 10	1 (2.5) 1	19 (11.9) 25
Not Resolved	0	0	0	0	0
Related to HLX11/Perjeta®	1 (2.5) 1	4 (10.0) 5	2 (5.0) 3	1 (2.5) 1	8 (5.0) 10
Unrelated to HLX11/Perjeta®	2 (5.0) 2	4 (10.0) 6	5 (12.5) 7	0	11 (6.9) 15

Table 26 Summary of Congestive heart failure/ Left ventricular dysfunction events in HLX11-BC301 study – Neoadjuvant Therapy Period

	HLX11 (N=453)	EU-Perjeta® (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant Therapy Period	453	454	907
Any Cardiac AEs			
Non-serious	31 (6.8) 40	37 (8.1) 49	68 (7.5) 89
Serious	0	2 (0.4) 2	2 (0.2) 2
Grade 1-2	31 (6.8) 40	37 (8.1) 49	68 (7.5) 89
Grade ≥3	0	2 (0.4) 2	2 (0.2) 2
Resolved	21 (4.6) 28	30 (6.6) 39	51 (5.6) 67
Not Resolved	10 (2.2) 12	9 (2.0) 12	19 (2.1) 24
Related to HLX11/Perjeta®	22 (4.9) 29	24 (5.3) 34	46 (5.1) 63
Unrelated to HLX11/Perjeta®	9 (2.0) 11	15 (3.3) 17	24 (2.6) 28
LVD			
Left ventricular dysfunction	1 (0.2) 1	0	1 (0.1) 1
Acute left ventricular failure	0	1 (0.2) 1	1 (0.1) 1
Non-serious	1 (0.2) 1	0	1 (0.1) 1
Serious	0	1 (0.2) 1	1 (0.1) 1
Grade 1-2	1 (0.2) 1	0	1 (0.1) 1
Grade ≥3	0	1 (0.2) 1	1 (0.1) 1
Resolved	0	0	0
Not Resolved	1 (0.2) 1	1 (0.2) 1	2 (0.2) 2
Related to HLX11/Perjeta®	1 (0.2) 1	1 (0.2) 1	2 (0.2) 2
Unrelated to HLX11/Perjeta®	0	0	0

Table 27 Summary of Congestive heart failure/ Left ventricular dysfunction events in HLX11-BC301 study – Adjuvant Chemotherapy Period

	HLX11 (N=453)	EU-Perjeta® (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Adjuvant Chemotherapy Period	186	197	383
Any Cardiac AEs			
Non-serious	7 (3.8) 11	17 (8.6) 18	24 (6.3) 29
Serious	2 (1.1) 2	0	2 (0.5) 2
Grade 1-2	8 (4.3) 12	17 (8.6) 18	25 (6.5) 30
Grade ≥3	1 (0.5) 1	0	1 (0.3) 1
Resolved	7 (3.8) 11	13 (6.6) 14	20 (5.2) 25
Not Resolved	2 (1.1) 2	4 (2.0) 4	6 (1.6) 6
Related to HLX11/Perjeta®	3 (1.6) 3	2 (1.0) 2	5 (1.3) 5
Unrelated to HLX11/Perjeta®	6 (3.2) 10	15 (7.6) 16	21 (5.5) 26

Table 28 Summary of Congestive heart failure/ Left ventricular dysfunction events in HLX11-BC301 study – Adjuvant HER2-Targeted Therapy Period

	HLX11-HLX11 (N=154)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)	Total (N=907)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-Targeted Therapy Period	154	79	79	312
Any Cardiac AE				
Non-serious	17 (11.0) 26	8 (10.1) 11	9 (11.4) 14	34 (10.9) 51
Serious	1 (0.6) 1	0	0	1 (0.3) 1
Grade 1-2	17 (11.0) 26	8 (10.1) 11	9 (11.4) 14	34 (10.9) 51
Grade ≥3	1 (0.6) 1	0	0	1 (0.3) 1
Resolved	9 (5.8) 17	6 (7.6) 9	6 (7.6) 9	21 (6.7) 35
Not Resolved	9 (5.8) 10	2 (2.5) 2	3 (3.8) 5	14 (4.5) 17
Related to HLX11/Perjeta®	15 (9.7) 24	8 (10.1) 11	5 (6.3) 9	28 (9.0) 44
Unrelated to HLX11/Perjeta®	3 (1.9) 3	0	4 (5.1) 5	7 (2.2) 8
LVD				
Cardiac failure	1 (0.6) 1	0	0	1 (0.3) 1
Non-serious	0	0	0	0
Serious	1 (0.6) 1	0	0	1 (0.3) 1
Grade 1-2	0	0	0	0
Grade ≥3	1 (0.6) 1	0	0	1 (0.3) 1
Resolved	0	0	0	0
Not Resolved	1 (0.6) 1	0	0	1 (0.3) 1
Related to HLX11/Perjeta®	1 (0.6) 1	0	0	1 (0.3) 1
Unrelated to HLX11/Perjeta®	0	0	0	0

Table 29 Summary of Congestive heart failure/ Left ventricular dysfunction events in HLX11-BC301 study – Overall Treatment Period

