27 June 2013
EMA/CHMP/751770/2012/corr1
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Herceptin

International non-proprietary name **trastuzumab**

Procedure No. **EMEA/H/C/000278**

Note

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

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Product information

Name of the medicinal product:	Herceptin
Applicant:	Roche Registration Ltd. 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
Active substance:	trastuzumab
International Nonproprietary Name/Common Name:	trastuzumab
Pharmaco-therapeutic group (ATC Code):	Monoclonal antibodies (L01XC03)
Therapeutic indications:	Breast Cancer Metastatic Breast Cancer (MBC) Herceptin is indicated for the treatment of patients with HER2 positive metastatic breast cancer: - as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. - in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable. - in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. - in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab. Early Breast Cancer (EBC) Herceptin is indicated for the treatment of patients with HER2 positive early breast cancer.

	- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). - following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. - in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. - in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin monotherapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.
Pharmaceutical form:	Solution for injection
Strength:	600 mg / 5 mL
Route of administration:	Subcutaneous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse events
ALT	alanine aminotransferase
APB	aminophenyl boronate
AS	active substance
AUC	area under the serum concentration time curve
CE	capillary electrophoresis
CHF	congestive heart failure
CHO	Chinese Hamster Ovary
CHT	ceramic hydroxyapatite
CI	confidence interval
CL	clearance
C_{max}	maximum serum concentration
CPPs	critical process parameters
CRM	critical raw materials
C_{trough}	minimum serum concentration
DFS	disease-free survival
DoE	Design of Experiments
EBC	early breast cancer
ECG	electrocardiography
ECLIA	electrochemiluminescence immunoassay
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Evaluation Agency
EoP	end of production
EPP	efficacy per-protocol population
ER	estrogen receptor
ET	enzyme titer
EVAM	ethylene vinylacetate copolymer, monomaterial
FMEA	Failure Mode and Effects Analysis
FEC	5-fluorouracil, epirubicin, cyclophosphamide
FP	Finished product
HCP	Host cell protein
HCP	Health Care Provider
HER2	human epidermal growth factor receptor 2
HPAEC-PAD	High-Performance Anion-Exchange Chromatography with pulsed amperometric detection
IBC	inflammatory breast cancer
ICH	International Conference on Harmonization
IE-HPLC	Ion-Exchange High Performance Liquid Chromatography
IHC	immunohistochemistry
IPC	in-process control
IRR	infusion related reaction
ISH	in-situ hybridization
ITT	intent-to-treat population
IV	intravenous
IVAC	integral viable accumulated cells
JP	Japanese Pharmacopoeia
LC-ESI/MS	Liquid Chromatography coupled with Electrospray Ionization/Mass Spectrometry
LRVs	log reduction values
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction

MAH	Marketing Authorization Holder
MBC	metastatic breast cancer
MCB	Master Cell Bank
MHRA	Medicines and Health products Regulatory Agency
MUGA	multigated acquisition scan
NCCN	National Comprehensive Cancer Network
ORR	overall response rate
OS	overall survival
pCR	pathological complete response
PEI	Paul Ehrlich Institute
PFA	perfluoroalkoxy
PFS	progression-free survival
PgR	progesterone receptor
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PQ	Process qualification
PS	phenyl sepharose
PST	primary systemic therapy
PVDF	polyvinylidene difluoride
q3w	3-weekly
QbD	quality by design
QS	Q Sepharose
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse events
SC	subcutaneous
S/D	solvent detergent
SE-HPLC	Size-exclusion high-performance liquid chromatography
SID	single-use injection device
SOC	system organ class
TCC	total cell count
TFF	tangential flow filtration
t_{max}	time to maximum serum concentration
tpCR	total pathological complete response
USP	United States Pharmacopeial Convention
Vc	volume of distribution
VCC	viable cell count
WCB	Working Cell Bank
X-MuLV	Xenotropic Murine Leukemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 19 and Annex I of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency (EMA) on 1 March 2012 an application for an extension of Marketing Authorisation.

The extension of the Marketing Authorisation concerns a new route of administration (subcutaneous injection) associated with a new strength 600 mg/5 mL and a new pharmaceutical form: solution for injection.

Roche Registration Ltd is already the MAH for Herceptin 150 mg, powder for concentrate for solution for infusion (EU/1/00/145/001).

The applicant applied for a part of the indication (metastatic and early breast cancer) as approved for already authorised route/ pharmaceutical form / strengths, as follows:

Breast cancer

Metastatic breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP which pertained to quality aspects of the dossier.

Licensing status

Herceptin has been given a Marketing Authorisation in the EU on 28 August 2000.

1.2. Manufacturers

Manufacturer of the active substance

Roche Diagnostics GmbH
Pharma Biotech Penzberg
Nonnenwald 2
D-82377 Penzberg
Germany

Responsibilities: Manufacture of trastuzumab SC active substance, batch release testing by Quality Control.

Manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Whylen
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ian Hudson

- The application was received by the EMA on 1 March 2012.

- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2012.
- During the CHMP meeting on 13 December 2012, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 27 March 2013.
- PRAC adopted the RMP Advice & Assessment Overview on 16 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 May 2013.
- During the CHMP meeting on 30 May 20013, the CHMP agreed on a 2nd list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 June 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 20 June 2013.
- During the meeting on 27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation on 27 June 2013.

2. Scientific discussion

2.1. Introduction

Herceptin contains the active substance trastuzumab, a recombinant humanized monoclonal antibody which targets the extracellular domain of the human epidermal growth factor receptor 2 (HER2), a trans-membrane glycoprotein with intrinsic tyrosine kinase activity. It was first approved in the EU on 28 August 2000 for metastatic breast cancer as a powder for solution for IV infusion in the strength of 150 mg and after subsequent extensions of the indication it is currently indicated for:

- Early breast cancer (EBC) as neoadjuvant-adjuvant therapy (in combination with neoadjuvant chemotherapy, followed by trastuzumab monotherapy for a total duration of 1 year); in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin; following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel, or following surgery, neoadjuvant or adjuvant chemotherapy and radiotherapy, if applicable.

- Metastatic breast cancer (MBC) as monotherapy or in combination with paclitaxel, docetaxel or an aromatase inhibitor.
- Metastatic gastric cancer in combination with chemotherapy.

To date, trastuzumab is approved in over 120 countries globally and is the current standard of care for patients with HER2-postive breast cancer. IV administration is initiated as a loading dose is given over 90 minutes, and if well tolerated, subsequent infusions may be given over 30 minutes.

This is a line-extension application for a subcutaneous (SC) formulation of trastuzumab presented in a vial and administered as a fixed dose for 3-weekly (q3w) administration via a syringe. Trastuzumab SC is intended to be made available as an alternative to the currently licensed trastuzumab intravenous injection (trastuzumab IV) for the treatment of patients with HER2 positive EBC and MBC. The SC administration of trastuzumab is enabled by the use of recombinant human hyaluronidase (rHuPH20), a key excipient in the trastuzumab SC formulation which acts as a permeation enhancer.

2.2. Quality aspects

2.2.1. Introduction

Herceptin is currently presented as a powder to be reconstituted with water for injection and added to an infusion bag containing sodium chloride. The MAH has developed a subcutaneous formulation containing recombinant human hyaluronidase (rHuPH20) as a permeation enhancer which facilitates subcutaneous delivery. The objective of Herceptin solution for injection (Herceptin SC) formulation development programme was to obtain a stable high concentrated liquid formulation for subcutaneous administration of trastuzumab.

The formulation consists of 120 mg/mL trastuzumab in L-histidine/histidine hydrochloride buffer, trehalose dihydrate, methionine, rHuPH20, and polysorbate 20. rHuPH20 is a recombinant human hyaluronidase which enables the subcutaneous injection of large volumes.

2.2.2. Active Substance

Trastuzumab is a recombinant humanized IgG1 antibody that contains human framework regions with complement-determining regions of a murine antibody that binds to the human epidermal growth factor 2 (HER2). Trastuzumab used for the subcutaneous (SC) formulation has the same physicochemical, biological and immunological properties and is of the same quality as trastuzumab used for the intravenous (IV) formulation.

Manufacture

The production process of trastuzumab SC (v1.1 SC) used to manufacture Herceptin SC is identical to the approved process of trastuzumab (v1.1) used to manufacture Herceptin for intravenous (IV) administration except for the modification to the final tangential flow filtration (TFF) and adjustment in the buffer.

The final tangential flow filtration (TFF) has been modified to accommodate the new Herceptin SC formulation and obtain a final protein concentration of 120 mg/mL for active substance (AS). In addition, the conditioning of active substance has been adjusted to reach a satisfactory stability of trastuzumab in the liquid formulation. Methionine is added and concentration of histidine, polysorbate 20 and trehalose was adapted.

As a consequence of the high protein concentration and small volumes, the conditioning buffer is prepared in single-use bags and the AS is filled into bottles and/or single-use bags.

The purification process consists of three chromatography steps and additional steps for removal, inactivation of potential viral contaminants and concentration/ diafiltration steps.

The applicant presented data from 5 runs to demonstrate process validation for SC trastuzumab which demonstrated that the existing fermentation and purification process is capable of producing trastuzumab of constant quality.

The dossier contains adequate detailed information on the manufacturing steps, operating conditions and media/solutions used. Regarding the MCB and WCB, these remain the same as for the trastuzumab v1.1 IV presentation. Adequate information on the derivation the cell banks, identity and safety testing is provided in the dossier. The MCB/WCB and end of production (EoP) cells have been characterised and appropriate information was also provided on the media and solutions used.

Specification

The proposed specification for trastuzumab v1.1 SC is developed on basis of the AS specification of the approved trastuzumab v1.1 process to ensure the same product quality of trastuzumab v1.1 SC and trastuzumab v1.1 AS. The specification for AS has been suitably justified and is supported by consistent data from multiple lots. The specification contains tests for pharmacopoeial methods as well as specific methods to ensure safety and quality with respect to identity, purity, quantity, potency.

Analytical methods are detailed in the dossier and remain the same as for the IV trastuzumab. The non-compendial methods were revalidated for performance in amended buffer and also, in the case of FP, for interference with rHuPH20.

Stability

Based on the data provided, the proposed shelf life of the active substance of 36 months when stored at -70°C and 1 month at + 4°C in either container (single-use bottles and single-use bags) is considered acceptable. Both containers have been qualified for levels of extractables over longer term storage.

A comparison of stress stability data at +25°C and +35°C of trastuzumab v1.1 SC and trastuzumab v1.1 material indicate comparable degradation pathways of the trastuzumab molecule.

Comparability exercise for Active Substance

The applicant outlines the main changes between trastuzumab active substance IV and SC, and between trastuzumab manufactured earlier in the process and later.

The potential impact of the implemented changes in the manufacturing process on the quality of trastuzumab v1.1 SC is addressed by comprehensive comparability studies.

The applicant has comprehensively studied the quality of trastuzumab across the processes using a combination of physicochemical, biological and impurity tests. Results support the comparability between material derived from each of the processes.

The data provided indicate that the trastuzumab v1.1 SC process is comparable to the trastuzumab v1.1 and trastuzumab v1.0 SC process. The implemented changes in the manufacturing process have no impact to the trastuzumab v1.1 SC purification process.

2.2.3. Finished Medicinal Product

The finished product formulation consists of 120 mg/mL trastuzumab in L-histidine/histidine hydrochloride buffer, trehalose dihydrate, methionine, rHuPH20, and polysorbate 20. rHuPH20 is a recombinant human hyaluronidase which allows the subcutaneous injection of large volumes. rHuPH20 is considered a novel excipient.

Herceptin solution for injection (Herceptin SC) finished product is a sterile, colorless to yellowish, clear to opalescent liquid solution (120 mg/mL) for subcutaneous use supplied in 6 mL single-use vials.

Pharmaceutical Development

The formulation of the finished product for this SC presentation differs to that of the IV product as methionine and recombinant hyaluronidase (rHUPH20) are additionally included and the formulation is presented as a solution for injection rather than a lyophilisate.

Data from characterisation studies demonstrated that the presence of rHuPH20 in Herceptin SC formulation has no impact on trastuzumab quality.

Release data for all lots demonstrate a consistent quality of trastuzumab between batches and no significant differences between Herceptin SC manufactured from earlier and later lots is verified.

The available data supports the conclusion that Herceptin SC clinical and commercial material is comparable at release and upon storage.

Manufacture of the product

The manufacturing process consists of thawing trastuzumab and hyaluronidase, mixing and sterile filtration and filling. Pooling of thawed trastuzumab bulks from multiple active substance storage containers is performed into a sterilized mixing/compounding vessel in order to yield the required batch size for the fill process. Subsequently to the transfer in the mixing/compounding vessel, the trastuzumab bulk solution is homogenized by stirring. The rHuPH20 solution is slowly poured into the compounding vessel to the trastuzumab bulk solution and mixed further to obtain a homogenized formulated Herceptin SC finished product bulk solution.

Following bioburden reduction filtration, the formulated Herceptin SC bulk solution is transferred into a steam sterilized receiving/transport vessel. The bioburden reduction filtration is performed with steam sterilized membrane filters. The resulting filtered finished product bulk solution is submitted to the final sterile filtration prior to filling into vials.

The MAH has run three process validation batches at the proposed commercial finished product facility. Finished product process development and validation studies have demonstrated that the finished product manufacturing process is robust.

Product specification

Appropriate Herceptin SC release and end of shelf-life specifications have been developed based on the knowledge gained from preclinical development, clinical development and Herceptin for IV administration. The specifications contain tests for pharmacopoeial methods as well as specific methods.

Stability of the product

The primary packaging materials used for the manufacture of Herceptin for SC injection finished product, 600 mg/5 mL solution, consist of a 6 mL colorless USP/Ph. Eur./JP Type I glass vial, sealed with a rubber stopper, and crimped with an aluminum overseal fitted with a flip-off disk. Details and specifications for the vial, stoppers and seals are provided and are satisfactory.

Based on the data provided, the proposed shelf-life of 18 months for the finished product when stored at 2-8°C, protected from light is considered acceptable. A maximum of 6 hours exposure at ambient temperature during in-use can also be accepted.

Adventitious agents

The existing virus clearance data for trastuzumab v1.1 IV remains valid for trastuzumab v1.1 SC subcutaneous administration. The data was not re-assessed within this procedure.

Novel excipient (rHuPH20)

The rHuPH20 degrades hyaluronan under physiological conditions and acts as a spreading factor *in vivo.* Thus, when combined or co-formulated with certain injectable drugs, rHuPH20 facilitates the absorption and dispersion of these drugs by temporarily clearing a path through the connective tissue in the subcutaneous space.

Recombinant human hyaluronidase is a glycosylated single chain protein with up to 447 amino acids.

Manufacture

Overall, description of the upstream (cell expansion and main fermentation) and downstream process (solvent/detergent, four column purifications, nanofiltration and filling) is given and IPCs stated. The steps, control parameters, test methods used for control, and acceptance criteria are indicated.

Detailed information about inoculum expansion, bioreactor operation and harvesting processes and the respective in-process controls are provided. Description of the single steps of the purification process is given. Respective maximum hold times are defined. Information about buffer volumes, flow rates, in process controls, maximum target mass, and collection mode is sufficient. The acceptance criteria for in-process controls are considered acceptable. Lists for the major equipment used during purification, chemical composition, sterilization method and equipment are provided. All equipment except for the viral inactivation tank and chromatography columns is single use. Each step in the filling, storage, and shipping steps is described adequately, along with in-process controls and tests that are monitored.

The specifications for the raw materials used for the fermentation, purification, and the bulk formulation process are provided. Description of the generation of the host cell line and the cell banking system is in line with the demands of the ICH guidelines Q5B, Q5D and CHMP 3AB1A. Critical

parameters were defined based on the ICH Q7A definition of a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within pre-determined criteria (operating range) to ensure that the rHuPH20 meets its specification. The critical controls and the numerical limits are considered acceptable.

The process validation protocol was developed based upon the expectation as defined by the “Guidance for Industry: Process Validation”. The rHuPH20 lots were manufactured under Good Manufacturing Practices.

The process was validated at full commercial scale with a five batch campaign. All five consecutive runs met the requirements for conformance with regard to run-to-run process performance and product quality attributes, as defined in the process qualification (PQ) protocol. The data confirmed that the process is robust and in a state of control. Information concerning general properties of the IMP, Manufacturing Process, Process Controls and specifications are in agreement with the demands of the guideline ICH Q6B.