	HLX11			EU-Perjeta®			Total	
	Not Re-randomized (N=299)	HLX11-HLX11 (N=154)	Total (N=453)	Not Re-randomized (N=296)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)	Total (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Overall Treatment Period	299	154	453	296	79	79	454	907
Any Cardiac AE								
Non-serious	20 (6.7) 25	22 (14.3) 52	42 (9.3) 77	24 (8.1) 33	17 (21.5) 24	20 (25.3) 35	61 (13.4) 92	103 (11.4) 169
Serious	0	3 (1.9) 3	3 (0.7) 3	2 (0.7) 2	0	0	2 (0.4) 2	5 (0.6) 5
Grade 1-2	20 (6.7) 25	23 (14.9) 53	43 (9.5) 78	24 (8.1) 33	17 (21.5) 24	20 (25.3) 35	61 (13.4) 92	104 (11.5) 170
Grade ≥3	0	2 (1.3) 2	2 (0.4) 2	2 (0.7) 2	0	0	2 (0.4) 2	4 (0.4) 4
Resolved	10 (3.3) 13	14 (9.1) 43	24 (5.3) 56	15 (5.1) 21	14 (17.7) 21	16 (20.3) 29	45 (9.9) 71	69 (7.6) 127
Not Resolved	10 (3.3) 12	11 (7.1) 12	21 (4.6) 24	11 (3.7) 14	3 (3.8) 3	4 (5.1) 6	18 (4.0) 23	39 (4.3) 47
Related to HLX11/Perjeta®	16 (5.4) 19	18 (11.7) 37	34 (7.5) 56	14 (4.7) 21	12 (15.2) 18	8 (10.1) 17	34 (7.5) 56	68 (7.5) 112
Unrelated to HLX11/Perjeta®	4 (1.3) 6	7 (4.5) 18	11 (2.4) 24	12 (4.1) 14	5 (6.3) 6	12 (15.2) 18	29 (6.4) 38	40 (4.4) 62
LVD								
Cardiac failure	0	1 (0.6) 1	1 (0.2) 1	0	0	0	0	1 (0.1) 1
Left ventricular dysfunction	1 (0.3) 1	0	1 (0.2) 1	0	0	0	0	1 (0.1) 1
Acute left ventricular failure	0	0	0	1 (0.3) 1	0	0	1 (0.2) 1	1 (0.1) 1
Non-serious	1 (0.3) 1	0	1 (0.2) 1	0	0	0	0	1 (0.1) 1
Serious	0	1 (0.6) 1	1 (0.2) 1	1 (0.3) 1	0	0	1 (0.2) 1	2 (0.2) 2
Grade 1-2	1 (0.3) 1	0	1 (0.2) 1	0	0	0	0	1 (0.1) 1
Grade ≥3	0	1 (0.6) 1	1 (0.2) 1	1 (0.3) 1	0	0	1 (0.2) 1	2 (0.2) 2
Resolved	0	0	0	0	0	0	0	0
Not Resolved	1 (0.3) 1	1 (0.6) 1	2 (0.4) 2	1 (0.3) 1	0	0	1 (0.2) 1	3 (0.3) 3
Related to HLX11/Perjeta®	1 (0.3) 1	1 (0.6) 1	2 (0.4) 2	1 (0.3) 1	0	0	1 (0.2) 1	3 (0.3) 3
Unrelated to HLX11/Perjeta®	0	0	0	0	0	0	0	0

Risk factors and risk groups:

Risk factors such as age of 60 years or older, prior chemotherapy, registration LVEF less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer.

Anthracycline exposure: Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease. The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose.

Concurrent trastuzumab: The cardiac changes associated with trastuzumab are mostly reversible, do not appear to be dose-related and do not involve histological changes in cardiac tissue. Identified risk factors include exposure to anthracyclines or paclitaxel, low LVEF at baseline, age > 60 years, obesity, previous heart disease and hypertension. Current monitoring of cardiac function uses changes in LVEF as a reference for cardiotoxicity. Age, anthracycline exposure, and the presence of cardiovascular risk factors predicted cardiac AEs in trastuzumab recipients. No clear relation to a cumulative dose of trastuzumab has been described. After treatment interruption, clinical and subclinical signs of heart failure are mostly reversible and reinitiating of trastuzumab after recovery is often well tolerated.

Adjuvant breast radiotherapy: A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s. Among patients treated during 1973 - 82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993 - 2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards. Internal mammary chain irradiation increases heart dose exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease.

Preventability:

Careful monitoring and early detection of (asymptomatic) LVEF reduction from baseline is a reliable screening mechanism for the individual patient decisions to continue or stop treatment with anticancer agents in general. All patients enrolled in pertuzumab trials undergo routine cardiac monitoring by ECHO or MUGA scan.

Impact on the risk-benefit balance of the product:

The impact of congestive heart failure/left ventricular dysfunction on the benefit-risk balance of pertuzumab is considered to be low. The incidence of CHF in patients receiving pertuzumab, trastuzumab and chemotherapy is low. Careful monitoring and following the dose management algorithm suggested in the product label further reduces the likelihood of a heart failure/left ventricular dysfunction event. The current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of this safety concern is considered to be low because of the low frequency of CHF in patients with advanced malignancy receiving pertuzumab, trastuzumab and chemotherapy and because most cardiac events appear to be asymptomatic reversible declines in LVEF.

Important Potential Risk 1: Oligohydramnios

Potential mechanisms:

Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in an embryo-fetal study when pertuzumab, the reference product, was administered intravenously from GD19 through GD50 to pregnant cynomolgus monkeys (the period of organogenesis in this species is GD20-50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 in 30 mg/kg and 1 of 2 in 100 mg/kg), ventricular septal defects (1 of 6 in 30 mg/kg), thin ventricular wall (1 of 2 in 100 mg/kg) and minor skeletal defects (external - 3 of 6 in 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations, were confirmed.

The embryo-fetal effects observed with pertuzumab and trastuzumab are consistent with the role HER-family members play in the development and differentiation of ectodermal/epithelial tissues, including that of renal tissue.

Evidence source(s) and strength of evidence:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 non-clinical safety data, HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

No clinical studies have been performed in pregnant women.

Characterisation of the risk:

There is no accepted standard definition for oligohydramnios. However, the incidence has been estimated as being between 0.4 and 1.7 % of pregnancies. 225,669 consecutive pregnancies births were reviewed and concluded that 0.99/1000 pregnancies were complicated by oligohydramnios.

- The data of the reference product:

No events of oligohydramnios have been reported in patients receiving pertuzumab in MotHER pregnancy registry as of 31Jan2018 (cut-off date for the Final annual data summary for this registry). Cumulatively, up to 07Jun2020, six initial cases of oligohydramnios and one relevant follow-up case reported PT Amniotic fluid volume decrease were reported. In addition, AEs were reported for 2 initial child cases: pulmonary hypoplasia and atrial septal defect.

Oligohydramnios is associated with serious risks to fetal development. Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development were observed in cynomolgus monkeys. Further clinical complications of oligohydramnios could include renal and pulmonary hypoplasia (which could be lethal) and skeletal malformations due to intrauterine growth restriction. The available data are consistent with the known information in the reference product pertuzumab SmPC. No events of fatal oligohydramnios have been reported in patients receiving pertuzumab.

Oligohydramnios is classified as a potential risk based on non-clinical data and because cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab and because of findings in non-clinical studies. No events of oligohydramnios have been reported in patients receiving pertuzumab.

- The data of HLX11 clinical studies:

a) HLX11-001: All subjects in this clinical study were male, and oligohydramnios is not applicable to male subjects. One case of the partner's pregnancy was reported in this study, which was followed by an elective abortion, and no events of oligohydramnios were reported.

b) HLX11-BC301: No available data, and no events of oligohydramnios were reported.

Impact on quality of life:

Oligohydramnios is associated with serious risks to fetal development and therefore may have a significant impact on an individual patient. Women of childbearing potential are advised to use effective contraceptive measures during treatment and for 6 months after the last dose of pertuzumab.

The need to avoid pregnancy during and for 6 months after pertuzumab treatment may affect patients' quality of life. However, patients are likely to face the same restrictions even if pertuzumab were not given, since most treatment for breast cancer (chemotherapy, trastuzumab, hormone therapy and radiotherapy) are associated with significant risks to the developing fetus.

Risk factors and risk groups:

Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive pertuzumab treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios. Pregnant women with sickle cell disease are at increased risk of oligohydramnios. Primiparity is associated with an increased rate of oligohydramnios.

Preventability:

The risk of oligohydramnios is avoidable providing effective contraceptive measures are applied by women of childbearing potential during treatment and for 7 months after the last dose of pertuzumab in combination with trastuzumab.

Impact on the risk-benefit balance of the product:

Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The public health impact associated with this safety concern is considered to be low. Pregnancies are usually contraindicated in patients with advanced malignancy due to the risks of cytotoxic drugs, hormone therapy and/or radiotherapy, as well as the limited life expectancy of the mother.

Important Potential Risk 2: Risk in fertility in humans

Potential mechanisms:

There is no known mechanism for the risk in fertility in humans as a result of treatment with pertuzumab. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab on fertility. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab. However, a non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses,

oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity.

Evidence source(s) and strength of evidence:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

This is a theoretical risk based on safety results of a non-clinical reproductivity study of the reference product.

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.

Characterisation of the risk:

- The data of the reference product:

Cumulatively, no cases of the risk in fertility in humans or fertility disorders have been reported for the reference product (up to 03May2017).

No SAEs of the risk in fertility in humans or fertility disorders have been reported in patients receiving the reference product in clinical trials.

- The data of HLX11 clinical studies:

No cases of the risk in fertility in humans or fertility disorders have been reported for HLX11 in the clinical trials.

Impact on quality of life:

Attention to future fertility following diagnosis of breast cancer in younger patients who are pre-menopausal or of child-bearing age are extremely important. Both ESMO and ASCO guidelines recommend referral to a fertility specialist for women interested in preserving their fertility.

Standard options for fertility preservation such as embryo and oocyte cryopreservation or other treatments for fertility in patients who may develop fertility disorders may have an impact on the quality of life of the patient. However, younger women are more likely to present with a more advanced stage of disease and are also more likely to develop more aggressive subtypes of breast cancer (including HER2-positive breast cancer) and have lower survival rates compared to older women. Therefore, it is more likely that the benefit of treatment for the underlying disease outweighs the impact in younger women.

Risk factors and risk groups:

The median age at diagnosis of HER2-positive breast cancer is the mid-50s, therefore at least half the patients likely to receive pertuzumab treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Preventability:

Currently there is no data of risk of fertility in humans following the use of pertuzumab. Pertuzuamb labelling indicates that women of childbearing potential and female partners of male patients of childbearing potential should use effective contraception while receiving pertuzumab

and for 6 months following the last dose of pertuzumab. Chemotherapies are likely to reduce the chances of conception, implantation and embryogenesis and clinical guidelines recommend referral to a fertility specialist for women of childbearing potential with breast cancer interested in preserving their fertility.

Impact on the risk-benefit balance of the product:

Current routine risk minimization measures in place recommend avoidance of pregnancy during the use of pertuzumab.

Public health impact:

The public health impact associated with this safety concern is considered to be low since to date there is no indication of the risk in fertility in humans following the use of pertuzumab.

Important Potential Risk 3: Risk in patients aged 75 years or older

Potential mechanisms:

The elderly population is more susceptible to AEs, including those related to their comorbidities.

Evidence source(s) and strength of evidence:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

This is a theoretical risk, and no pertuzumab dose adjustment is required for adult patients of any age, including patients aged 65 years or older.

Characterisation of the risk:

- The data of the reference product:

No upper age limit was applied and adult patients of any age could enter the pertuzumab clinical trials if they met the other eligibility criteria. The relative lack of patients in the ≥ 75 year age category likely reflects the higher incidence of comorbidities (such as cardiac failure or renal impairment) in older patients and concerns about administration of chemotherapy to elderly patients. A total of 464 patients aged ≥ 65 years have been evaluated in key pertuzumab clinical studies, including 47 patients aged ≥ 75 years (~10% of patients aged ≥ 65 years). An estimated cumulative total of 75,800 patients aged ≥ 65 years have received pertuzumab in routine clinical practice, and assuming a similar ratio to that seen in clinical trials, approximately 7,500 of these patients may have been aged ≥ 75 years.

No significant differences in safety of pertuzumab have been observed between elderly patients aged 65 - 75 years and patients aged below 65 years, with the exception of decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhoea which had at least 5% higher in patients aged 65 years of age or higher, compared to patients aged less than 65 years of age. There are no distinct biological differences between patients aged 65 - 75 years and patients aged ≥ 75 years, and patients in these two age categories are likely to show considerable overlap in biological characteristics such as cardiac, renal and hepatic function, performance status and presence of comorbidities.

Accordingly, no differences in safety of pertuzumab are expected for patients aged ≥ 75 years compared to patients aged 65 - 75 years. No meaningful increase in frequency, severity or

specificity or a pattern of the reported events in patients aged 75 years and older was observed. No differences in efficacy have been observed.