The current manufacturing process of rHuPH20 was developed using an amplified cell line. The generation of the host cell line and the cell banking system is described in satisfactory detail. Comprehensive information on the cloning and establishment of the MCB and WCB has been provided. The MAH has adequately characterised the MCB, WCB and EoP cells for phenotype, genotype and safety. The applicant has also calculated the total number of generation required between MCB and EoP cells and shown that this is within the *in vitro* cell age as calculated in small scale stability studies with extended MCB passaging.

Detailed biophysical and biochemical characterization of seven HUB batches using state-of-the-art methods is provided.

Impurities present in rHuPH20 purified bulk may result from product related impurities, process related impurities or microbiological impurities. Process related impurities are eliminated throughout the manufacturing process to an acceptable low level.

Specification

The specification for hyaluronidase has been suitably justified and is supported by consistent data from multiple lots. The specification contains tests for pharmacopoeial methods as well as specific methods to ensure safety and quality with respect to identity, purity, quantity, potency.

The proposed specification for rHuPH20 is considered adequate to confirm the high quality of the excipient. Validation of analytical procedures used for the release or stability of rHuPH20 was performed in accordance with the principles outlined in ICH Q2 (R1).

Stability

The description of the container closure system for hyaluronidase is considered appropriate.

The stability testing is conducted in line with the recommendations of the ICH Guideline Q5C. These data support the shelf-life at the recommended storage for the rHuPH20 at -80 °C up to 30 months.

Adventitious agents

The parental CHO cell line and the cell banks (MCB, WCB, and EOP) were all generated using synthetic media and there are no materials of animal origin used in the process. In addition, the media used to propagate the cell banks did not contain bovine serum albumin or trypsin. It is noted that the Insulin

used is produced on yeast. In its manufacture, bovine materials are used. The supplier provided a declaration that they comply with the TSE requirements in the EU.

Five process steps were identified as virus clearance steps and were scaled-down and evaluated. Results of virus removal studies demonstrated that the additive effect of different steps give good assurance of virus clearance ability.

On the viral distribution, and carryover studies the applicant presented data which demonstrated that for both new and aged resins, that virus distribution and carry over seem consistent. The viral clearance study was used to assess the viral inactivation/removal for selected chromatography steps at highest protein load capacities (worst case). The virus log reduction values (LRVs) were comparable between the maximum compared to the typical load conditions, except the Xenotropic Murine Leukemia Virus (X-MuLV) removal by a column. The MAH states that the inequality of the mass balance data is partially due to inactivation during washes; however, this has not been demonstrated directly. The CHMP recommended conducting additional viral inactivation studies to determine the mechanism of action of X-MuLV inactivation during the respective chromatography used in the manufacture of rHuPH20 to fully validate the inactivation process.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the new pharmaceutical form (solution for injection); new route of administration (subcutaneous use) and new strength (600mg/5ml) of Herceptin SC has been presented in a satisfactory manner.

The manufacturing process is overall, well described. The in-process control (IPC) tests are described and deemed suitable for controlling and monitoring the manufacturing process.

Appropriate general information about the novel excipient rHuPH20 has been provided. The potency assay is adapted from the USP method for activity. The differences between the in-house method and the USP assay are stated and are acceptable. Nevertheless, it is recommended that the applicant evaluates ways to improve the current hyaluronidase bioassay procedure to increase assay precision or investigates alternate potency assays which have less variability.

Based on the submitted information the HCP assay cannot be regarded as fully validated. However, any potential risk from the rHuPH20 is conceivably small due to the small quantities of in the final FP. Nevertheless, the MAH is recommended to quantitatively validate that the current HCP assay reliably measures CHO proteins present in the rHuPH20. Should this validation reveal that the generic current test is not capable of this, a process specific test should be developed.

Results from the adventitious agents safety evaluation studies demonstrated that the mass balance data for X-MuLV on a chromatographic column does not agree and spiked virus was not recovered. The applicant is recommended to conduct studies to determine the mechanism of action of X-MuLV inactivation during chromatography used in the manufacture of rHuPH20 to fully validate the inactivation process.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the submitted data, the application for Herceptin SC is recommended for approval based on quality grounds.

Overall, information on manufacture and control of the active substance, finished product and novel excipient (rHuPH20) has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics. A list of recommended measures will ensure an adequate maintenance of the quality of the product.

2.2.6. Recommendations for future quality development

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

1. The CHMP recommends that the applicant evaluates ways to improve the current hyaluronidase bioassay procedure to increase assay precision or investigates alternate potency assays which have less variability.

2. The applicant is recommended to quantitatively validate that the current HCP assay is capable of detecting the majority of HCP present in the rHuPH20. Should this validation reveal that the current method is not capable of this, a process specific method should be developed.

3. The CHMP recommends conducting studies to determine the mechanism of action of X-MuLV inactivation during chromatography used in the manufacture of rHuPH20 to fully validate the inactivation process.

2.3. Non-clinical aspects

2.3.1. Introduction

rHuPH20 is a transiently active, locally-acting permeation enhancing enzyme that allows for the subcutaneous delivery of therapeutics that have been traditionally delivered intravenously. The mode of action of the rHuPH20 is to locally depolymerize the substrate, hyaluronan (or hyaluronic acid), at the site of injection in the skin. Hyaluronan is a repeating polymer of N-acetyl glucosamine and glucuronic acid that contributes to the soluble gel-like component of the extracellular matrix of the skin. Depolymerisation of hyaluronan by hyaluronidase is accomplished by hydrolysis of the repeating polysaccharide polymer. This depolymerisation of hyaluronan results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix. The subsequent reduction in the hyaluronan viscosity is responsible for the increased hydraulic conductance that facilitates the dispersion and absorption of injected drugs.

The pharmacodynamic action of trastuzumab is adequately characterised. PD studies submitted additionally for this extension aim to show that rHuPH20 facilitates dispersion and absorption of trastuzumab and indicate that trastuzumab retains its primary pharmacodynamic effect to inhibit xenografted tumour growth in nude mice.

There are extensive data of non-clinical pharmacology in vitro and in vivo after IV administration available with trastuzumab. In support of this proposed line-extension, the applicant provided additional pharmacology, pharmacokinetics and toxicology studies with the objective to characterise exposure, distribution and elimination kinetics of rHuPH20 in animals; characterise the toxicity profile of rHuPH20 in mice and in cynomolgus monkeys, including effects on reproduction; characterise the pharmacokinetics of subcutaneously administered trastuzumab when given with rHuPH20 in mice, minipigs and cynomolgus monkeys. In addition SC local tolerance data with trastuzumab in rabbits and a 13-week repeat-dose toxicity study with SC administration of trastuzumab in Cynomolgus

monkeys (both with formulations containing rHuPH20) supplemented the current knowledge of non-clinical aspects of the substance.

No manufacturing changes were implemented over the course of the pivotal nonclinical safety studies with rHuPH20. The batches used in the non-clinical safety studies are representative of material that was used in the clinical studies.

GLP aspects

Studies submitted in support of this application were in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Dye dispersion assays in mice

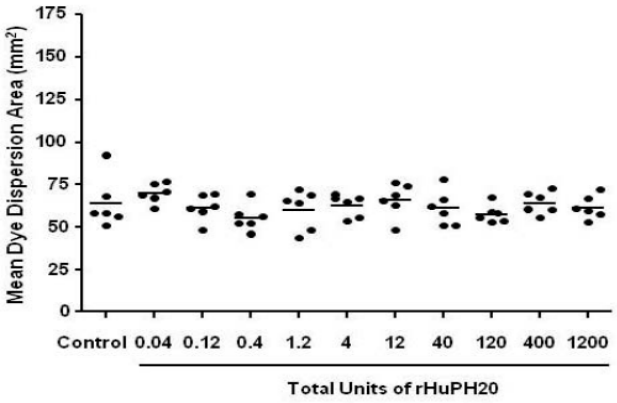
Nude mice were injected intradermally with dye and the area of dye dispersal was quantified at 1, 2.5, 5 and 20 minutes after injection. Anaesthetised mice were either co-injected or injected sequentially, 1-15 minutes apart, with rHuPH20 at 0, 2, 10 or 100 units/animal and trypan blue dye at the same anatomical site. Quantitative results are in Table 4.

Table 4: Summary of Dye Dispersion Area - All Cohorts

Cohort #	rHuPH20 Conc. (U/mL)	Time Between rHuPH20 and Trypan Blue (min)	1 min		2.5 min		5 min		20 min	
			AVG (mm^2)	SEM	AVG (mm^2)	SEM	AVG (mm^2)	SEM	AVG (mm^2)	SEM
1	0	0	**42.63**	4.03	**46.42**	6.01	**50.14**	5.25	**58.48**	3.96
2		1	**33.85**	2.79	**40.21**	2.33	**45.5**	2.99	**55.52**	2.83
3	100	0	**45.79**	1.44	**57.64**	2.6	**69.88**	3.46	**82.09**	4.6
4	500		**52.08**	2.04	**67.92**	1.6	**83.37**	2.71	**100.15**	3.58
5	5000		**68.98**	2.44	**84.47**	3.7	**103.35**	4.82	**122.34**	5.26
6	100	1	**69.93**	1.96	**81.48**	3.92	**91.62**	5.21	**91.61**	5.87
7		5	**67.95**	5.11	**77.41**	3.99	**82.46**	6.06	**84.71**	3.61
8		15	**62.88**	4.01	**75.68**	5.82	**87.54**	5.01	**97.62**	6.51

With co-injection, the area of dispersal of dye was significantly increased by rHuPH20 in a dose-dependent manner. When injected sequentially at fixed concentrations of rHuPH20, there was no difference in the degree of dye dispersal, indicating that the effect of rHuPH20 is very rapidly achieved (ie that the maximal effect is reached within 1 minute) and very short lasting. Comparing different concentrations of rHuPH20, the time to reach maximal effect was decreased by increasing rHuPH20 concentration. When the anatomical site of administration of the dye and of rHuPH20 were markedly different (ie the right and the left sides of the mouse), the area of dye dispersal was not increased despite rHuPH20 being used at amounts up to 1200 units/animal (see Figure 1 below).

Figure 1: **Dye Dispersion Area 5 Minutes Post Dye Injection ($p > 0.05$ for all test agent groups when compared to the control)**



A rabbit-derived neutralising antibody against rHuPH20 was given IV to mice 24 hours before ID injection of dye with and without 80 units of rHuPH20. One further group were also injected ID with the rabbit antibody mixed with rHuPH20 and dye (tables 2, 3). Those injected with rHuPh20 and no antibody (Cohort 4) showed greater areas of discoloured skin than those given no rHuPH20 (Cohort 2) - ie the primary effect of rHuPH20 was shown. Prior administration of the antibody did not affect the action of rHuPH20 to aid dispersal (Cohort 7 [highest dose of antibody] vs Cohort 4 [no antibody]). However, when coadministered, the antibody inhibited the action of rHuPH20 (Cohort 1 vs Cohort 7). Additional testing indicated that the antibody was detectable in mouse plasma in dose-dependent concentrations.

Table 2: **Description of Cohorts**

Cohort #	Rabbit α-rHuPH20 Antibody Conc. (µg/mL)	Final Total Dose of Rabbit α-rHuPH20 Antibody (µg)[A]	Route of Administration of Antibody	Test or Control Article	Route of Administration of Test or Control Article	Final Total Dose of rHuPH20 (U)	Total Mass of rHuPH20 at Final Conc. (ng)*
1[B]	2450	37	ID	rHuPH20	ID	80	667
2	0	0	IV	Vehicle		N/A	N/A
3	1000	100					
4	0	0		rHuPH20		80	667
5	10	1					
6	100	10					
7	1000	100					

* = Calculations based on a mean specific activity of 120,000 U/mg.
[A] = The dose concentration range of antibody to be delivered was selected based on previous Halozyme data (2) that demonstrated a functional neutralizing titer of rabbit α-HuPH20 antibody, in the background of rat and monkey plasma, to be approximately 1.5 µg/mL against 3 U/mL of rHuPH20 enzyme. It is expected that the neutralizing titer of the antibody in the presence of mouse plasma would be similar.
[B] = Cohort 1 is a rHuPH20 neutralization control where the rabbit α-rHuPH20 antibody was directly mixed with 80 total units of rHuPH20 prior to injection into the dermis.

Table 3: **Summary Data of Mean Dye Dispersion Area**

Cohort	5 Min Mean Area (mm^2 ± SEM)	15 Min Mean Area (mm^2 ± SEM)	30 Min Mean Area (mm^2 ± SEM)
1	41.67 ± 3.14	47.46 ± 4.52	55.89 ± 3.78
2	40.20 ± 6.79	62.42 ± 5.85	68.62 ± 6.07
3	40.05 ± 4.81	49.97 ± 3.18	56.89 ± 2.28
4	73.44 ± 6.38	107.81 ± 9.86	114.11 ± 4.55
5	64.80 ± 3.08	84.32 ± 5.96	99.47 ± 8.26
6	70.15 ± 4.13	95.32 ± 6.71	103.96 ± 5.25
7	67.25 ± 2.15	78.22 ± 5.69	91.51 ± 5.36

The effect of rHuPH20 was tested when given intravenously to nude mice, subsequently injected with dye intradermally. In this study, nude mice were given a single intravenous injection of rHuPH20 at doses of up to 3000 units/animal and 45 minutes later were given an intradermal injection of trypan blue dye and the area of discoloured skin was quantified 5 and 15 minutes later. There was a dose-dependent increase in the area with increasing dose of intravenous rHuPH20. At 5 minutes, the area was 58.07 mm sq at 30 units rHuPH20 compared to 117.54 mm sq at 3000 units rHuPH20 with 30 units being the minimally effective dose. Similar results were obtained when measured at 15 minutes, although the minimally effective dose was 10 units. Thus, systemic administration of the dispersal agent, rHuPH20, was able to result in local expression of the intended effect.

A study was done extending the period of observation of dispersal of dye following administration of rHuPH20 to determine effects when dye was given to mice intradermally at timepoints of 0.5, 1, 6, 18, 24 and 48 hours after dosing with the rHuPH20. The area of discoloured skin was determined at 5 and 20 minutes after injection of dye. In mice given rHuPH20, the area of dispersion was greater than in controls at 0.5, 1 and 6 hours but there was no difference at 18, 24 or 48 hours . Therefore, dermal reconstitution was complete between 6 and 18 hours.

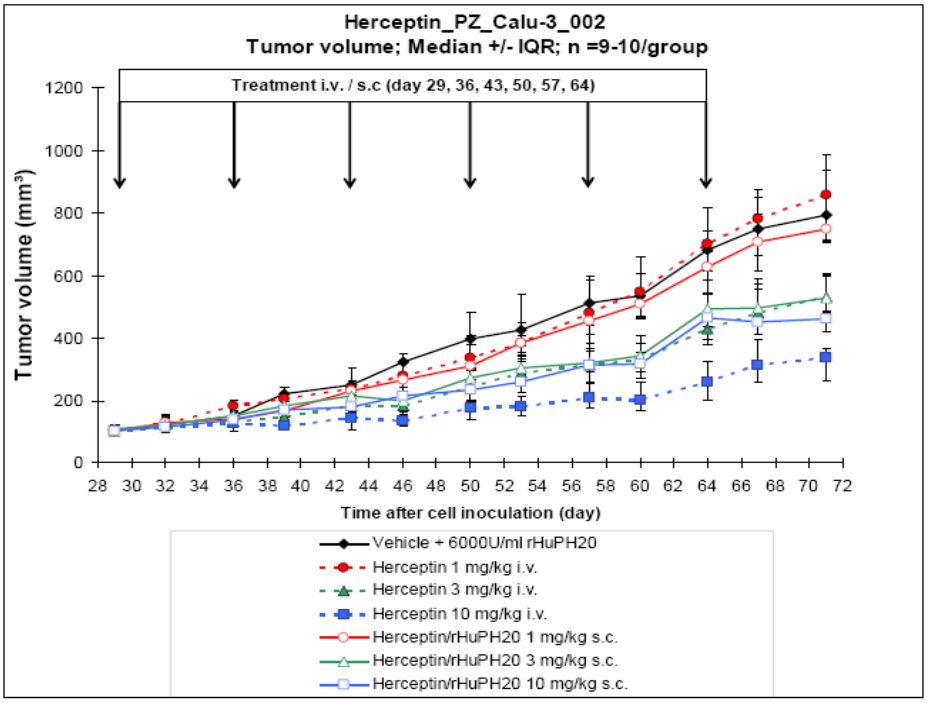
Antitumor activity of a Herceptin IV and SC formulation containing rHuPH20 against Calu-3 NSCLC xenografts in female Balab/c nude mice*

Initially, the systemic exposure to trastuzumab was tested in mice given one IV injection or one SC injection of trastuzumab containing rHuPH20, each at 10 mg/kg. Steady state with intravenous and subcutaneous injection was projected on the basis of these results and it was determined that 10 mg/kg whether given intravenously or subcutaneously, resulted in similar plasma concentration profiles, following 5 once-weekly injections. This was selected as the high dose to determine effect on tumour growth and lower doses of 3 and 1 mg/kg were selected to delineate a dose-response effect.

Nude mice were dosed subcutaneously with Calu-3 non small cell lung cancer cells ($5x10^6$ / animal) allowed to grow for 29 days, when trastuzumab dosing was initiated, given once weekly for 5 w eeks at 1, 3 and 10 mg/kg either IV or SC, with the latter including a fixed dose of 4642 U/ml rHuPH20. The last dose was given on day 64 and efficacy was assessed by tumour volume determinations on from days 29-71. Serum trastuzumab concentrations were also determined just prior to the final dose was given. (Figure x). There was no difference in the tumour volume across groups prior to dosing starting on day 29. At the dose of 1 mg/kg trastuzumab, there was no effect of treatment on tumour volume. At 3 and at 10 mg/kg, there were clear effects to reduce tumour volume, by 38 and 39% for IV and SC routes respectively at the lower dose on day 71 and by 66 and 48% at the higher dose at the same time. This apparent difference in activity (ie 66 v 48%) paralleled the plasma concentration on day 64 (96 and 61 µg/ml for intravenous and subcutaneous routes, respectively).

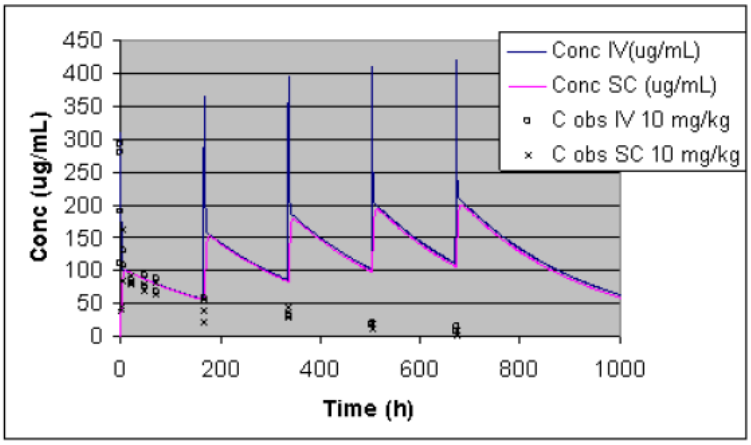
Figure 2 Effect of treatment on tumor growth

Median; n = 9-10 animals/group



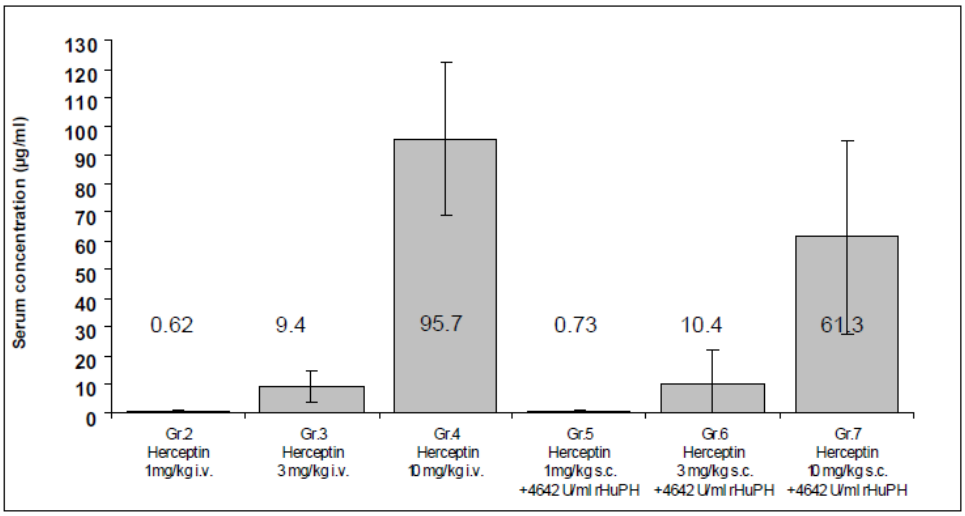
As trough concentrations were nearly identical after IV and SC administration, the same Herceptin dose levels after IV and SC dosing were selected for the present study.

Figure 1 Simulations for 5x weekly dosing of 10 mg/kg Herceptin IV and Herceptin SC to mice and observed serum concentrations following single doses 10 mg/kg Herceptin IV and SC



In contrast to the predicted Herceptin serum levels of approximately 100 µg/ml after 5x weekly administrations of 10 mg/kg IV or SC (see section 2), a comparable mean serum level was reached only with the 10 mg/kg IV treatment group (95.7 µg/ml) but not with the 10 mg/kg SC treatment group (61.3 µg/ml).

Figure 8 **Trough serum levels of Herceptin on Day 64 after the 5th administration (mean ± SD) (µg/ml)**



Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted as part of this application.

Safety pharmacology programme

No safety pharmacology studies were submitted as part of this application.

Pharmacodynamic drug interactions

No PD drug interaction studies were submitted as part of this application.

2.3.3. Pharmacokinetics

Methods

Hyaluronidase activity in mouse plasma was quantified by a biotin – streptavidin binding assay. Neutralising antibodies to rHuPH20 in cynomolgus monkey plasma were quantified using a method based on the inhibition of hyaluronidase resulting in quantification of serum turbidity. A bridging ELISA method was developed to quantify antibodies to rHuPH20 in cynomolgus monkey plasma. An electrochemiluminescence method was developed to quantify anti-rHuPH20 antibodies in human plasma. Trastuzumab was quantified in cynomolgus monkey serum using a validated enzyme-linked immunosorbent assay. Antibodies to trastuzumab were quantified in cynomolgus monkey serum using a validated electrochemiluminescence assay.

Systemic kinetics of rHuPH20 were determined in mice. The elimination half-life was at ~2.4 minutes.

Repeated dose PK study of rHuPh20 in cynomolgus monkeys: Two groups of naïve female cynomolgus monkeys were dosed iv at 0.3 mg/kg on day 1 and 30 mg/kg on day 2 (Group 1) and 3 mg/kg on day 1 and 15 mg/kg on day 2 (Group 2). Group 1 were dosed SC on day 3 with 1 mg/kg and on day 5 with 10 mg/kg and Group 2 were dosed SC on day 3 with 3 mg/kg and on day 5 with 30 mg/kg. For the intravenous doses, blood samples were taken pre-dose and at 1, 2.5, 5, 10, 15, 30 and 60 minutes

post-dose and for the SC doses blood was taken at 0.25, 0.5, 1, 4, 8 and 24 hours (and also at 48 hours after the dose on day 5 only). (Table 9).

In monkeys, rHuPH20 had a short half-life when given IV and its bioavailability after SC dosing was very low at <2.3%; at this level, accurate assessment of bioavailability is compromised. Elimination of rHuPH20 was saturable resulting in a reduced elimination rate at higher doses with a consequent increase in half life and disproportionate increases in exposure with dose. After SC dosing, T_{max} was 1-4 hours and increased with dose. By SC dosing, its half-life was at ~10 hours.

Table 9

Summary Pharmacokinetic Parameters of rHuPH20 in Female Cynomolgus Monkeys Following Intravenous and Subcutaneous Doses

Intravenous Administration

Parameter	Dose, mg/kg (U/kg)			
	0.3 (34800)	3 (348000)	15 (1740000)	30 (3480000)
AUC(0-T), U·min/mL	11500	410000	2670000	6430000
AUC(0-inf), U·min/mL	11700	442000	5630000	17700000
CL, mL/min/kg	3.03	0.801	0.315	0.201
Vss, mL/kg	21.3	19.1	29.0	26.5
$T_{1/2}$, min	4.96	14.1	64.4	91.4

Subcutaneous Administration

	Dose, mg/kg (U/kg)			
	1 (116000)	3 (348000)	10 (116000)	30 (3480000)
Cmax, U/mL	11.0	26.3	141	480
Tmax, min	135	60.0	240	240
AUC(0-T), U·min/mL	2790	9880	66500	303000
F, %	-	2.24	-	1.71

The possible impact of rHuPH20 on trastuzumab kinetics was tested as follows. A single dose study was done in three naïve male cynomolgus monkeys injected with trastuzumab formulated with rHuPH20. Trastuzumab was formulated at 120 mg/ml and given subcutaneously at 25 mg/kg in a volume of 1.8 ml: test material also contained 6000 units/ml rHuPH20. Blood was taken at multiple points between 0, 2 and 1344 hours after dosing and an enzyme-linked immunosorbent assay was used to determine trastuzumab concentrations. Trastuzumab Tmax was at 24 hours and the elimination half-life was long at up to 356 hours. It is concluded that this formulation could result in high exposure to trastuzumab.

A comparative study between IV and SC dosing was done in female mice, presented in the pharmacology section as supporting dose selection for a subsequent study in xenografted mice. In the pharmacokinetic study, separate groups of mice were given 10 mg/kg of trastuzumab formulated with 4600 units/ml rHuPH20 (6000 units/ml had been intended) for the SC route. It was determined that the subcutaneous bioavailability of trastuzumab was high at 83.4% and that T_{max} was 7 hours. C_{max} was 287 and 125 µg/ml by intravenous and subcutaneous routes respectively. Elimination characteristics were similar with half-life being 221 and 199 hours by these respective routes. High exposures to trastuzumab can be achieved by SC dosing. Once C_{max} had been reached the serum concentrations were similar after IV and SC routes.

A study was conducted in nude mice to explore the distribution of rHuPH20 when injected either ID or IV. In each case, 40 µl containing 2000 units/ml rHuPH20 was injected once. A further group of mice were not dosed but served as controls. For those dosed intravenously, blood was taken at 1, 15, 30,

60, 240, 480 and 1440 minutes (up to 24 hours) for analysis of rHuPH20. For those dosed ID, plasma, regional lymph nodes and skin were taken acquired at these same timepoints.

This study indicated that rHuPH20 was detected within the dermis but rapidly dissipated with a half-life of 13-20 minutes. Amounts in lymph were variable but low and there was no systemic exposure noted after intradermal injection. With intravenous injection, rHuPH20 activity was detectable at 1 minute but was not detectable at 15 minutes and later timepoints. The applicant concluded that these data show that rHuPH20 was both locally acting and transiently active.

Bioavailability

Study RO0452317 (Herceptin, Trastuzumab): SC Bioavailability Study of Trastuzumab/rHuPH20 Co-formulations in Göttingen Minipigs

Five groups of 5 Göttingen female minipigs, in a narrow weight range were used for the investigation of PK received a single dose of co-formulated test compounds in table …:

RO0452317 (Herceptin, Trastuzumab): SC Bioavailability Study of Trastuzumab/rHuPH20 Formulations in Göttingen Minipigs- Compartmental Pharmacokinetic Evaluation*

Treatment	• Group 1: 10 mg/kg trastuzumab IV (0.083 mL/kg) • Group 2: 120 mg trastuzumab SC (1.0 mL/animal) • Group 3: 120 mg trastuzumab + 2000 U rHuPH20 SC (1.0 mL/animal) • Group 4: 120 mg trastuzumab + 6000 U rHuPH20 SC (1.0 mL/animal) • Group 5: 240 mg trastuzumab + 4000 U rHuPH20 SC (2.0 mL/animal)

*: Nominal dose levels, actual dose levels were 9 mg/kg, 108, 108, 108 and 216 mg for Groups 1,2,3,4, and 5, respectively

Table 16 Overview of average pharmacokinetic parameters of trastuzumab in serum after single subcutaneous administration of trastuzumab at doses of 108 or 216 mg to minipigs on day1 (0-672h) (Groups 2 – 5)

Parameter	Unit	Group 2: 108 mg Trastuzumab SC	Group 3: 108 mg Trastuzumab SC 2000 U PH20	Group 4: 108 mg Trastuzumab SC 6000 U PH20	Group 5: 216 mg Trastuzumab SC 2000 U/mL PH20
Cmax	[µg/mL]	101	126	129	266
tmax	[h]	67.2	28.8	24	24
AUC(0-inf)	[(µg·h)/mL]	36700	31300	33400	87200
AUC(rest, tlast-inf)	[%]	11.4	5.1	6.0	15.3
t1/2	[h]	206	148	156	256
MRT(tot)	[h]	320	242	248	358
CL/F	[mL/min]	0.0564	0.0584	0.0546	0.0428
AUC(0-2h)	[(µg·h)/mL]	13.6	23.9	24.4	49.3
AUC(0-7h)	[(µg·h)/mL]	133	239	254	610
AUC(0-24h)	[(µg·h)/mL]	1080	1840	1920	4360
AUC(0-48h)	[(µg·h)/mL]	3090	4630	4750	10300
AUC(0-72h)	[(µg·h)/mL]	5310	7080	7140	15600
AUC(0-96h)	[(µg·h)/mL]	7500	9190	9410	20400
AUC(0-168h)	[(µg·h)/mL]	13500	14500	15300	32800
AUC(0-240h)	[(µg·h)/mL]	18200	18500	19800	42200
AUC(0-336h)	[(µg·h)/mL]	22800	22700	24300	52000
AUC(0-504h)	[(µg·h)/mL]	28600	27700	29100	65500
AUC(0-672h)	[(µg·h)/mL]	31900	29600	31300	73600
F	[%]	90.2	81.8	87.2	NC

After IV administration the PK parameters of trastuzumab were in the expected range for an immune globulin G in animals. The average clearance was 0.00616 mL/min/kg (equivalent to 0.370 mL/h/kg). Average volume of distribution at steady-state and apparent terminal half-life were 0.0776 L/kg and 136 h. The shape of the serum concentration-time curves suggests a non-linear pharmacokinetics of trastuzumab in the minipig.

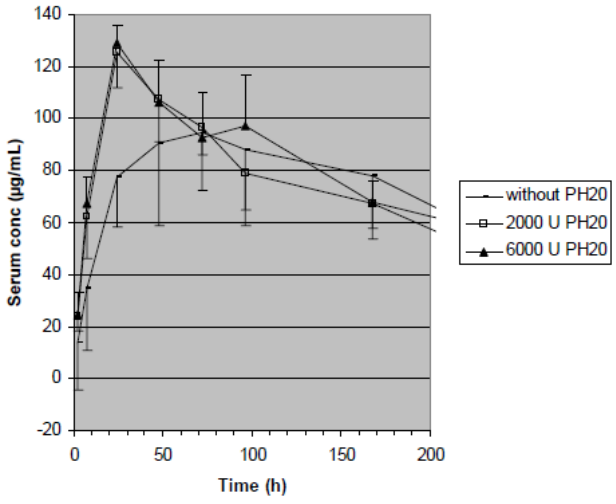
After SC administration trastuzumab absorption was more rapid from rHuPH20 containing formulations. After SC administration of the trastuzumab formulation without rHuPH20 (Group 2) trastuzumab was relatively slowly absorbed (median time to maximum serum levels 72 h). With all rHuPH20 containing formulations median times to maximum serum levels were 24 h.

After SC administration, maximum trastuzumab concentrations tended to be increased with rHuPH20 containing formulations. At the 108 mg trastuzumab dose average maximum serum levels (±SD) were 101 (±21.7), 126 (±13.2) and 129 (±6.78) µg/mL with formulations containing 0, 2000 and 6000 U rHuPH20.

At a 108 mg trastuzumab dose average average SC bioavailabilities (±SD) were estimated at 90.2 (±23.1), 81.8 (±10.2) and 87.2 (±10.8) µg/mL with formulations containing 0, 2000 and 6000 U rHuPH20. With the very high SC bioavailability of trastuzumab in the minipig there was no further increase in bioavailability to be expected by addition of rHuPH20 in the formulation.