- The data of HLX11 clinical studies:

a) HLX11-001: There were no subjects aged 75 years or older, and no relevant data to this risk are available.

b) HLX11-BC301: In the overall treatment period, a total of 83 (9.2%) subjects aged ≥65 years participated in the study, including 3 (0.3%) subjects aged ≥75 years (HLX11 (Not re-randomized) group: 2 [0.4%] subjects; EU-Perjeta® (Not re-randomized) group: 1 [0.2%] subject). None of these 3 subjects aged ≥75 years experienced serious adverse events. The number of subjects aged ≥75 years was too small to draw any meaningful conclusions about efficacy for this age group.

Impact on quality of life:

Not applicable.

Risk factors and risk groups:

Patients aged ≥ 75 years.

Preventability:

In elderly patients (≥ 65 years), diarrhoea has been observed at a higher rate (increased risk of diarrhoea in elderly patients is already included in pertuzumab product label). Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients.

Impact on the risk-benefit balance of the product:

The impact of the risk of use of pertuzumab in patients 75 years or older on the overall benefit-risk balance of the product is considered low. Age-related information is already included in the product label for Poherdy, notably the warning about increased risk of diarrhoea in elderly patients. Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of pertuzumab-related AEs in patients aged 75 years or older is considered low, due to the small number of these patients receiving pertuzumab. The event of diarrhoea which is seen at a higher rate in these patients is manageable with treatment.

Important Potential Risk 4: Lack of efficacy due to immunogenicity

Potential mechanisms:

The production of ADAs is considered to occur via well-understood humoral responses to foreign antigens, namely coordination between antigen presenting cells, T-helper cells and B-cells.

Nearly all biopharmaceuticals may induce antibodies by various mechanisms, however, the frequency of these antibodies and the clinical impact, if any, varies widely. The mechanisms by which ADAs may impact efficacy include increased clearance of ADA/drug immune complexes thereby lowering drug exposure, as well as directly interfering with drug/target interactions (so-called neutralizing ADA).

Evidence source(s) and strength of evidence:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

This is a theoretical risk based on the potential mechanism, a low incidence of ADA formation has been observed in pertuzumab clinical trials.

Characterisation of the risk:

- The data of the reference product:

According to the clinical trials of the reference product, the incidence of ADA in the Phase I/II studies was lower (0.5%) than in the Phase III studies (2.9%) but the duration of therapy/observation was relatively short, reflecting the Phase I/II patient populations (which generally include patients with advanced refractory disease after failure of standard therapies) and the inclusion of patients with tumor types now known not to respond to pertuzumab-based therapy.

In the pivotal CLEOPATRA study, the median progression-free survival (PFS) was 12.5 months (95% CI: 2; 14) for Perjeta-treated patients in the ADA positive subgroup, which was consistent with results of the intent-to-treat (ITT) population in the control arm (12.4 months [95% CI: 10; 13]), whereas the median PFS for the Perjeta-treated/ADA negative subgroup was 18.7 months (95% CI: 16; 25). Overall response rate (ORR) was also lower in Perjeta-treated patients with ADA-positive samples than in the Perjeta-treated patients who were ADA-negative (ORR 45.5% [95% CI: 16.7; 76.6] vs. 80.2% [95% CI: 77.1; 85.7], respectively). However, these results should be viewed with caution since a low number of patients tested positive for ADA and the CIs were wide for PFS and ORR in the ADA positive subgroup. In addition, examination of individual independent review facility-assessed PFS data for each patient revealed that several of the patients with a positive ADA response receiving pertuzumab treatment achieved prolonged disease control and there was no clear temporal association between development of a positive ADA response and independent review facility- assessed progressive disease.

A search of the post-marketing data did not identify any cases of lack of efficacy due to reported ADA or immunogenicity from clinical and post-marketing sources (Perjeta PBRER [reporting interval: 08Jun2019 to 07Jun2020]). However, this is to be expected given that patients are rarely tested for ADAs outside of clinical trials.

The immunogenicity of the reference product has been assessed in more than 1500 pertuzumab treated patients in clinical trials. Based on data available to date, the incidence of ADA formation is low (~2.4%). ADA formation is also not generally associated with hypersensitivity reactions or anaphylaxis. Although an adverse effect of ADA formation on pertuzumab efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common.

- The data of HLX11 clinical studies:

a) HLX11-001:

The immunogenicity analysis showed that the serum concentration of ADA-positive subjects was similar to that of ADA-negative subject in each group, the differences in mean values of primary PK parameters were less than 10%, and no obvious effect of ADAs on PK were observed. No data relevant to this risk are available.

b) HLX11-BC301:

In the neoadjuvant therapy period and adjuvant chemotherapy period, the incidence of ADA/NAb was similar between the HLX11 and EU-Perjeta® groups (4.9% vs. 4.0% for ADA and 2.2% vs. 2.0% for NAb, respectively).

In the adjuvant HER2-targeted therapy period, the ADA incidence was 1.3% in the HLX11 total group (HLX11-HLX11 plus EU-Perjeta®-HLX11) and 3.8% in the EU-Perjeta® group (EU-Perjeta®-EU-Perjeta®), and no NAb was identified, indicating that the immunogenicity of HLX11 and EU-Perjeta® was comparable. In addition, the ADA incidence was 1.3% in the transition arm (EU-Perjeta®-HLX11) and 3.8% in the non-transition arm (EU-Perjeta®-EU-Perjeta®), indicating that the single transition of treatment from EU-Perjeta® to HLX11 did not increase the risk of immunogenicity.

In the overall treatment period, the overall ADA/NAb incidence was similar across the HLX11 total (HLX11 [not re-randomized] and HLX11-HLX11), EU-Perjeta®-HLX11, and EU-Perjeta® total (EU-Perjeta® [not re-randomized] and EU-Perjeta®-EU-Perjeta®) groups (5.3% vs. 7.6% vs. 4.3% for ADA, 2.2% vs. 3.8% vs. 1.6% for NAb, respectively).

In conclusion, the incidences of ADA/NAb of HLX11 and EU-Perjeta® were similar and the single transition of treatment from EU-Perjeta® to HLX11 did not increase the risk of immunogenicity. The exploratory analyses results showed that immunogenicity had no clinically meaningful impact on the PK exposure, efficacy, or safety of HLX11/EU-Perjeta®. (Table 30, Table 31, Table 32)

Impact on quality of life:

The impact of lack of efficacy due to immunogenicity on quality of life is considered low.