Doubling of the trastuzumab dose had no obvious impact on the SC absorption. At the 216 mg trastuzumab SC dose, exposure was roughly twice as a high as for the 108 mg trastuzumab SC dose using the same formulation.

Figure 2 **Average (± SD) serum concentration-time profiles of trastuzumab during the first week following subcutaneous administration of 108 mg/individual trastuzumab containing 0, 2000 and 6000 U PH20 (Groups 2, 3 and 4) to female minipigs**



After subcutaneous (SC) administration trastuzumab absorption was more rapid from rHuPH20 containing formulations. After SC administration of the trastuzumab formulation without rHuPH20 (Group 2) trastuzumab was relatively slowly absorbed (median time to maximum serum levels 72 h). With all rHuPH20 containing formulations median times to maximum serum levels were 24 h.

After SC administration maximum trastuzumab concentrations tended to be increased with rHuPH20 containing formulations. At the 108 mg trastuzumab dose average maximum serum levels (±SD) were 101 (±21.7), 126 (±13.2) and 129 (±6.78) µg/mL with formulations containing 0, 2000 and 6000 U rHuPH20. Bioavailabilities (±SD) were estimated at 90.2 (±23.1), 81.8 (±10.2) and 87.2 (±10.8) µg/mL with formulations containing 0, 2000 and 6000 U rHuPH20. At the 216 mg trastuzumab SC dose, exposure was roughly twice as a high as for the 108 mg trastuzumab SC dose using the same formulation.

Pharmacokinetics of trastuzumab (RO0452317) after SC administration of trastuzumab/rHuPH20 to Cynomolgus monkey

Trastuzumab was administered SC at a dose level of 25 mg/kg in a formulation containing recombinant human hyaluronidase (rHuPH20) as excipient (6000 U rHuPH20/mL formulation). The mean Cmax was 307 µg/mL. Cmax was reached after 24 h in all monkeys. The mean AUC (0-inf) was 116 000 (µg·h)/mL. The terminal half-life was 295 h, i.e. 12.3 d; the MRT was 426 h (17.8 d). The mean apparent clearance (CL/F) was 0.00377 mL/min/kg (equivalent to 5.43 mL/d/kg).

Bioavailability

The pharmacokinetic studies in all three species indicated a high bioavailability of trastuzumab after SC administration (bioavailabilities determined by non-compartmental analysis, table …).

Species	**Trastuzumab dose (mg/kg)**	**rHUPH20 concentration (U/mL)**	**Tmax* (h)**	**F** (%)**
Mouse (n=2/time point)	10	4600	7	83.4
Cynomolgus monkey (n=3)	25	6000	24	ca. 100
Minipig (n=5)	13-14***	0	72	90.2 ± 23.1
Minipig (n=5)	13-14***	2000	24	81.8 ± 10.2
Minipig (n=4)	13-14***	6000	24	87.2 ± 10.8

2.3.4. Toxicology

The preclinical safety of trastuzumab has been established. General SC repeat dose toxicity studies submitted with this application were done with

- rHuPH20 alone dosed for 7 days or 39 weeks to cynomolgus monkeys and
- trastuzumab formulated with rHuPH20 dosed for 13 weeks to cynomolgous monkeys.

Single dose toxicity

No single dose toxicity studies were submitted as part of this application.

Repeat dose toxicity

In the 7 -day study, rHuPH20 was given once daily for 7 consecutive days at 5 mg/kg to male and female cynomolgus monkeys. 4 animals were dosed subcutaneously, 4 were dosed intravenously and 4 further monkeys were assigned to a control group and dosed by both routes. Clinical observations, body weights and food consumption were monitored daily. Ophthalmology, haematology, serum chemistry, coagulation, urinalysis parameters and toxicokinetic data were generated at specific time points. Post mortem was scheduled at day 8.

This dosing was well tolerated and there were no findings of toxicity on clinical or other measures. There were increases in liver enzymes and in creatinine kinase prior to dosing on day 2 in one control female and one male from each of the two groups given rHUPH20. At post mortem, minimal hepatocytic vacuolation was seen in both males dosed subcutaneously, but the applicant judged this seemed unlikely to be treatment-related as it was not seen in the females and was not seen in any monkey dosed intravenously. The applicant concluded that 5 mg/kg rHuPH20 was well tolerated by intravenous and by subcutaneous routes.

In the 39 –week study, doses were selected at 0, 0.02, 0.2 and 2 mg/kg rHuPH20. Dosing was by subcutaneous injection once weekly and this was given to groups of 6 male and 6 female cynomolgus monkeys, aged 4-7 years, with 4 males and 4 females from each group being euthanized for post-mortem analyses at day 274 and the remainder formed a recovery group, being euthanized on day 302, 4 weeks after their last dose. Clinical observations were performed twice daily; testicular volumes were determined predose and at weeks 5, 18 and 38; menstrual cycles were monitored; food consumption was determined qualitatively, daily, and body weights were determined once weekly. Electrocardiograms were done predose and at weeks 13 and 36 at ~2, ~5 hours postdose, respectively and also in week 43. Ophthalmology examinations were done predose and once during weeks 13, 39 and 43. Semen analyses were done predose and in weeks 12/13, 26/27 36/37 and in weeks 43/44. Haematology, serum chemistry, coagulation, urinalysis parameters and toxicokinetic data were generated at specific time points. Blood was taken for pharmacokinetic analyses predose and at 0.25, 0.5, 1, 2, 4, 6, 12 and 16 hours following days 1 and again at the same points after dosing in weeks 3, 13, 27 and 39; hyaluronidase activity was quantified using the ELISA described in the pharmacokinetics section of this report. Antibodies to rHuPH20 were screened in samples taken predose and at days 7, 14, 42, 70, 95, 123, 140, 154, 182, 210, 238, 266, 274 in all monkeys and also at days 295 and 304 in those in the recovery group using the method described above.

In this study, there were no abnormalities noted on clinical observations, body weight, food consumption, respiratory rates, blood pressures, electrocardiography, testicular volumes, semen analyses, menstrual cycling, ophthalmology (except for one instance of bilateral mucoid discharges on day 268 in one female given 0.2 mg/kg rHuPH20), haematology, coagulation, serum chemistry, or urinalysis. There were no abnormal findings on gross pathological examination and no effect on organ weights was identified, apart from an increase in spleen weight and a decrease in thymus weights in males. These were not dose-related and were without histological correlate and the applicant judged these to be not related to rHuPH20. Minimal subcutaneous perivascular lymphoplasmacytic infiltrations were noted at injection sites and these changes were attributed to rHuPH20 but this was reduced in the recovery groups, indicating reversibility. Although an effect attributed to rHuPH20, this is considered by the applicant to be a non-specific response to injection of a human protein. It was not judged adverse. The no observed adverse effect level was set at 2 mg/kg

In the study of the reformulated product with rHuPH20 for subcutaneous use, trastuzumab was given to male and female cynomolgus monkeys once weekly by subcutaneous injection of 0.25 ml/kg for 13 weeks with a planned 17 week recovery phase. Trastuzumab was given at the dose of 30 mg/kg and rHuPH20 was present at 12,000 units/ml, resulting in a dose of 3,000 units/kg. This dose of trastuzumab was selected with an intent to give the same exposure as was achieved when given intravenously for 6 months at 25 mg/kg. Toxicity was assessed by clinical observation, body weight, ophthalmology, electrocardiography, blood pressure and post mortem evaluations and blood was taken for toxicokinetic evaluations. In this study, there were no unscheduled deaths and there were no adverse effects attributed to the test article. The applicant assigned a no observed adverse effect level of 30 mg/kg at which dose the trastuzumab C_{max} and AUC measured on day 78 were 1,160 µg/ml and 166,000 µgh/ml. Antibodies to trastuzumab were detected but only in 3 of 36 samples, during the recovery stage. Samples were also tested for rHuPH20 but this was not detected and the applicant inferred that it is not absorbed after its subcutaneous injection.

Genotoxicity

No genotoxicity studies were submitted in this application.

Carcinogenicity

No carcinogenicity studies were submitted in this application.

Reproduction Toxicity

Embryofoetal development

An evaluation of the potential for rHuPH20 was conducted, given subcutaneously, to affect fetal development in pregnant mice. In an initial dose range finding study, groups of 8 mated, presumed pregnant mice were dosed once daily on days 6-15 of pregnancy at doses of 0, 1, 3, 10 and 30 mg/kg. The mice were euthanized on day 18 and effects on fetuses and pregnancy were determined. There were no findings indicating toxicity of rHuPH20 at the lower three doses, except that one mouse at 10 mg/kg showed a litter that was 68.8% resorbed: one had a fluid-filled bursal cyst on the right ovary. At the highest dose, there were three mice that had completely resorbed litters. This finding was related by the applicant to the effect of rHuPH20. Hyaluronic acid is a major glycoaminoglycan and component of cardiac jelly in the embryo that leads to the formation of the heart. Other studies in mice deficient in hyaluronan and in whole embryos in which hyaluronan is degraded have shown resulting abnormalities in development of the heart. This initial study concluded that the full study could be conducted with doses of 0, 3, 9, and 18 mg/kg. In the main study, rHuPH20 was given as before at the doses just indicated to groups of 25 mated presumed pregnant mice. The parameters of viability, clinical observations, body weight and body weight changes, food consumption, mating performance, necropsy observations Caesarean-sectioning, fetal sex ratio, fetal body weights, fetal gross external and soft tissue and skeletal alterations were evaluated. Toxicokinetic data were generated in other mice dosed in the same manner. There were 4 mice that were found dead with no cause identified; the applicant did not believe these were related to the test article because these mice had shown no signs of toxicity, the deaths were not dose-dependent and if related to rHuPH20, more deaths in the highest dose group on earlier gestation days would have been expected. The deaths occurred in one satellite and one main study mouse at 18 mg/kg and two main study mice at 9 mg/kg. Otherwise, there were no adverse clinical or necropsy observations in maternal mice. Pregnancy occurred in 23 or 24 of the 25 mice in each dose group. Fetal body weights were reduced at 9 and 18

mg/kg and there were increases in the number of late resorptions in these two groups compared to control, but unlike the fetal body weights, these were not statistically different from control. No gross external, soft tissue or skeletal fetal alterations were noted. C_{max} and AUC of rHuPH20 on day 15 were 20.9, 17.1 and 99.2 units/ ml and 55.1, 79.0 and 363 unit hours/ml at the 3, 9 and 18 mg/kg doses respectively. The applicant set the maternal no observed adverse effect level at 18 mg/kg (as the deaths were not attributed to rHuPH20) and the developmental no observed adverse effect level at 3 mg/kg. rHuPH20 was concluded to be embryofetotoxic but not to induce overt dysmorphogenesis.

Prenatal and postnatal development, including maternal function

The purpose of this study was to detect effects of rHuPH20 in pregnant mice from implantation through gestation and parturition and lactation and to determine if there were detectable effects on the development and behaviour of the offspring. rHuPH20 was given once daily by subcutaneous injection to mated, presumed pregnant mice from day 6 to day 22 of gestation if they did not deliver, or if they did, to day 20 postpartum. There 25 mice per group and doses were 0, 3, 6 and 9 mg/kg. Mice were examined for clinical observations, abortions, premature deliveries and body weights. This observation included during gestation, parturition and the pre-weaning period and observations of litter size and pup viability at birth were included. At day 21 postpartum, maternal mice were euthanised and subject to gross necropsy. The offspring were followed and clinical observations, body weight, age at vaginal patency or of preputial separation, and behavioural tests (passive avoidance for effects on learning, short- and longer-term memory) and motor activity and mating performance were also assessed. Sex organs of the F1 males were examined post mortem after the males had completed their period of cohabitation with a female. Pregnant females of the F1 generation were euthanised on gestation day 18. In this study, one maternal mouse at each of 6 and 9 mg/kg was found dead and one further mouse at 9 mg/kg was euthanized due to their clinical condition: all these deaths were attributed by the applicant to reactions to human protein, rather than specific toxicity associated with rHuPH20. In surviving mice, body weights and weight gains were unaffected by rHuPH20. Pregnancy occurred in 88.0, 80.0, 84.0 and 80.0% of mice in the four respective test groups (control, low, mid and high dose) and there were no abnormalities noted during pregnancy and delivery and litter observations were all normal. In the offspring, one female mouse was found dead on post-partum day 31 without specific cause of death identified, but there were no other deaths. There were no findings of toxicity in the F1 generation, but lower body weights were noted at 9 mg/kg than in the controls. Sexual maturation and performance, learning, memory and locomotor activity were all unaffected by rHuPH20. The applicant concluded that in maternal mice and in their offspring, the no observed adverse effect level was 9 mg/kg.

Toxicokinetic data

No toxicokinetic studies were submitted as part of this application.

Local Tolerance

Male New Zealand White rabbits were given a single subcutaneous dose of trastuzumab at 123 mg/ml in a dose volume of 0.5 ml (~61.5 mg/kg) and a similar dose of saline as control. The SC trastuzumab formulations used contained 2216 U/mL rHuPH20. The dosing site was shaved prior to dosing and clinical observations were made during the in life period. Three rabbits were euthanized at 24 hours after dosing and three were euthanized 98 hours after dosing and necropsy of the injection site was performed. There were no unscheduled deaths. The injection sites occasionally showed slight reddening, attributed to the needle and injection procedure. There were no adverse findings at the injection site whether by clinical observation or at post mortem other than those attributable to the physical effects of injection (eg focal subcutaneous haemorrhaging).

2.3.5. Ecotoxicity / environmental risk assessment

No ERA studies were submitted as part of this application.

2.3.6. Discussion on non-clinical aspects

Experiments were conducted to demonstrate the principle of facilitation of the systemic dispersion of trastuzumab via hyaluronan, in the form of rHuPH20. Proof of relevant activity was shown in the study in mice where intradermal injection of dye resulted in greater areas of skin discolouration when the dye was given with increasing doses of rHuPH20. The effect was shown on coadministration of dye plus rHuPH20, resembling the coadministration intended with trastuzumab plus rHuPH20. The time course of effect was explored and it is indicated that recovery from the effect of rHuPH20 will take place well within the clinical inter-dosing period.

Testing was also done in animals to indicate whether there was any detrimental effect of formulating the product with rHuPH20 in terms of anti-tumour activity. Pharmacodynamic effects of a Herceptin formulation (containing rHuPH20) administered SC were compared to those of Herceptin IV in a xenograft model employing the HER2-positive Calu-3 cell line in female Balb/c nude mice. At 3 mg/kg Herceptin given IV or SC there was no difference in tumor growth inhibition comparing each treatment. Also terminal serum trough concentrations of Herceptin were similar for both dose routes. At 10 mg/kg Herceptin given IV or SC tumor growth inhibition was tended to be slightly higher after IV dosing, which was in line with the higher serum concentrations after IV dosing. In contrast to the predicted Herceptin serum levels of approximately 100 µg/ml after 5x weekly administrations of 10 mg/kg IV or SC (see section 2), a comparable mean serum level was reached only with the 10 mg/kg IV treatment group (95.7 µg/ml) but not with the 10 mg/kg SC treatment group (61.3 µg/ml). Digestion of tissue brought about by rHuPH20 allows a higher volume to be given subcutaneously, such that the amounts needed for therapeutic activity can be delivered by this route.

Pharmacokinetic studies with trastuzumab SC were conducted in mice using a mouse xenograft model and in cynomolgus monkeys as part of an SC toxicology study. Additional studies on trastuzumab absorption were conducted in minipigs to demonstrate the permeation enhancing effect of rHuPH20 in the trastuzumab SC formulation and to support the selection of the rHuPH20 concentration in the trastuzumab SC formulation. The minipig was considered an appropriate model as the structure of its subcutaneous tissue is close to that in humans.

Regarding the pharmacokinetic studies after intravenous administration the pharmacokinetic parameters of trastuzumab were in the expected range for an immune globulin G in animals. The average clearance was 0.00616 mL/min/kg (equivalent to 0.370 mL/h/kg). Average volume of distribution at steady-state and apparent terminal half-life were 0.0776 L/kg and 136 h. The shape of the serum concentration-time curves suggests a non-linear pharmacokinetics of trastuzumab in the minipig. After SC administration trastuzumab absorption of rHuPH20 containing formulations was more rapid. After SC administration of the trastuzumab formulation without rHuPH20 trastuzumab was relatively slowly absorbed (median time to maximum serum levels 72 h). With all rHuPH20 containing formulations median times to maximum serum levels were 24 h. After subcutaneous administration maximum trastuzumab concentrations tended to be increased with rHuPH20 containing formulations. At a 108 mg trastuzumab dose average average SC bioavailabilities (±SD) were estimated at 90.2 (±23.1), 81.8 (±10.2) and 87.2 (±10.8) µg/mL with formulations containing 0, 2000 and 6000 U rHuPH20. With the very high SC bioavailability of trastuzumab in the minipig there was obviously no further increase in bioavailability to be expected by addition of rHuPH20 in the formulation.

Compartmental pharmacokinetic analysis revealed approximately 2-fold higher absorption rate constants associated with the rHuPH20-containing formulations. However, there was no relevant increase in absorption rate constants for the formulation containing 6,000 vs. 2,000 U/mL.

A formal rHuPH20 dose-finding study with trastuzumab SC formulations including lower enzyme concentrations such as 20 or 200 U/mL (0.2 or 2 µg/mL) was not performed in the minipig model. Lower enzyme concentrations ranging from 5 to 5000 U/mL were tested only in the mouse dye dispersion model indicating that a rHuPH20 concentration exceeding 500 U/mL (5 µg/mL) would be required to ensure the high dispersion effect.

Data from a clinical study with a rHuPH20 co-formulation of an undisclosed large protein molecule therapeutic (LPMT) suggested a concentration-dependent effect of rHuPH20 on LPMT absorption, with the highest effect on LPMT absorption at rHuPH20 concentrations of 1800 and 3500 U/mL. These data were the basis for the doses used in the minipig model. The results of the minipig study demonstrated that rHuPH20 concentrations of 2000 and 6000 U/mL yielded similar results in terms of trastuzumab absorption rate, indicating that higher rHuPH20 concentrations than the selected 2000U/mL were not necessary to further enhance the absorption rate. Therefore the usage of the lower dose is considered justified. Furthermore the proposed dose seems to have an acceptable safety margin (250-fold, based on human-equivalent doses, at the no adverse effect level of the 9-months SC toxicity study in cynomolgus monkeys.

General toxicity studies were done with rHuPH20 alone and with the reformulated product, both using the SC route. In the original assessment of trastuzumab, the only notable toxicity in cynomolgus monkeys was injection site trauma (presumably by intravenous injection). The preclinical strategy to assess safety of the reformulated product for subcutaneous use was to conduct one study with trastuzumab formulated with rHuPH20, which was considered acceptable.

Weekly SC administration of Herceptin/rHuPH20 at 30 mg/kg/dose for 13 weeks to cynomolgus monkeys was well-tolerated and did not result in any adverse test article-related effects, and as such, the no-observable-adverse effect level was 30 mg/kg/dose. It is noted that in the trastuzumab SC group the trastuzumab exposure levels were comparable to the levels achieved in the highest dose (25 mg/kg once weekly) applied in the trastuzumab IV chronic toxicity study. No toxicity was noted in the 13-week toxicity study with trastuzumab SC. Local tolerability was also assessed by clinical observation and histopathology during the toxicity studies. Under the condition of the local tolerance study in male rabbits, assessment of local tolerance in the rabbit after a single subcutaneous application of 60 mg/injection site of Herceptin (0.5 mL/injection site) showed no findings that were attributable to treatment with the test item trastuzumab. Since the safety profile of the trastuzumab SC formulation is in general considered to be similar to that associated with IV dosing, the existing IV toxicology data for trastuzumab are considered to be relevant for SC administration as well. The IV data, however, were supplemented by local tolerance data in rabbits with trastuzumab SC and a 13-week repeat-dose SC toxicity data in Cynomolgus monkeys.

When given alone, rHuPh20 was without significant toxicity and the applicant set the highest doses tested as the no observed adverse effect levels. In the 39 week study this was 2 mg/kg compared to a typical human dose of 0.0025 mg/kg when the reformulated product is given to patients. The toxicity study with Herceptin SC containing rHuPH20 did not indicate any notable toxicity either. Local tolerance testing supports the subcutaneous use of Herceptin SC containing rhuPH20.

In this testing, weekly subcutaneous injection of up to 2 mg/kg rHuPH20 alone was well tolerated over 39 weeks. Weekly subcutaneous injection of reformulated product at a dose of 30 mg/kg trastuzumab and 3000 units/kg rHuPH20 was also judged well tolerated. In this study, the trastuzumab Cmax and AUC were 1160 µg/ml and 166,000 µghr/ml. These exposures exceed those in patients given the

intended therapeutic dose. For instance, Cmax and AUC at 12 mg/kg were 151 μg/ml and 3,550 μgday/ml in patients.

With regard to reproductive toxicity, studies indicated the possibility of an adverse effect with rHuPH20. Based on clinical post-marketing experience, the SmPC for Herceptin advises that women should use effective contraception during treatment and for 7 months thereafter; use in pregnancy can be permitted where the women is advised of the possibility of harm to the foetus. The existing warnings can apply to the reformulated product too.

The toxicity data provided for this application suffice to support the expectation of safety with rHuPH20 in the formulation and for the product to be given subcutaneously.

An exemption for the need for an environmental risk assessment with reference to the Guideline on the environmental risk assessment of human medicinal products (EMEA/CHMP/SWP/4447/00) is justified on the basis that amino acids, peptides, proteins, carbohydrate and lipids are excluded because they are unlikely to result in significant risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Extensive data of non-clinical pharmacology in vitro and in vivo after IV administration available through the long experience with Herceptin are supplemented by a single dose local tolerance study in rabbits and a 13-week repeat dose toxicity study in Cynomolgus monkeys performed to confirm that the change in route of administration and the use of the novel excipient recombinant human hyaluronidase (rHuPH20) did not have an effect on the Herceptin safety characteristics. Herceptin subcutaneous formulation was locally and systemically well tolerated.

Non-clinical data for recombinant human hyaluronidase reveal no concerns based on conventional studies of safety pharmacology, and repeated dose toxicity. Reproductive toxicity studies revealed mechanism of action related embryofetotoxicity at high systemic exposure levels in mice. rHuPH20 did not influence reproduction in rabbit, mouse, cynomolgus monkey, and sheep. Reversible infertility has been reported in male and female guinea pigs.

In conclusion non-clinical aspects are adequately described in support of this application, new information related to the subcutaneous formulation is included in the SmPC section 5.3.

2.4. Clinical aspects

2.4.1. Introduction

Two clinical trials have been conducted to support this line extension (Table 1).

Table 1. Tabular overview of clinical studies

Study ID	Study Population	Study Design	Study Objectives	Status

BO22227 (HannaH)	HER2+ EBC patients (N=596)	Phase III, open-label, randomized, multiple-dose, multi-center	Non-inferiority of pre-surgery C_{trough} and pCR between trastuzumab IV and trastuzumab SC	Ongoing (primary analysis completed)
BP22023	Healthy male volunteers (N=24) HER2+ EBC patients (N=42)	Phase I, open-label, parallel group, single dose, multi-center	Dose-finding Select the dose of trastuzumab SC which results in comparable exposure to that achieved with trastuzumab IV	Completed

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Study BP22023

Methods

Study BP22023 (NCT00800436) was an open-label, two-part, multi-center, trastuzumab dose-finding study in healthy male volunteers and HER2-positive female EBC patients. The primary objective was to select the dosing regimen of a new formulation of trastuzumab SC that resulted in exposure comparable to that achieved with the approved q3w IV regimen (8 mg/kg loading dose followed by 6 mg/kg maintenance dose). Secondary objectives were to assess the safety and tolerability of trastuzumab SC versus trastuzumab IV. The primary variable for the pharmacokinetic analysis was the observed trastuzumab Ctrough at pre-dose Cycle 8. The pre-dose Cycle 8 time-point was chosen as it provides an estimate of the steady-state trastuzumab concentration prior to surgery in the neoadjuvant phase of treatment.

This was a single dose administration study. The single dose of trastuzumab SC, which was expected to result in comparable exposure to a 6 mg/kg IV dose, was first identified in HV (Part 1) and subsequently confirmed in female patients (Part 2, Table 3). In Part 1, the SC trastuzumab doses of 6 and 10 mg/kg were selected for cohorts 3 and 4 based on different SC bioavailability assumptions (100% and 60%, respectively). The selected SC dose of trastuzumab based on cohorts 3 and 4 was subsequently administered to an additional cohort of 6 male subjects (cohort 5).

In Part 2 of the study (confirmation), 40 female HER2-positive EBC patients were given a single dose of trastuzumab SC (8 or 12 mg/kg). Patients were enrolled into Cohort A to receive the dose level of SC trastuzumab defined in Part 1 of the study in HV. The dose of 12 mg/kg SC trastuzumab was selected for an additional cohort (cohort 5) to investigate comparability of trastuzumab exposure to that of the approved IV loading trastuzumab dose of 8 mg/kg based on historical data in breast cancer.

The concentration of rHuPH20 of 2000 U/mL used in this study was guided by data from the study in mini-pigs (see non-clinical section). The concentration of trastuzumab in the SC formulation was 120 mg/mL (for a dose of 12 mg/kg trastuzumab, a 70 kg subject would receive a SC dosing volume of approximately 7 mL, containing 14 000 U rHuPH20).

To adequately characterise the PK characteristics of trastuzumab SC, serum concentrations were obtained pre-dose and at 5 time points up to day 1, followed by 11 time points between day 1 and day 85, and at 5 months post-dose. Values for the primary PK parameter (AUC0–inf) were derived by non-compartmental analysis (NCA). In addition, a population PK approach was used to analyse the IV and SC PK data collected and to support the selection of a fixed SC dose for Phase III using simulations. The PK analysis was performed using First Order Conditional Estimation method (FOCE) with interaction in NONMEM version 6.0. The determination of the SC trastuzumab fixed dose was made by using modelling and simulation.

Results

Results from this single-dose administration study are summarised in Tables 3 and 4. From an interim PK analysis, the SC trastuzumab dose that would result in comparable exposure to the 6 mg/kg IV trastuzumab dose was predicted to be 8 mg/kg. The absolute bioavailability based on AUC0-inf in HV was 83.9, 91.3 and 93.2% for 6, 8 and 10 mg/kg trastuzumab SC, respectively, and 87.1 and 98.6% for 8 and 12 mg/kg trastuzumab SC in patients. Plasma rHuPH20 concentrations were below the limit of quantification (0.3125 U/mL) at all sampling time-points in all subjects.

Table 3. Summary of trastuzumab administration (Study BP22023)

Cohort	Route of Administration	Subjects	Trastuzumab Dose (mg/kg)
BP22023 Part 1: Dose-finding			
1	IV	6 Male subjects	6
2	IV	6 Female HER2+ BC patients	6
3	SC	6 Male subjects	6
4	SC	6 Male subjects	10
5	SC	6 Male subjects	8
BP22023 Part 2: Dose-confirmation*			
A	SC	20 Female HER2+ BC patients	8
B	SC	20 Female HER2+ BC patients	12

* four patients entered from Part 1 of the study

Table 4. Trastuzumab serum pharmacokinetic parameters (Study BP22023)

Cohort	Route	Subjects (n)	Dose (mg/kg)		C_{max} (µg/mL)	t_{max}[1] (h)	AUC_{inf} (µg*day/mL)	$t_{1/2}$ (h)	C_{Day22} (µg/mL)
1	IV	HV	6	Mean	150	1.65	1610	254	25.6
		(6)		CV%	(9.57)	(1.6-24.0)	(18.9)	(12.7)	(47.1)
				Median	151	1.65	1700	264	-
2	IV	Patients	6	Mean	185	3.00	1800	244	27.5
		(6)		CV%	(23.2)	(1.55-24.0)	(13.9)	(28.4)	(27.1)
				Median	178	3.00	1830	269	-
3	SC	HV	6	Mean	66.8	156.0	1350	227	31.6
		(6)		CV%	(17.1)	(96.0-216)	(23.7)	(24.7)	(38.1)
				Median	64.3	156	1270	237	-
5	SC	HV	8	Mean	82.0	96.0	1960	236	39.4
		(6)		CV%	(13.8)	(96.0-216)	(12.4)	(18.6)	(13.9)
				Median	78.8	96.00	1990	228	-
4	SC	HV	10	Mean	102	132	2500	240	51.4
		(6)		CV%	(16.8)	(96.0-216)	(20.6)	(14.3)	(30.8)
				Median	107	132	2370	231	-
A	SC	Patients	8	Mean	88.4	97.13	2090	241	37.8
		(20)		CV%	(37.7)	(47.9-217)	(30.6)	(19.9)	(27.5)
				Median	83.2	97.1	2020	246	-
B	SC	Patients	12	Mean	151	96.05	3550	270	60.8
		(20)		CV%	(38.7)	(24.5-241)	(27.7)	(29.6)	(36.2)
				Median	140	96.1	3660	241	-

[1] t_{max} is reported as median (range). HV – Healthy Volunteers IV – Intravenous SC – Subcutaneous.

Data source: BP22023 CSR (Table 9; Appendix 4, Table 1-6)

Median C_{Day22} concentration data by cohort not calculated

Selection of trastuzumab SC dose for the Phase III trial was based on a target Ctrough of 20 µg/mL or higher (based on mouse xenograft studies and early clinical response data in metastatic breast cancer: 9269, 8738, BL130972/0000, 90-099-1445 submitted with the initial marketing authorisation) and model-based evaluations of the Phase I data to select a fixed dose regimen without requirement of an initial loading dose. From a range of doses investigated in the model-based evaluations (400 to 700 mg), a fixed dose of 600 mg trastuzumab SC (formulated with rHuPH20 at a concentration of 2000 U/mL) was selected by the applicant for Phase III since it was the dose able to achieve serum Ctrough levels in Cycle 8 (median 79 µg/mL) that were at least as high as those achieved by the q3W weight-based dosing of trastuzumab IV (median 46 µg/mL). Predicted AUC at the end of the dosing period (AUC_{tau}) exposure in cycle 8 was approximately 40% higher (2425 mg*day/L) with the SC regimen compared with the IV regimen (1723 mg*day/L).

Study BO22227

Sparse PK data were collected during the treatment up to 21 days after each dose for both neoadjuvant and adjuvant phases (see Main Study for a full description of study BO22227). In addition to the sparse sampling, rich PK sampling was obtained following the Cycle 7 dose in the neoadjuvant treatment phase and following the Cycle 12 dose during the adjuvant treatment phase.

The PK hypothesis was set up to conclude that the SC dose was non-inferior to the IV dose if the geometric mean ratio CtroughSC/CtroughIV was equal or greater than 0.8, based on the lower bound of the two-sided 90% confidence interval.

The protocol pre-defined pharmacokinetic per protocol population (PKPP) consisted of all the patients who had at least one measurable trastuzumab serum concentration excluding patients whose deviations from the planned administration schedule could have had a significant impact on PK and thereby affect the assessment of non-inferiority. Exclusion criteria (including significant deviations in terms of dosing, delays in the date of sampling, missing data, injection site) were predefined for the population for the primary endpoint serum Ctrough at pre-dose Cycle 8 (PKPP1) and for the secondary endpoint Ctrough at pre-dose Cycle 13 (PKPP2).

Results

Pharmacokinetic analysis populations and results are summarised in Tables 5-7. A cross-study comparison is presented in table 8.

The geometric mean Ctrough ratio at pre-dose Cycle 8 lower limit of the two-sided 90% confidence interval was 1.24 (Table 6), which was larger than the pre-specified non-inferiority margin of 0.8. A total of 98.7% of patients in the trastuzumab IV arm and 97% in the trastuzumab SC arm had Ctrough values at pre-dose Cycle 8 greater than 20 µg/mL. The geometric mean ratio (GMR) of the observed Ctrough of trastuzumab SC to trastuzumab IV at pre-dose Cycle 13 was 1.51 (90% CI: 1.40, 1.63). Median AUC exposure in cycle 12 also tended to be higher (19 %) after SC vs. IV exposure (2470 vs. 2080 µg*day/ml).