Table 30 Summary of immunogenicity results for pertuzumab in Neoadjuvant Therapy Period and Adjuvant Chemotherapy Period

	HLX11 (N=453)	EU-Perjeta® (N=454)
n	453	454
ADA Positive	22 (4.9)	18 (4.0)
NAb Positive	10 (2.2)	9 (2.0)

Table 31 Summary of immunogenicity results for pertuzumab in Adjuvant HER2-Targeted Therapy Period

	HLX11			EU-Perjeta®-EU-Perjeta® (N=79)
	HLX11-HLX11 (N=154)	EU-Perjeta®-HLX11 (N=79)	Total (N=233)	
First positive result for ADA	2 (1.3)	1 (1.3)	3 (1.3)	3 (3.8)
First positive result for NAb	0	0	0	0
n	153	77	230	79
ADA Positive	2 (1.3)	1 (1.3)	3 (1.3)	3 (3.8)
NAb Positive	0	0	0	0

Table 32 Summary of immunogenicity results for pertuzumab in Overall Treatment Period

	HLX11			EU-Perjeta®-HLX11 (N=79)	EU-Perjeta®		
	Not Re-randomized (N=299)	HLX11-HLX11 (N=154)	Total (N-453)		Not Re-randomized (N=296)	EU-Perjeta®-EU-Perjeta® (N=79)	Total (N=375)
n	299	154	453	79	296	79	375
ADA Positive	12 (4.0)	12 (7.8)	24 (5.3)	6 (7.6)	7 (2.4)	9 (11.4)	16 (4.3)
NAb Positive	4 (1.3)	6 (3.9)	10 (2.2)	3 (3.8)	3 (1.0)	3 (3.8)	6 (1.6)

Risk factors and risk groups:

Risk factors for the development of ADAs include genetic factors, patient immune status, and concomitant medications. However, there is currently no way to predict which patients will generate ADAs and of these which (if any) will lose drug benefits as a result.

Preventability:

Based on data available to date, the incidence of ADA formation is low (~2.4%). When ADAs are detected, they are often transient and titers also tend to be low, and are not generally associated with hypersensitivity reactions or anaphylaxis. Although an adverse effect of ADA formation of pertuzumab PK and/or efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common. Further investigation of ADA formation in pertuzumab clinical trials is not likely to yield significant new information or to change this conclusion. The low incidence of ADA formation in pertuzumab-treated patients and the lack of apparent clinical consequences in most patients mean that ADA testing is unlikely to be introduced into routine clinical practice in the future. No additional pharmacovigilance or specific risk minimization measures are planned for patients receiving petuzumab.

Impact on the risk-benefit balance of the product:

The impact of the risk of lack of efficacy due to immunogenicity on the overall benefit-risk balance of the product is considered low given the risk factors cited above and because of the low incidence of ADA formation observed to date. In particular, pertuzumab is a humanized monoclonal antibody with no endogenous counterpart is administered intravenously to cancer patients whose immune systems are generally suppressed and does not have immunomodulatory activity further supporting its low immunogenic potential.

Public health impact:

The potential public health impact of lack of efficacy due to immunogenicity is considered low, due to the low incidence of ADA formation in pertuzumab-treated patients.

Important Potential Risk 5: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)

Potential mechanisms:

Patients with hereditary fructose intolerance (HFI) cannot break down fructose. Poherdy contains sorbitol as an excipient, which is a source of fructose.

Evidence source(s) and strength of evidence:

This is considered an important potential risk based on the known effects of administering other parenteral sorbitol/fructose-containing medicines to patients with HFI. In the HLX11 clinical trials, subjects with a medical history of HFI were not included.

Characterisation of the risk:

The worldwide incidence of HFI at birth is estimated at 1:20 000 to 1:30 000. In patients with HFI, forced ingestion of a large amount of fructose (sorbitol) may lead to acute hepatic decompensation, with major hepatocellular insufficiency, haemorrhagic syndrome and jaundice. Biochemical signs are postprandial hypoglycaemia, hypophosphatemia, hyperlactacidemia and hyperuricaemia. Prolongation of coagulation time increased hepatic enzymes and increased bilirubin are also often

present. Methionine and plasma tyrosin are often elevated. A proximal and distal renal tubulopathy is frequent. Therefore, inadvertent administration of parenteral fructose (sorbitol) solutions can have life-threatening consequences for HFI patients.

- The data of HLX11 clinical studies:

In the HLX11 clinical trials, subjects with a medical history of HFI were not included.

Impact on quality of life:

Risk factors and risk groups:

The risk group is patients with HFI.

Preventability:

Poherdy is contraindicated in patients with HFI. Prior to initiating treatment, HFI should be excluded via medical history or on clinical grounds. In case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.

Impact on the risk-benefit balance of the product:

The impact of the risk of serious metabolic harms due to sorbitol exposure in patients with HFI on the overall benefit-risk balance of the product is considered low. The contraindication information and the special warning about excipients with known effect are already included in the product label for Poherdy. Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

Since the incidence of HFI is very low and Poherdy is indicated for adult breast cancer patients rather than higher-risk babies or children below 2 years of age with potentially undiagnosed HFI (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014), the potential public health impact is considered low.

SVII.3.2. Presentation of the missing information

Important Missing Information: Risk in pregnant or lactating women

Evidence source:

Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 non-clinical safety data, HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.

Pregnant or lactating women were excluded from all reference product and HLX11 trials. A non-clinical reproductivity study of the reference product in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have also been reported in pregnant women receiving trastuzumab, which (like pertuzumab) is an antibody that targets the HER2 receptor. Professional labeling documents indicate that pertuzumab should be avoided during pregnancy unless the potential benefit for the

mother outweighs the potential risk to the fetus. Women of childbearing potential and female partners of male patients of childbearing potential should use effective contraception while receiving pertuzumab and for 6 months following the last dose of pertuzumab.

Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a recommendation should be made to discontinue nursing during and after pertuzumab treatment, taking into account the importance to the mother and the half-life of pertuzumab.