An evaluation of the time course of all available Ctrough levels from all treatment cycles confirmed that in the IV group steady state has been reached at cycle 8 whereas in the SC group values tend to increase further up to cycle 13. A slight decline in Ctrough at pre-dose Cycle 9 of about 10-20% was observed in both arms. This was consistent with the observation of delays in dosing following surgery, whereby, 114 patients were found to have delays in dosing ranging from 23-56 days. All changes were within the observed PK variability.

In patients with a body weight < 50 kg mean steady state AUC of trastuzumab SC was about 80% higher than after IV treatment. The percentage of patients with trough levels greater than 20 µg/mL was lower in the higher weight group (92%) after SC dosing in patients with body weights ≥ 90 kg in comparison to 100% after IV dosing on a mg/kg body weight basis. An approximately bioequivalent SC dose based on AUCss would be 8 mg/kg, which corresponds to about 400 mg, 600 mg, and 750 mg flat doses for the respective BW groups <51, 51-90, and > 90 kg BW.

In a population PK analysis, trastuzumab PK was described by a two-compartment linear model with first-order absorption and first-order elimination following SC administration. The bioavailability of trastuzumab following SC administration was estimated to be 82.2%. CL and Vc were estimated to be 0.216 L/day and 2.89 L, respectively. After inclusion of all significant covariates in the final model, inter-individual variability was reduced from 28.9% to 23.7% for CL and from 17.8% to 14.9% for Vc. Body weight (WT) was identified as a statistically significant covariate for trastuzumab CL and Vc following SC and IV administration. Baseline body weight alone explained 22.3% of variability on CL. Ctrough at pre-dose Cycle 8 and Cycle 13 of trastuzumab was not affected by the formation of anti-trastuzumab antibodies or by the formation of anti-rHuPH20 antibodies. No significant association between Ctrough at pre-dose Cycle 8 and pCR or between AUC and overall occurrence of SAE or grade >3 AE was observed. pCR rates were broadly similar for the IV and SC arm irrespective of exposure and weight quartiles (Table 7).

Table 5. Summary of pharmacokinetic analysis population (Study BO22227).

	Trastuzumab IV	**Trastuzumab SC**
No. of Patients Randomized	298	297
No. of Patient with pre-dose Cycle 8 PK measurement	276	278
No. Included in PKPP1	235	234
No. Excluded from PKPP1	41	44
Patients in IV group with dose delay > 7 days for Cycle 6, who did not receive re-loading with 8 mg/kg at Cycle 7	4*	NA
2 days deviation from planned date for C_{trough} collection	39*	44
SC injection site other than the thigh at Cycle 7	NA	0
Abnormal C_{trough} value	1	0
No. of Patient with pre-dose Cycle 13 PK measurement	236	236
No. Included in PKPP2	223	227
No. Excluded from PKPP2	13	9
Dose amount deviated from the planned dose by > 20% at any dose within 3 cycles (from Cycle 10)	1**	0
Patients in IV group with dose delay > 7 days for Cycle 12, who did not receive re-loading with 8 mg/kg at Cycle 12	4	NA
2 days or greater deviation from planned date for C_{trough} collection	9**	9

NA = not applicable; *three patients excluded for two different reasons; **One patient-excluded for two different reasons.

Table 6. Summary of statistics for the observed serum Ctrough (µg/mL) at pre-dose cycle 8 (PKPP1 population, Study BO22227).

	Trastuzumab IV N = 235	Trastuzumab SC N = 234
Mean	57.8	78.7
Geometric mean	51.8	69.0
Range	14.2—222.0	6.0—400.0
SD	30.3	43.9
%CV	52.5%	55.8%
GMR[a]	1.33	
90% CI of the GMR	1.24- 1.44	

CI = confidence interval; %CV = percent coefficient of variation; GMR = geometric mean ratio; SD = standard deviation; [a] ratio of test treatment group (Trastuzumab SC) to reference treatment group (Trastuzumab IV).

Table 6b. Summary of PK parameters at pre-dose cycle 8 (PKPP1 population, Study BO22227).

Treatment Arm	PK Parameters	N	Mean	SD	Median	Min	Max	%CV
Trastuzumab IV	C_{max} (µg/mL)	235	221	118	198	80	1350	53.4
	T_{max} (day)	235	0.05	0.04	0.04	0.02	0.25	79.2
	$AUC_{0\text{-}21days}$ (µg/mL*day)	235	2056	598	1950	758	5480	29.1
	Observed C_{trough} pre-dose at Cycle 8 (µg/mL)	235	57.8	30.3	50.3	14.2	222	52.5
	Predicted C_{trough} pre-dose at Cycle 8 (µg/mL)[a]	235	52.2	19.6	50.1	11.3	114	37.6
Trastuzumab SC	C_{max} (µg/mL)	233	149	64.8	141	40.2	585	43.6
	T_{max} (day)	233	4.12	2.91	2.96	0.635	14.1	70.6
	$AUC_{0\text{-}21days}$ (µg/mL*day)	233	2268	875	2180	593	7240	38.6
	Observed C_{trough} pre-dose at Cycle 8 (µg/mL)	234	78.7	43.9	71.2	6.04	400	55.8
	Predicted C_{trough} pre-dose at Cycle 8 (µg/mL)[a]	234	80.3	34.0	76.9	19.0	208	42.3

[a] Summary statistics for Predicted C_{trough} pre-dose at Cycle 8 are presented for the PKPP1 analysis population in this table.
Data source: t_pkconc_sum_cyc8_pkpp1 on page 14

Table 6c. Summary of PK parameters at pre-dose cycle 13 (PKPP2 population, Study BO22227).

Treatment Arm	PK Parameters	N	Mean	SD	Median	Min	Max	%CV
Trastuzumab IV	C_{max} (µg/mL)	223	230	118	206	95.5	1240	51.3
	T_{max} (day)	223	0.06	0.13	0.03	0.01	1.03	224
	$AUC_{0\text{-}21\ days}$ (µg/mL*day)	223	2179	725	2080	931	5460	33.3
	Observed C_{trough} pre-dose at Cycle 13 (µg/mL)	223	62.1	37.1	55.0	7.98	387	59.7
	Predicted C_{trough} pre-dose at Cycle 13 (µg/mL)[a]	223	52.5	20.1	50.2	12.5	115	38.3
Trastuzumab SC	C_{max} (µg/mL)	223	166	58.8	151	48.6	366	35.4
	T_{max} (day)	222	4.08	2.87	2.98	0.759	14.1	70.4
	$AUC_{0\text{-}21\ days}$ (µg/mL*day)	223	2610	945	2470	742	6320	36.2
	Observed C_{trough} pre-dose at Cycle 13 (µg/mL)	227	90.4	41.9	83.1	20.3	307	46.3
	Predicted C_{trough} pre-dose at Cycle 13 (µg/mL)[a]	227	81.1	33.4	77.6	19.0	209	41.2

Table 7. Summary of pCR by weight quartiles (Per protocol population)

	Trastuzumab IV (N=263)			Trastuzumab SC (N=260)		
		Responders			Responders	
	n	No.	(%)	n	No.	(%)
Weight Quartiles at Baseline (kg)						
<58	62	23	(37%)	56	30	(54%)
≥58, <67	74	32	(43%)	63	28	(44%)
≥67, <79	68	28	(41%)	68	31	(46%)
≥79	59	24	(41%)	73	29	(40%)

Table 8. Cross-study comparison of PK parameters

	MBC (+Paclitaxel) (BO15935, cycle 12)	EBC adjuvant (HERA, cycle 13)	MBC (predicted popPK// WO16229 (Mono), cycle 6)	AGC (predicted popPK, ToGA trial)	EBC neo-adjuvant IV (BO22227, cycle 7 (12))	EBC neo-adjuvant SC (BO22227, cycle 7 (12))
Ctrough (µg/mL)	72.3	63.2	47.3//46.3	27.6	57.8 (62.1)	78.7 (90.4)
Cmax (µg/mL)	237	216	189//221	132	221 (231)	149 (166)
AUCtau,ss	2221	2255	1793//1814	1213	2056 (2177)	2268 (2610)

Immunogenicity

Twice as many patients developed antibodies to trastuzumab with the SC formulation compared to the intravenous formulation (7.1% [21/296] vs. 14.6% [43/295]) (cut-off date for ADA, Jan 2013). No influence of ADA occurrence on PK could be detected by population PK covariate analysis (see above). During the treatment free-follow-up phase at Months 3, 6, and 12, only one patient in the IV group and two patients in the SC group tested positive for neutralizing antibodies.

The ADA occurrence rate for rHuPH20 was 15.3% (45/295) in Study B022227 and 15.5% (9/58) in Study BP22023 (baseline rates 7.6% and 12.1%, respectively). Neutralizing antibodies to rHuPH20 were not detected in any of the ADA positive samples.

2.4.3. Discussion on clinical pharmacology

In general, the approach and the methodology employed are considered acceptable. Overall, sufficient data have been provided to characterise the pharmacokinetic behaviour of the SC formulation.

Similar Cmax and AUC0-inf were observed between patients and HV in Part 1-2 of the Phase I study. Based on serum pharmacokinetic results, the selected dose of 8 mg/kg SC provided 22% higher exposure based on AUCinf compared to 6 mg/kg IV in HV (1960 vs. 1610 µg*day/mL). Similarly, a dose of 8 mg/kg SC in female patients provided higher exposure (16%) based on AUCinf compared to 6 mg/kg IV (AUCinf 2090 vs. 1800 µg*day/mL).

The selected rHuPH20 concentration of 2000 U/mL in trastuzumab SC has an acceptable safety margin (250-fold, based on human-equivalent doses, at the NOAEL of the 9-months SC toxicity study in *Cynomolgus* monkeys). In the Phase I study, rHuPH20 was not detected at any time point. However, based on the detection limit of the assay and on preclinical data, an absorption rate of 5% corresponding to maximum rHuPH20 plasma concentrations of up to 0.3 U/ml and potential accumulation of rHuPH20 after multiple dose administration cannot be excluded. This is considered acceptable since accumulation is considered unlikely in view of the rapid plasma clearance observed in non-clinical studies and any potential accumulation of rHuPH20 is expected to be below NOAEL.

The Applicant will investigate improvement of the detection limit of the rHuPH20 assay (targeting a 30-fold improvement) and, if a meaningful reduction in LLOQ is achieved, determine absolute systemic bioavailability and half-life of rHuPH20 in a clinical study

In the Phase III trial, the SC formulation was shown to be non-inferior to the IV regimen for the co-primary PK endpoint. The proportion of patients with trough (pre-dose) levels greater than 20 µg/mL was very high and similar for the two regimens prior to cycle 8 and 13. Since no significant relationship between exposure (AUC and Ctrough) and response parameters (pCR rate or best response parameters) or safety parameters could be identified for the IV and SC arms, there is no good rationale for dose adjustment according to body weight.

Although the incidence of neutralizing antibodies in the treatment-free follow-up phase was reassuringly low in both groups, more patients developed anti-trastuzumab antibodies with the subcutaneous formulation than with the IV formulation. More data are needed to finally evaluate this finding and its impact. Monitoring of ADA formation in the extension of the follow-up phase of the BO22227 trial is included as an additional pharmacovigilance activity linked to the potential risk of immunogenicity (see RMP). A clinical impact of cross-reactivity of ADA with endogenous PH20, which plays a role in fertility and neurogenesis/neuronal repair, cannot be excluded (see non-clinical section).

The applicant will provide follow-up data from immunogenicity analyses on anti-trastuzumab and anti-rHuPH2 antibodies as part of the BO22227 Annual Report to be submitted with the March Data Lock Point (DLP) Herceptin PSUR.

2.4.4. Conclusions on clinical pharmacology

The pharmacokinetics of trastuzumab at a dose of 600 mg administered three-weekly by the subcutaneous route was compared to the pharmacokinetics of trastuzumab intravenous route (8 mg/kg loading dose, 6 mg/kg maintenance every three weeks) in the phase III study BO22227. The pharmacokinetic results for the co primary endpoint, C_{trough} pre dose Cycle 8, showed non-inferiority of the Herceptin subcutaneous compared to the Herceptin intravenous formulation dose adjusted by body weight.

The mean C_{trough} during the neoadjuvant treatment phase, at the pre dose Cycle 8 time point, was higher in the Herceptin subcutaneous formulation arm (78.7 µg/mL) than the Herceptin intravenous formulation arm (57.8 µg/mL) of the study. During the adjuvant phase of treatment, at the pre-dose Cycle 13 time point, the mean C_{trough} values were 90.4 µg/mL and 62.1 µg/mL, respectively. While steady state with the intravenous formulation was reached at cycle 8, concentrations tended to increase further up to cycle 13 with the subcutaneous administration. The mean C_{trough} at the subcutaneous pre- dose cycle 18 was 90.7 µg/mL and is similar to that of cycle 13, suggesting no further increase after cycle 13.

The median T_{max} following subcutaneous administration of the cycle 7 dose was approximately 3 days, with high interindividual variability (range 1-14 days). The mean C_{max} following the cycle 7 SC dose was expectedly lower in the trastuzumab subcutaneous formulation (149 µg/mL) than in the intravenous arm (end of infusion value: 221 µg/mL).

The Applicant will investigate the improvement of the detection limit of the rHuPH20 assay (targeting a 30-fold improvement) and, if a meaningful reduction in LLOQ is achieved, determine absolute systemic bioavailability and half-life of rHuPH20 in a clinical study which is to be further discussed in the context of the next RMP revision, depending on the feasibility.

Monitoring of ADA formation in the extension of the follow-up phase of the BO22227 trial is included as an additional pharmacovigilance activity linked to the potential risk of immunogenicity (see RMP).

The applicant will provide follow-up data from immunogenicity analyses on anti-trastuzumab and anti-rHuPH2 antibodies as part of the BO22227 Annual Report to be submitted with the March Data Lock Point (DLP) Herceptin PSUR.

2.5. Clinical efficacy

2.5.1. Dose response studies

Determination of trastuzumab SC dose for Phase III

See clinical pharmacology.

2.5.2. Main study

Title of Study

A phase III, randomized, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with HER2-positive early breast cancer (EBC) (BO22227; NCT00950300; “HANNAH”).

Study Participants

The study included female patients aged ⩾ 18 years with non-metastatic primary invasive adenocarcinoma of the breast which was clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) including inflammatory and multicentric/multifocal breast cancer, histological confirmation, HER2-positive status centrally confirmed (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH]+), at least one measurable lesion in breast or lymph nodes (⩾ 1 cm by ultrasound or ⩾ 2 cm by palpation), except for inflammatory carcinoma (T4d), performance status Eastern Cooperative Oncology Group (ECOG) of 0 or 1, baseline left ventricular ejection fraction (LVEF) ⩾ 55%.

Treatments

Treatments consisted of neoadjuvant trastuzumab plus neoadjuvant chemotherapy (docetaxel followed by 5-fluorouracil, epirubicin, cyclophosphamide), then adjuvant trastuzumab up to 1 year.

- Trastuzumab SC: fixed dose of 600 mg SC irrespective of the patient’s body weight was administered every three weeks throughout the treatment phase

- Trastuzumab IV: loading dose of 8 mg/kg infused over a 90-min period. All subsequent doses were 6 mg/kg and these could be administered over a 30-min period if the first administration was well-tolerated
- Docetaxel (75 mg/m2 IV infusion) after completion of trastuzumab administration, every 3 weeks for 4 cycles (cycles 1-4)
- FEC: 5-Fluorouracil (500 mg/m2 IV bolus or infusion), epirubicin (75 mg/m2 IV bolus or infusion) and cyclophosphamide (500 mg/m2 IV bolus or infusion), every 3 weeks for 4 cycles (cycles 5-8).

Trastuzumab IV and SC were administered 3-weekly for 18 cycles unless intolerable toxicity occurred or investigator assessed disease progression had occurred. Trastuzumab IV and SC were administered before starting the infusion of chemotherapy. All doses of trastuzumab SC were administered as a subcutaneous injection into the thigh over 2-5 minutes by a trained health care professional.

Objectives

To compare the following parameters between trastuzumab IV and trastuzumab SC in the neoadjuvant setting:

- Serum trough concentrations observed pre-surgery;
- Efficacy (pathological complete response).

Outcomes/endpoints

Co-primary endpoints

The co-primary endpoints were observed Ctrough pre-surgery and pathological complete response (pCR). For the pharmacokinetic endpoint see clinical pharmacology.

Pathological complete response of the primary tumor was defined as absence of invasive neoplastic cells at microscopic examination of the primary tumor remnants after surgery following primary systemic therapy. The response was classified as “pCRis” in case only in-situ carcinoma was found in the tumor remnants. pCR was assessed by the local pathologist following surgery (no independent review).

Post-baseline tumor assessments were to be performed every other cycle and prior to surgery. Patients whose pCR assessment was missing were counted as not having achieved pCR.

Secondary endpoints

- *Total pathological Complete Response (tpCR)*, defined as the absence of invasive neoplastic cells in the primary tumor remnants and in the axillary lymph nodes
- *Overall Response Rate (ORR)*, defined as clinical complete response or partial best tumor response. Clinical tumor response was evaluated according to RECIST. Cinical tumor response was measured using assessment by caliper and ultrasound in order to achieve consistency in tumor assessments across sites. In addition to the primary breast tumor(s), affected lymph nodes if present, were considered target lesions, provided they have a size of ≥ 1 cm by ultrasound or ≥ 2 cm by palpation. Inflammatory breast cancer was considered as non-target lesion. Response of inflammatory breast cancer was assessed based on erythema/edema, which were both considered as non-measurable lesions in the protocol.
- *Overall Survival (OS)* defined as the time from the date of randomization to the date of death, regardless of the cause of death.

- *Event-free survival (EFS)* defined as the time from the date of randomization to the date of disease recurrence or progression or death due to any cause.

Other secondary endpoints included Time to Response (TTR), Pathological Complete Response in Situ (pCRis) (data not shown).

Sample size

The hypothesis for the co-primary variable pCR was one of non-inferiority with a margin of 12.5%. The null-hypothesis was rejected if the lower limit of the one-sided 97.5 % confidence interval for the difference in pCR proportion using the continuity correction of Anderson and Hauck (1986) was greater than -12.5%. Assuming pCR rates of at least 40% in both arms and 10% drop-out, 552 patients were required (power 80%).

The non-inferiority margin was based on a meta-analysis of two studies (Buzdar, 2005; Gianni, 2010), where the difference in proportion [pCRIV-pCRchemo alone] was estimated to be 23.7% (95% CI: 12.76%; 34.56%); 12.5% was selected as the lower bound of the 95% CI [pCRSC-pCRIV] that would ensure that the lower bound of the "indirect" 95%CI [pCRSC-pCRchemo alone] would be above zero.

Randomisation

Randomization (central) was stratified by breast cancer type (operable versus locally advanced versus inflammatory breast cancer), and estrogen receptor status (positive, negative, unknown).

Blinding (masking)

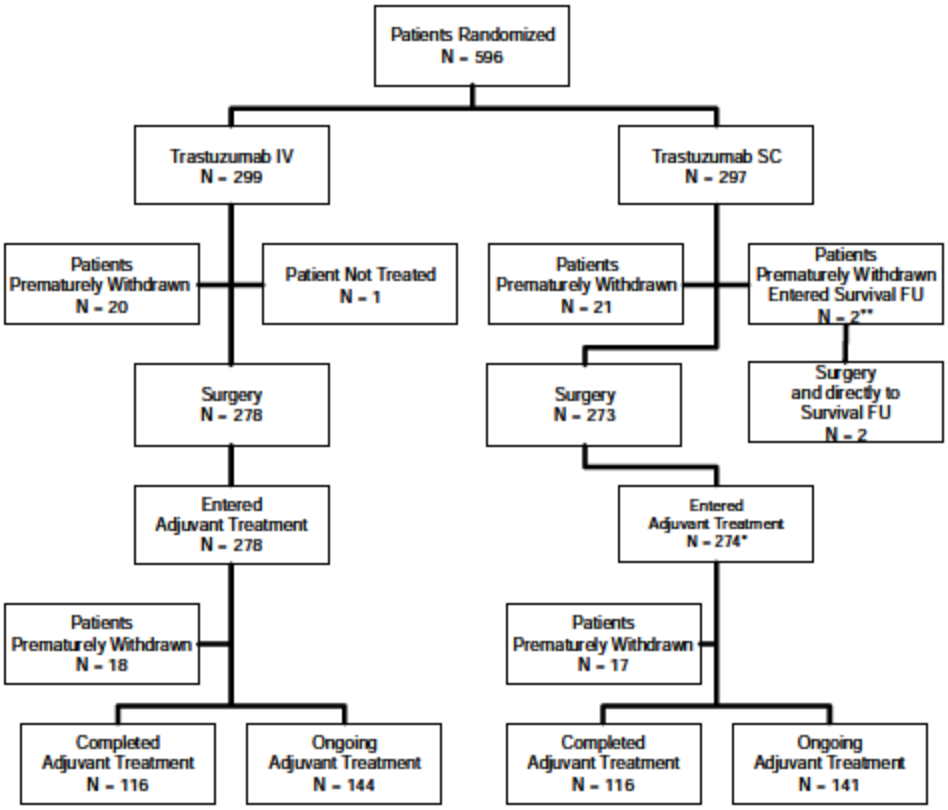
The study was open-label.

Statistical methods

The intent to treat population (ITT) set included all patients having at least one efficacy assessment after first study drug administration (treatment assignment as randomized for analysis purposes). The efficacy per protocol (EPP) set was defined as the subset of the ITT set defined by the following exclusions: less than 8 cycles of trastuzumab/chemotherapy treatment; metastatic breast cancer before entering the study; previous anti-cancer therapy; HER2 negative patients; major violation of inclusion/exclusion criteria. Treatment assignment followed treatment actually received for analysis purposes. Standard statistical methods were used. The EPP set was the main analysis set.

Results

Participant flow (at clinical cut-off date of 12 July 2011)



* One patient did not undergo the primary surgery after completion of the neoadjuvant treatment phase.
** Two patients were prematurely withdrawn due to disease progression after completion of 8 cycles of treatment but nevertheless underwent surgery and are included in the analyses.

Recruitment

A total of 833 patients were screened and 596 patients were randomized at 81 centres in 24 countries: 106 patients from Germany (No. of centres=8), France (5), Spain (5), Italy (3), Sweden (2); 95 patients from Hungary (3), Poland (3), Czech Republic (2), Slovakia (2), Estonia (1); 134 patients from Russia (10); 96 patients from Brazil (6), Peru (5), Colombia (3), Guatemala (1), Mexico (1), Panama (1); 122 patients from Taiwan (4), Thailand (4), Korea (3), China (1); and 43 patients from South Africa (4), Turkey (3), and Canada (1).

The main reasons for screening failure was Her-2 status not confirmed centrally (n=136) and withdrawal of consent (n=31). The first subject was randomised in October 2009 and the last patient in December 2010; the clinical cut-off date for the primary analysis was 12 July 2011 and for the follow-up analysis 09 July 2012.

Conduct of the study

Protocol amendments included updated pharmacokinetic and safety information from trial BP22023, minimum tumour size, response criteria for inflammatory breast cancer.

Baseline data

Table 9 Summary of Baseline Characteristics (EPP)

		Trastuzumab IB (N=263)	Trastuzumab SC (N=260)
Age in years	Mean	49.6	50.2
	Min-Max	24 - 77	25 - 81
Weight in kg	Mean	68.42	70.23
	Min-Max	44.4 - 137.1	43.0 - 136.0
Age category (years)	<40 years	47 (17.9%)	45 (17.3%)
	40-<50 years	76 (28.9%)	77 (29.6%)
	50-<65 years	120 (45.6%)	111 (42.7%)
	>=65 years	20 (7.6%)	27 (10.4%)
Region	Asia Pacific	54 (20.5%)	59 (22.7%)
	Eastern European Area	105 (39.9%)	94 (36.2%)
	South Africa	11 (4.2%)	13 (5.0%)
	South America	42 (16.0%)	46 (17.7%)
	Western EU incl. Canada	51 (19.4%)	48 (18.5%)
Race Category	Asian	56 (21.3%)	60 (23.1%)
	Other	26 (9.9%)	29 (11.2%)
	White	181 (68.8%)	171 (65.8%)
Reproductive status	Childbearing potential with contraceptive protection	136 (51.7%)	125 (48.1%)
	Post-menopausal	90 (34.2%)	107 (41.2%)
	Surgically sterilized	37 (14.1%)	28 (10.8%)
ECOG at baseline	0	223 (85.1%)	221 (85.3%)
	1	39 (14.9%)	38 (14.7%)
	n	262	259
LVEF (%) at baseline	Mean	65.8	66.6
	Min-Max	55 - 82	53 - 83
	n	262	259
ECG at baseline	Abnormal	1 (0.4%)	5 (1.9%)
	Normal	260 (99.6%)	254 (98.1%)
	n	261	259
Breast cancer type	Inflammatory	15 (5.7%)	19 (7.3%)
	Locally advanced	99 (37.6%)	105 (40.4%)
	Operable	149 (56.7%)	136 (52.3%)
Estrogen receptor status	Negative	132 (50.2%)	125 (48.1%)
	Positive	130 (49.4%)	135 (51.9%)
	Unknown	1 (0.4%)	0

Table 10 Summary of History of Breast Cancer (EPP)

		Trastuzumab IV (n=263)	**Trastuzumab IV (n=260)**
Focality	Multicentric	25 (9.5%)	32 (12.3%)
	Multifocal	44 (16.8%)	56 (21.5%)
	Unifocal	193 (73.7%)	172 (66.2%)
	N	262	260
Breast cancer subtype	Ductal	240 (91.3%)	240 (92.3%)
	Lobular	17 (6.5%)	12 (4.6%)

		Trastuzumab IV (n=263)	Trastuzumab IV (n=260)
	Other	6 (2.3%)	8 (3.1%)
Histological grade	Well differentiated	5 (1.9%)	12 (4.6%)
	Moderately differentiated	136 (51.7%)	142 (54.6%)
	Poorly differentiated	121 (46%)	106 (40.8%)
	Anaplastic	1 (0.4%)	0
Hormone Receptor Status (ER/PgR)	Negative/unknown	2 (0.8%)	0
	Negative/negative	124 (47.1%)	118 (45.4%)
	Negative/positive	6 (2.3%)	7 (2.7%)
	Positive/negative	32 (12.2%)	36 (13.8%)
	Positive/positive	98 (37.3%)	99 (38.1%)
	Unknown/unknown	1 (0.4%)	0
Clinical Nodal Status	cN0	57 (21.7%)	64 (24.6%)
	cN1	137 (52.1%)	115 (44.2%)
	cN2	41 (15.6%)	54 (20.8%)
	cN3	28 (10.6%)	27 (10.4%)
Clinical Tumor Status	T1B	0	1 (0.4%)
	T1C	19 (7.2%)	17 (6.5%)
	T2	119 (45.2%)	113 (43.5%)
	T3	45 (17.1%)	47 (18.1%)
	T4ABC	65 (24.7%)	63 (24.2%)
	T4D	15 (5.7%)	19 (7.3%)
Sentinel Node Biopsy Prior to Treatment	Positive	20 (7.6%)	11 (4.2%)
	Negative	11 (4.2%)	7 (2.7%)
	No	232 (88.2%)	242 (93.1%)

sttr11prms_pp Summary of Type of Primary Surgery (EPP Population)
Protocol(s): J22227O
Analysis: PER-PROTOCOL Center: ALL CENTERS

Class/ Other Treatment or Procedure	TRASTUZUMAB IV N = 263 No. (%)	TRASTUZUMAB SC N = 260 No. (%)
ALL CLASSES		
Total Pts with at Least one Treatment	263 (100.0)	260 (100.0)
Total Number of Treatments	518	518
SURGICAL & MEDICAL PROCEDURES		
Total Pts With at Least one Treatment	263 (100.0)	260 (100.0)
SURGERY	231 (87.8)	223 (85.8)
MASTECTOMY	216 (82.1)	204 (78.5)
BREAST LUMP REMOVAL	47 (17.9)	56 (21.5)
MASS EXCISION	-	2 (0.8)
BREAST RECONSTRUCTION	-	1 (0.4)
LYMPHADENECTOMY	1 (0.4)	-
Total Number of Treatments	495	486
INVESTIGATIONS		
Total Pts With at Least one Treatment	23 (8.7)	32 (12.3)
BIOPSY LYMPH GLAND	23 (8.7)	32 (12.3)
Total Number of Treatments	23	32

Percentages are based on N.
Multiple occurrences of the same treatment in one individual counted only once.
TR11 26JUN2013:14:19:40 (1 of 1)

Post-surgery patients received radiotherapy as per the investigator's clinical decision. Radiotherapy to the axilla, chest wall or "other" site was given to 47.7% of patients in the trastuzumab IV arm and 54.2% of patients in the trastuzumab SC arm. Local or regional lymph nodes were irradiated in 40.6% and 43.1% of patients under trastuzumab IV and SC, respectively. Radiotherapy to the breast was performed in 33.9% and 37.4% of patients in the trastuzumab IV and trastuzumab SC arms, respectively.

Hormonal therapy was initiated in hormone receptor positive patients only after primary surgery. As per clinical cut-off, tamoxifen was the most frequent hormonal treatment given to 26.5% of patients in the trastuzumab IV arm and 33.7% of patients in the trastuzumab SC arm. Anastrozole and letrozole were used for treatment in 6.7% and 7.0% of trastuzumab IV patients, and in 6.1% and 4.7% of patients of the trastuzumab SC arm, respectively. Among the gonadotropin and analogues class, goserelin was the drug given most frequently: 2.7% and 3.0% in the trastuzumab IV and trastuzumab SC arms, respectively.

Numbers analysed

A total of 591 patients (297 patients in trastuzumab IV and 294 patients in trastuzumab SC) were included in the ITT population. Five patients (2 patients in trastuzumab IV, 3 in trastuzumab SC) were excluded from the ITT population because they did not have an efficacy assessment after baseline.

The EPP set included 523 patients (263 patients in trastuzumab IV and 260 patients in trastuzumab SC). A total of 73 patients were excluded from the EPP population due to at least one major protocol violation, 36 patients from the trastuzumab IV arm and 37 patients from the trastuzumab SC arm. The

most common reason for exclusion from the EPP was that patients were withdrawn prematurely from the neoadjuvant phase (received < 8 cycles of treatment; 21 patients in each treatment arm).

Outcomes and estimation

Summary of efficacy for trial B022227

Endpoint	Trastuzumab IV	Trastuzumab SC	Difference in proportions (SC-IV) (95% CI)
Primary			
pCR, n/N (%) EPP	107/263 (40.7%)	118/260 (45.4%)	4.70 (-4.0; 13.4)
pCR, n/N (%) ITT	111/297 (37.4%)	124/294 (42.2%)	4.80 (-3.3; 12.9)
Secondary			
tpCR, n/N (%) EPP	90/263 (34.2%)	102/260 (39.2%)	5.01 (-3.5; 13.5)
tpCR, n/N (%) ITT	94/297 (31.6%)	108/294 (36.7%)	5.08 (-2.7; 12.9)
ORR, n/N (%) EPP	231/260 (88.8%)	225/258 (87.2%)	-1.64 (-7.4; 4.2)
ORR, n/N (%) ITT	244/293 (83.3%)	245/292 (83.9%)	0.63 (-5.6; 6.8)

EFS and OS data were not sufficiently mature at the time of the clinical cut-off date for the primary analysis (12 July 2011). 15 patients (5.7%) in the trastuzumab IV arm and 13 patients (5.0%) in the trastuzumab SC arm (EPP population) had experienced an EFS event. Six months after randomization, 98% of patients in each treatment arm were event-free. One patient in each arm had died within the EPP population.