Part II: Module SVIII - Summary of the safety concerns

Table 33 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infusion-related reactions, Hypersensitivity reactions / anaphylaxis • Congestive heart failure / Left ventricular dysfunction
Important potential risks	• Oligohydramnios* • Risk in fertility in humans • Risk in patients aged 75 years or older • Lack of efficacy due to immunogenicity • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)
Missing information	• Risk in pregnant or lactating women

* Oligohydramnios has not been reported in patients treated with HLX11 or the reference product but occurred in cynomolgus monkeys administered the reference product pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

- Guided Questionnaire – Pregnancy-Related Adverse Events

Oligohydramnios has been classified as an important potential risk for pertuzumab. The guided questionnaire will be implemented as part of the Global Enhanced Pharmacovigilance Pregnancy Program to request additional information on the mother's medical and obstetric history, the current pregnancy, fetal and infant condition, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life (Annex 4).

- **Other forms of routine pharmacovigilance activities:**

Presentation of cumulative data in Periodic Safety Update Reports (PSURs) for the following risks:

- Infusion-related reactions, Hypersensitivity reactions/ anaphylaxis
- Congestive heart failure/ Left ventricular dysfunction
- Patients aged 75 years or older
- Lack of efficacy due to immunogenicity
- Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)

Global Enhanced Pharmacovigilance Pregnancy Program for safety concern:

- Oligohydramnios
- Risk in fertility in humans
- Risk in pregnant or lactating women

The Organon standard pregnancy follow-up process was implemented for Poherdy to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

- Cumulative data will be presented in PSURs/PBRERs.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 34 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	Routine risk communication: • EU SmPC Section 4.8: Undesirable effects • Package Leaflet (PL) Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.4 of the EU SmPC, 'Infusion reactions' and 'Hypersensitivity reactions/anaphylaxis' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Congestive heart failure / Left ventricular dysfunction	Routine risk communication: • EU SmPC Section 4.8: Undesirable effect • PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.2 of the EU SmPC, 'Left ventricular dysfunction' part and Section 4.4 'Left ventricular dysfunction (including congestive heart failure)' provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Oligohydramnios	Routine risk communication: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.

Safety concern	Routine risk minimisation activities
Risk in fertility in humans	Routine risk communication: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Risk in patients aged ≥75 years	Routine risk communication: • EU SmPC Section 4.2: Elderly patients • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.4 of the EU SmPC: 'Diarrhoea' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Lack of efficacy due to immunogenicity	Routine risk communication: • EU SmPC Section 5.1: 'Immunogenicity' part Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)	Routine risk communication: • EU SmPC Section 2: Excipients with known effect and Section 4.3: Contraindications • Outer packaging Sections 3 and 7 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.4 of the EU SmPC: 'Excipients with known effect - Sorbitol' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	• Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Risk in pregnant or lactating women	Routine risk communication: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Table 35 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infusion-related reactions, Hypersensitivity reactions/ anaphylaxis	Routine risk minimisation measures: • EU SmPC Section 4.8: Undesirable effects • PL Section 2 and 4 • In Section 4.4 of the EU SmPC, 'Infusion reactions' and 'Hypersensitivity reactions/anaphylaxis' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Presentation of cumulative data in PSURs Additional pharmacovigilance activities: • None
Congestive heart failure / Left ventricular dysfunction	Routine risk minimisation measures: • EU SmPC Section 4.8: Undesirable effect • PL Section 2 and 4 • In Section 4.2 of the EU SmPC, 'Left ventricular dysfunction' part and Section 4.4 'Left ventricular dysfunction (including congestive heart failure)' provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Presentation of cumulative data in PSURs Additional pharmacovigilance activities: • None
Oligohydramnios	Routine risk minimisation measures: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Global Enhanced Pharmacovigilance Pregnancy Program Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • None	
Risk in fertility in humans	Routine risk minimisation measures: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Global Enhanced Pharmacovigilance Pregnancy Program • Presentation of cumulative data in PSURs Additional pharmacovigilance activities: • None
Risk in patients aged ≥75 years	Routine risk minimisation measures: • EU SmPC Section 4.2: Elderly patients • PL Section 2 • In Section 4.4 of the EU SmPC: 'Diarrhoea' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Presentation of cumulative data in PSURs Additional pharmacovigilance activities: • None
Lack of efficacy due to immunogenicity	Routine risk minimisation measures: • EU SmPC Section 5.1: 'Immunogenicity' part • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Presentation of cumulative data in PSURs Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)	Routine risk minimisation measures: • EU SmPC Sections 2: Excipients with known effect and 4.3: Contraindications • Outer packaging Sections 3 and 7 • PL Section 2 • In Section 4.4 of the EU SmPC: 'Excipients with known effect - Sorbitol' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Presentation of cumulative data in PSURs Additional pharmacovigilance activities: • None
Risk in pregnant or lactating women	Routine risk minimisation measures: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Global Enhanced Pharmacovigilance Pregnancy Program Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan

A summary of the RMP of Poherdy is presented below.

Summary of risk management plan for Poherdy (Pertuzumab)

This is a summary of the risk management plan (RMP) for Poherdy. The RMP details important risks of Poherdy, how these risks can be minimised, and how more information will be obtained about Poherdy's risks and uncertainties (missing information).

Poherdy's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Poherdy should be used.

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

Important new concerns or changes to the current ones will be included in updates of Poherdy's RMP.

I. The medicine and what it is used for

Poherdy is authorised for Metastatic Breast Cancer as well as Neoadjuvant & Adjuvant Treatment of Early Breast Cancer (see SmPC for the full indications). It contains pertuzumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Poherdy's benefits can be found in Poherdy's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Poherdy, together with measures to minimise such risks and the proposed studies for learning more about Poherdy's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - 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 Poherdy is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Poherdy 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 Poherdy. 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 (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Infusion-related reactions, Hypersensitivity reactions / anaphylaxis • Congestive heart failure / Left ventricular dysfunction
Important potential risks	• Oligohydramnios* • Risk in fertility in humans • Risk in patients aged 75 years or older • Lack of efficacy due to immunogenicity • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)
Missing information	• Risk in pregnant and lactating women

*Oligohydramnios has not been reported in patients treated with pertuzumab but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

II.B Summary of important risks

Important identified risk: Infusion-related reactions, Hypersensitivity reactions / anaphylaxis	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to infusion-associated reactions, hypersensitivity or anaphylaxis to pertuzumab. History of asthma, eczema or hay fever (atopy), hypersensitivity to any of the excipients may slightly increase the risk of developing an IRR (on the day of or the day after a pertuzumab infusion), but it's without any firm conclusion due to small number of patients with a history of atopy. Moreover, patients with a history of atopy did not appear to be at increased risk of anaphylaxis or hypersensitivity reactions. Prior and concomitant trastuzumab exposure did not appear to reduce or exacerbate the infusion-associated events seen with pertuzumab.
Risk minimisation measures	Routine risk measures: • EU SmPC Section 4.8: Undesirable effects

	• PL Sections 2 and 4 • In Section 4.4 of the EU SmPC, 'Infusion reactions' and 'Hypersensitivity reactions/anaphylaxis' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Important identified risk: Congestive heart failure / Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC.
Risk factors and risk groups	Risk factors such as age of 60 years or older, prior chemotherapy, registration LVEF less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer. **Anthracycline exposure:** Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease. The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose. **Concurrent trastuzumab:** The cardiac changes associated with trastuzumab are mostly reversible, do not appear to be dose-related and do not involve histological changes in cardiac tissue. Identified risk factors include exposure to anthracyclines or paclitaxel, low LVEF at baseline, age > 60 years, obesity, previous heart disease and hypertension. Current monitoring of cardiac function uses changes in LVEF as a reference for cardiotoxicity. Age, anthracycline exposure, and the presence of cardiovascular risk factors predicted cardiac AEs in trastuzumab recipients. No clear relation to a cumulative dose of trastuzumab has been described. After treatment interruption, clinical and subclinical signs of heart failure are mostly reversible and reinitiating of trastuzumab after recovery is often well tolerated. **Adjuvant breast radiotherapy:** A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s. Among patients treated during 1973 - 82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993 - 2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards. Internal mammary chain irradiation increases heart dose

	exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Section 4.8: Undesirable effect • PL Section 2 and 4 • In Section 4.2 of the EU SmPC, 'Left ventricular dysfunction' part and Section 4.4 'Left ventricular dysfunction (including congestive heart failure)' provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Important potential risk: Oligohydramnios	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 non-clinical safety data, HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC. No clinical studies have been performed in pregnant women.
Risk factors and risk groups	Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive pertuzumab treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur. Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios. Pregnant women with sickle cell disease are at increased risk of oligohydramnios. Primiparity is associated with an increased rate of oligohydramnios.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach.

	• Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Important Potential Risk: Risk in fertility in humans	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC. This is a theoretical risk based on safety results of a non-clinical reproductivity study of the reference product. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.
Risk factors and risk groups	The median age at diagnosis of HER2-positive breast cancer is the mid-50s, therefore at least half the patients likely to receive pertuzumab treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 • In Section 4.6 of the EU SmPC: ‘Fertility, pregnancy and lactation’ part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Important Potential Risk: Risk in patients aged 75 years or older	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from

	available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC. This is a theoretical risk, and no pertuzumab dose adjustment is required for adult patients of any age, including patients aged 65 years or older.
Risk factors and risk groups	Patients aged ≥ 75 years.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Section 4.2: Elderly patients • PL Section 2 • In Section 4.4 of the EU SmPC: 'Diarrhoea' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Important Potential Risk: Lack of efficacy due to immunogenicity	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC. This is a theoretical risk based on the potential mechanism, a low incidence of ADA formation has been observed in pertuzumab clinical trials.
Risk factors and risk groups	Risk factors for the development of ADAs include genetic factors, patient immune status, and concomitant medications. However, there is currently no way to predict which patients will generate ADAs and of these which (if any) will lose drug benefits as a result.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Section 5.1: 'Immunogenicity' part • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Important Potential Risk: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)	
Evidence for linking the risk to the medicine	This is considered an important potential risk based on the known effects of administering other parenteral sorbitol/fructose-containing medicines to patients with HFI. In the HLX11 clinical trials, subjects with a medical history of HFI were not included.
Risk factors and risk groups	The risk group is patients diagnosed with HFI.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Sections 2: Excipients with known effect and 4.3: Contraindications • Outer packaging Sections 3 and 7 • PL Section 2 • In Section 4.4 of the EU SmPC: 'Excipients with known effect - Sorbitol' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

Missing Information: Risk in pregnant and lactating women	
Evidence for linking the risk to the medicine	Poherdy is a biosimilar medicinal product and the reference product is Perjeta®. Data to evaluate the safety concerns were derived from available data sources, including HLX11 non-clinical safety data, HLX11 clinical trials, Perjeta® RMP and Perjeta® SmPC. Pregnant or lactating women were excluded from all reference product and HLX11 trials. A non-clinical reproductivity study of the reference product in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have also been reported in pregnant women receiving trastuzumab, which (like pertuzumab) is an antibody that targets the HER2 receptor. Professional labeling documents indicate that pertuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Women of childbearing potential and female partners of male patients of childbearing potential should use effective contraception while receiving pertuzumab and for 6 months following the last dose of pertuzumab. Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a recommendation should be made to discontinue nursing during and after pertuzumab

	treatment, taking into account the importance to the mother and the half-life of pertuzumab.
Risk minimisation measures	Routine risk minimisation measures: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. • Legal status: Poherdy is a medicinal product subject to restricted medical prescription. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Poherdy.

II.C.2 Other studies in post-authorisation development plan

There are no studies in post-authorization development plan for Poherdy.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Guided Questionnaire Pregnancy-Related Adverse Events.

Note: The Guided Questionnaire in Annex 4 is separately paginated and not included in the main document’s total page count.

Guided Questionnaire
Pregnancy-Related Adverse Events

AER:	
Site No:	
Patient ID/Initials:	
Patient Gender:	☐ M ☐ F

Local Case ID:	
Patient Date of Birth (DD-MMM-YYYY):	
Other Patient Identifiers	

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with trastuzumab, a HER2-targeted monoclonal antibody, in the post-marketing setting. Oligohydramnios has been identified as an import identified for trastuzumab, while for pertuzumab (Poherdy), also a HER2-targeted monoclonal antibody, oligohydramnios has been classified as an important potential risk.

By filling out this questionnaire, you will help us to understand more fully the risk factors for this condition and associated abnormalities, to communicate potential adverse pregnancy complications and fetal/infant outcomes to Health Authorities, Healthcare Professionals and patients.

Reporter Information	
Name of reporter completing this form **(if other than addressee. please provide contact information below):**	
Health Care Provider? ☐ Yes ☐ No – Please Specify:	
Phone number:	Fax number:
Email address:	

☐ Drug: **Poherdy** Lot Number(s): _____

Maternal Information

	Selected Medical History		Comment
☐	None	☐ Unknown	
☐	Hypertension		
☐	Diabetes; if yes, please, specify type		
☐	Seizure disorders		
☐	Thyroid disorder		
☐	Smoking / use of alcohol; specify		
☐	Family history of diabetes mellitus		
☐	Family history of congenital renal anomalies; if yes, please specify		
☐	Other; specify		

	Selected Obstetric History (previous pregnancies)		Please, provide specifics including contributing factors
☐	None	☐ Unknown	

Guided Questionnaire
Pregnancy-Related Adverse Events

☐	Gestational hypertension/preeclampsia/eclampsia	
☐	Gestational diabetes	
☐	Spontaneous or induced abortions; if yes and known, please specify cause	
☐	Oligohydramnios	
☐	History of other pregnancy complications; specify	
☐	Other; specify	

	Fetal Abnormalities in Previous Pregnancies		Please, provide specifics including contributing factors
☐	None	☐ Unknown	
☐	Delayed renal development		
☐	Death in utero; if yes/known, specify reason		
☐	Birth defects; if yes, specify		
☐	Family history of birth defects; if yes, specify		
☐	Other; specify		

Current Pregnancy

Pre-pregnancy weight and height	Weight:	Height:
Blood pressure prior to conception	Date:	BP:

Prenatal Imaging and Aneuploidy Screening/testing (e.g., ultrasound, amniocentesis, etc.)
Was a prenatal test performed? ☐ Yes ☐ No

If yes, Prenatal Test Type	**Date**	**Indication for test**	**Was a defect noted?**	**Specify**

Ultrasound Assessment Log

Date	**Gestational Age**	**Amniotic Fluid (AF) Measurement**	**Provider's Assessment of AF**	**Estimated Fetal Weight**	**Reported Percentile Growth**	**Provider's Assessment of Growth**
	_____ weeks	AF Index___ cm	1 Normal 2 Abnormal	_____ Grams	_____	☐ Normal ☐ Abnormal

Guided Questionnaire
Pregnancy-Related Adverse Events

		Maximum Vertical Pocket __ cm Other _____ ☐ AF not measured	3 Oligohydramnios 4 Anhydramnios 5 Polyhydramnios 6 Delayed renal development 7 Other: _____ 8 Not assessed	☐ Not estimated	☐ Not reported ☐ Growth not measured	☐ IUGR* (<10%ile) ☐ Severe IUGR (<3%ile) ☐ Large for Gestational Age (>90%ile) ☐ Growth not measured

* IUGR=Intrauterine growth retardation

Concomitant Medications, including ACE inhibitors and prostaglandin synthase inhibitors and all known teratogens up to 6 months prior to conception or during pregnancy:

Product Name	Indication	Total daily dose	Start date	Stop date/Ongoing

	Maternal Medical Conditions During Current Pregnancy *Please check all that apply and provide detailed information on pregnancy-related complications on last page*			
☐	Gestational Hypertension/ Preeclampsia/Eclampsia ☐ chronic hypertension ☐ pregnancy-induced hypertension ☐ Preeclampsia-eclampsia ☐ Preeclampsia superimposed on chronic hypertension	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Gestational Diabetes	Diagnostic tests:	Start date / Gestational age	Contributing factors
☐	Spontaneous or induced abortions; if yes/known, specify cause	Pathology results:	Start date / Gestational age	Contributing factors
☐	Chronic leakage of amniotic fluid	Start date / Gestational age		Contributing factors

☐	Other; specify	Pathology results:	Start date / Gestational age	Contributing factors
☐	**Fetal Conditions During Current Pregnancy** *Please check all that apply and provide detailed information on fetal complications on last page*			
☐	Renal abnormalities in fetus ☐ Normal fetal kidneys and fluid filled bladder ☐ Delayed renal development ☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction	Diagnostic tests: ☐ Ultrasonography	Start date / Gestational age	Contributing factors
☐	Fetal abnormalities, including genetic disorders; if yes, specify	Diagnostic tests: ☐ Ultrasound ☐ Alpha-fetoprotein ☐ Amniocentesis ☐ Aneuploidy screening ☐ Other	Date / Gest. age	Specify
☐	Post-maturity syndrome	Evidence:	Start date / Gestational age	Contributing factors
☐	Death in utero; if yes/known, specify reason	Pathology results:	Date / Gestational age	Contributing factors
☐	Other; specify			

Infant information

Mode of birth	☐ Spontaneous vaginal delivery ☐ Forceps/vacuum ☐ Cesarean section	Date	
Gestational age at birth		Apgar score	

Please check all that apply and provide detailed information on complications in infants on last page.

	Date of Assessment			Contributing factors
☐	Birth outcome	☐ Live birth ☐ Neonatal death	Cause	
☐	Small for gestational age at birth (SGA)	☐ Gestational age ☐ Weight/length	Date of assessment	
☐	Congenital anomalies	☐ Major malformation A defect that has either cosmetic or functional	Specify	

		significance to the child		
		☐ Minor malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify	
		☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify	
		☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify	
☐	Abnormal renal function	☐ Proteinuria ☐ Electrolyte imbalance ☐ Other	Lab results	
☐	Other; specify			

<Contact details to be updated prior sending to reporter, example for Germany is given below>

Organon Tel: 0800-338 4726

Office email: dpoc.germany@organon.com

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.