A follow-up analysis (clinical cut-off date of 9 July 2012) of EFS was provided after a median duration of follow-up of approximately 20 months in both arms (as compared to about 12 months for the main analysis). In this analysis, the 1-year rate was .95 (95%CI: .92; .97) and .95 (.93; .98) for trastuzumab IV and SC, respectively (EPP population). The 2-year EFS rates were .82 (.76; .87) in the trastuzumab IV arm and .83 (.78; .89) in the trastuzumab SC arm (EPP).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial BO22227

Title: A phase III, randomized, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with HER2-positive early breast cancer (EBC)		
Study identifier	BO22227; NCT00950300; "HANNAH"	
Design	Randomized, open-label	
	Duration of main phase:	neoadjuvant trastuzumab plus neoadjuvant chemotherapy (docetaxel followed by 5-fluorouracil, epirubicin, cyclophosphamide), then adjuvant trastuzumab up to 1 year
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority		
Treatments groups	Trastuzumab IV		loading dose of 8 mg/kg infused over a 90-min period. All subsequent doses were 6 mg/kg and these could be administered over a 30-min period if the first administration was well-tolerated
	Trastuzumab SC		fixed dose of 600 mg SC irrespective of the patient's body weight was administered every three weeks throughout the treatment phase
Endpoints and definitions	Pathological Complete Response	pCR	Absence of invasive neoplastic cells at microscopic examination of the primary tumor remnants after surgery following primary systemic therapy (local pathologist)
	Ctrough pre-surgery	Ctrough	Based on geometric mean ratio CtroughSC/CtroughIV
clinical cut-off date	12 July 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol			
Descriptive statistics and estimate variability	Treatment group	Trastuzumab IV	Trastuzumab SC	
	Number of subject	263	260	
	pCR (%)	40.7%	45.4%	
	Mean Ctrough	57.8	78.7	

Effect estimate per comparison	Co-Primary endpoint: pCR	Comparison groups	SC-IV
		Difference in proportions (SC-IV)	4.70
		95% CI	(-4.0; 13.4)
		P-value	N/A
	Co-Primary endpoint: Ctrough		CtroughSC/CtroughIV
		Geometric mean ratio	1.33
		95% CI	1.24-1.44
		P-value	N/A
Notes			
Analysis description	Primary analysis of efficacy/PK		

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

Not available.

Clinical studies in special populations

Not available.

Supportive studies

Not available.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Potential advantages of the EBC setting for comparing trastuzumab IV and SC are that patients are treatment-naïve and the population was considered more homogenous with fewer confounding factors than patients with MBC.

The choice of pCR as primary efficacy endpoint is generally acceptable but pCR can only be considered a surrogate parameter and non-inferiority in terms of pCR should be supported by long-term outcome data. The Applicant will update the analysis on EFS and OS once the last patient has completed the 24 months follow-up period and will present the final analysis including efficacy once the last patient has completed the 60 months follow-up period.

The efficacy data from the neoadjuvant(/adjuvant) setting can be extrapolated to the metastatic breast cancer setting based on the clinical efficacy and pharmacological outcomes.

Although pCR adjudication was done according to local review, the Applicant provided data from a retrospective questionnaire demonstrating that for 71% of patients the pathologist was blinded to treatment by local procedures (data not shown).

In general the demographic data and baseline disease characteristics are balanced between the treatment groups.

In principle a single pivotal Phase III trial comparing the new SC formulation and dose regimen with the current standard intravenous trastuzumab regimen is considered adequate to support this line extension, the objective of this trial being to demonstrate non-inferiority of the subcutaneous injection to the intravenous infusion. The choice of the clinical setting (neoadjuvant treatment in early breast cancer) and co-primary PK and efficacy endpoints (trastuzumab Ctrough and pCR) were endorsed in scientific advice meetings; indeed, this clinical model was considered sufficiently sensitive to enable the detection of differences between the two regimens.

In the chemotherapy regimen chosen for this study, the dose of docetaxel was reduced from the registered dose of 100 mg/m² to 75 mg/m² to increase the tolerability. This dose reduction might have influenced the relatively low pCR-results (especially in the trastuzumab IV arm) compared to other studies in the neoadjuvant setting. A higher docetaxel dose used in clinical practice could lead to an increased toxicity in combination with trastuzumab SC (see discussion on clinical safety).

The MAH has chosen the non-inferiority margin (-12.5%) in order to ensure assay sensitivity of SC trastuzumab + chemotherapy with respect to no trastuzumab treatment (i.e., chemotherapy alone).

Such margin, through indirect comparisons would allow to conclude that SC trastuzumab + chemotherapy is superior to chemotherapy alone. The choice of non-inferiority margin was not in line with the EMA "Guideline on the choice of the non-inferiority margin" EMEA/CPMP/ewp/2158/99. If the objective is to show that there is no important loss of efficacy if the test product is used instead of the reference, the choice of delta for such an objective cannot be obtained by only looking at past trials of trastuzumab IV plus chemotherapy against chemotherapy alone. To adequately choose delta an informed decision must be taken, supported by evidence of what is considered an unimportant difference in the particular disease area. Nevertheless, despite this shortcoming, the results are sufficiently convincing to allow excluding important loss of efficacy for the SC trastuzumab + chemotherapy, compared to IV trastuzumab +chemotherapy, in the population studied.

Efficacy data and additional analyses

The point estimate for pCR was in favour of the subcutaneous administration and a potential maximum loss of efficacy of 4.0% for the subcutaneous route, as shown by the confidence interval, is not considered to be clinically relevant.

Non-inferiority in terms of pCR was demonstrated in the EPP analysis. The results from the EPP and ITT populations were consistent. This is also supported by the results of tpCR as secondary endpoint.

Due to the short duration of follow-up there were insufficient events to draw reliable conclusions on time related outcome measures like EFS or OS (see above).

2.5.4. Conclusions on the clinical efficacy

The single pivotal study B022227 demonstrated non-inferior efficacy of the fixed dose trastuzumab SC formulation compared with the standard trastuzumab IV formulation. Efficacy was demonstrated by comparable pCR-rates in the neoadjuvant setting in patients with early breast cancer. pCR as primary efficacy endpoint and the extrapolation of the efficacy data to the metastatic breast cancer setting was considered acceptable. Overall, a comparable efficacy of a fixed dose of trastuzumab SC with trastuzumab IV is considered sufficiently established.

The Applicant will update of the analysis on EFS and OS once the last patient has completed the 24 months follow-up period and will present the final analysis including efficacy once the last patient has completed the 60 months follow-up period (see RMP).

2.6. Clinical safety

For Study BO22227 all safety analyses were based on the Safety Analysis Population (SP). The SP included all patients who received at least one dose of study medication (chemotherapy or trastuzumab), and comprises 595 patients who were included as of the clinical cut-off date July 12, 2011 (298 patients in the trastuzumab IV arm and 297 patients in the trastuzumab SC arm; of the 596 patients randomized, one patient from the trastuzumab IV arm did not receive study medication). For many analyses, an updated data set with cut-off date of July 2012 was provided (the latter are described in this report, when available).

Patient exposure

As expected with the fixed dose of trastuzumab SC, the median dose intensity was lower in the trastuzumab IV arm (135.63 mg/week) compared with that in the trastuzumab SC arm (196.36 mg/week). The median relative dose intensity (ie, percentage of planned dose) was high (at least 98% in both treatment arms), indicating good tolerability of trastuzumab SC versus trastuzumab IV. The

median number of cycles received was 18.0 (range 1-20) in the trastuzumab IV arm and 18.0 [range 1-18] in the trastuzumab SC arm, indicating that the majority of patients included in the analysis set nearly completed the full treatment phase (8 cycles concomitantly with chemotherapy before surgery followed by 10 cycles after surgery to complete one year of treatment with trastuzumab). Two patients received more than 18 cycles of treatment in the trastuzumab IV arm.

Dose-delay or interruption of trastuzumab was overall balanced between both treatment arms. A total of 64.2% (382/595) of patients experienced at least one dose-delay/interruption during the overall treatment phase (193/298 [64.8%] in trastuzumab IV, 189/297 [63.6%] in trastuzumab SC) which included concomitant treatment with chemotherapy before surgery.

There were no relevant differences between the two treatment arms for docetaxel exposure , 5-fluorouracil exposure , epirubicin exposure or cyclophosphamide exposure , with respect to the median values for the planned dose intensity and the median number of cycles (data not shown). The median number of cycles was 4 and the planned dose intensity was at least 99% in both groups. The proportion of patients with at least one dose delay, interruption or modification of docetaxel was slightly lower in the trastuzumab IV arm (45/298 patients [15.1%]) than in the trastuzumab SC arm (62/297 [20.9%]).

Most patients received at least one treatment for adverse events before or during the course of the study (81.2% in trastuzumab IV, 85.5% in trastuzumab SC). The most frequently used treatments were non-steroidal anti-inflammatories (31.2% vs. 33.7%), analgesics (26.2% vs 29.3%) and corticosteroids (24.8% vs 27.3%). During the neoadjuvant phase, there were slightly fewer patients receiving at least one treatment for adverse events in the trastuzumab IV arm (75.5%) compared to the trastuzumab SC arm (80.8%). The most frequently used treatments were G-CSF (21.8% vs 25.9%), analgesics (22.5% vs 24.2%), non-steroidal anti-inflammatories (20.8% vs 24.9%), corticosteroids (19.5% vs 22.2%), antihistamines (19.8% vs 19.5%), anti-emetics (18.1% vs 18.2%) and 5-HT3 antagonist class (16.4% vs 14.8%). During the adjuvant period there were a similar proportion of patients receiving at least one medication for adverse events in both treatment arms (51.7% in trastuzumab IV vs 50.5% in trastuzumab SC). The most commonly used treatments were non-steroidal anti-inflammatories (15.1% vs 17.8%), analgesics (10.1% vs 13.8%) and antihistamines (7.4% vs 10.1%).

Adverse events

There was no apparent difference in the types of and incidence of the most common AEs across study groups. The most frequently occurring AEs were alopecia, nausea, neutropenia, diarrhoea, asthenia, fatigue and vomiting. The overall safety profile in both groups was consistent with that expected from combination treatment with trastuzumab, anthracycline, taxane and trastuzumab. As to be expected the majority of adverse events occurred during the neo-adjuvant treatment phase because of the concomitant chemotherapy.

Overall, the proportion of patients reporting a Grade ≥ 3 AE was similar in both treatment arms (9 July 2012 cut-off; 52.3% vs 53.5% in the trastuzumab IV and SC respectively). The distribution of patients with Grade ≥ 3 AEs was comparable across both arms for all SOCs. The highest incidence of Grade ≥ 3 AEs was reported in the SOC blood and lymphatic system disorders with neutropenia, leucopenia and febrile neutropenia being the most common events in both the trastuzumab IV and the trastuzumab SC arms. However, the proportion of patients reporting an SAE was higher in the trastuzumab SC arm (21.5%) than in the trastuzumab IV arm (14.1%).

While the overall incidence of cardiac AEs was similar in both study arms, the incidence of Grade ≥ 3 cardiac AEs and SAEs were numerically slightly higher in the trastuzumab SC arm (severe AEs 1.0%

vs. 1.7% of patients [n= 3 vs. 5] and SAEs 0.7% vs. 1.7% of patients [n= 2 vs. 5] in the trastuzumab IV and trastuzumab SC arms, respectively). In total a similar proportion of patients had LVEF decreases of ≥ 10% to a value < 50% (2.1 and 2.4%), but in the trastuzumab SC arm one patient was withdrawn because of symptomatic CHF (NYHA class II, the patient had cardiac risk factors). No CHF of NYHA class III or IV was observed. In addition, there were three other possible cases of cardiac events in the trastuzumab SC arm (sudden death, chest pain, and pleural effusion).

As to be expected the majority of adverse events occurred during the neo-adjuvant treatment phase because of the concomitant chemotherapy. However, similar to the safety profile in the neoadjuvant treatment phase) also for the adjuvant treatment phase a higher rate of serious AEs (3.4% vs. 8.1%), and AEs leading to withdrawals (1% vs. 3.7%) were reported for the trastuzumab SC arm (trastuzumab IV vs. trastuzumab SC, respectively. In the adjuvant phase also a trend for more severe AEs were reported in the trastuzumab SC arm (10.4% vs. 12.8%). The SAE imbalance between both treatment arms was mainly due to events in the SOC infections and the difference in the infectious SAEs and severe infection events between both treatment arm was driven by SAEs and severe events reported during the adjuvant treatment phase. The infections of the SC arm in the adjuvant treatment phase included infections both with and without neutropenia. From a clinical point of view these events were manageable (resolved within a mean of 13 days and 17 days in the IV and SC arms respectively), however relevant from a patients perspective (requiring hospitalization or IV antibiotics for systemic infections).

In the trastuzumab SC arm a higher percentage of patients experienced AEs suggestive of administration-related reactions (37.2% vs. 47.8% in the trastuzumab IV vs. trastuzumab SC arm, respectively; grade 3 events 2.0% vs 1.7%). The most common AEs reported included rash, pruritus, cough and dyspnea. Most of these events were non severe (Grade <3). There were no Grade 4 or 5 administration- related reactions reported in either arm. The Applicant will further characterize time to onset of ARRs after administration of trastuzumab SC in the ongoing study SafeHer.

Table 11. Summary of Frequencies of Serious and Severe Adverse Advents (Overall and by Treatment phase, total patients with at least one AE)

	Trastuzumab IV (N=298) n (%)	Trastuzumab SC (N=297) n (%)
All Adverse Events	282 (94.6)	290 (97.6)
Neoadjuvant phase	275 (92.3)	287 (96.6)
Adjuvant phase	201 (67.4)	206 (69.4)
Serious Adverse Events	42 (14.1)	64 (21.5)
Neoadjuvant phase	30 (10.1)	42 (14.1)
Adjuvant phase	10 (3.4)	24 (8.1)
Treatment free follow-up	3 (1.0)	3 (1.0)

Severe Adverse Events	156 (52.3)	159 (53.5)
Neoadjuvant phase	146 (49.0)	141 (47.5)
Adjuvant phase	31 (10.4)	38 (12.8)
Treatment free follow-up	3 (1)	3(1)

Summary of Non-Severe Adverse Events By System Organ Class (Preferred Terms with Incidence Rate of at least 5%; Safety Population)

Body System/ Adverse Event	TRASTUZUMAB IV N = 298 No. (%)	TRASTUZUMAB SC N = 297 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	279 (93.6)	288 (97.0)
Total Number of AEs	2907	3039
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts with at Least one AE	214 (71.8)	224 (75.4)
ALOPECIA	183 (61.4)	183 (61.6)
RASH	44 (14.8)	48 (16.2)
NAIL DISORDER	31 (10.4)	29 (9.8)
PRURITUS	27 (9.1)	26 (8.8)
SKIN HYPERPIGMENTATION	24 (8.1)	20 (6.7)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	17 (5.7)	20 (6.7)
DERMATITIS	15 (5.0)	14 (4.7)
ERYTHEMA	8 (2.7)	21 (7.1)
GASTROINTESTINAL DISORDERS		
Total Pts with at Least one AE	199 (66.8)	211 (71.0)
NAUSEA	145 (48.7)	145 (48.8)
DIARRHOEA	106 (35.6)	98 (33.0)
VOMITING	68 (22.8)	67 (22.6)
STOMATITIS	50 (16.8)	56 (18.9)
CONSTIPATION	45 (15.1)	43 (14.5)
DYSPEPSIA	30 (10.1)	33 (11.1)
ABDOMINAL PAIN UPPER	27 (9.1)	21 (7.1)
ABDOMINAL PAIN	15 (5.0)	22 (7.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts with at Least one AE	179 (60.1)	188 (63.3)
ASTHENIA	74 (24.8)	75 (25.3)
FATIGUE	77 (25.8)	70 (23.6)
MUCOSAL INFLAMMATION	39 (13.1)	31 (10.4)
PYREXIA	34 (11.4)	35 (11.8)
OEDEMA PERIPHERAL	32 (10.7)	26 (8.8)
OEDEMA	15 (5.0)	10 (3.4)
INJECTION SITE PAIN	-	18 (6.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts with at Least one AE	143 (48.0)	138 (46.5)
MYALGIA	54 (18.1)	61 (20.5)
ARTHRALGIA	51 (17.1)	48 (16.2)
PAIN IN EXTREMITY	25 (8.4)	30 (10.1)
MUSCULOSKELETAL PAIN	29 (9.7)	24 (8.1)
BACK PAIN	23 (7.7)	26 (8.8)

BONE PAIN	10 (3.4)	19 (6.4)
INFECTIONS AND INFESTATIONS		
Total Pts with at Least one AE	132 (44.3)	132 (44.4)
NASOPHARYNGITIS	40 (13.4)	24 (8.1)
UPPER RESPIRATORY TRACT INFECTION	29 (9.7)	30 (10.1)
URINARY TRACT INFECTION	22 (7.4)	10 (3.4)
NERVOUS SYSTEM DISORDERS		
Total Pts with at Least one AE	114 (38.3)	138 (46.5)
HEADACHE	43 (14.4)	49 (16.5)
PERIPHERAL SENSORY NEUROPATHY	27 (9.1)	33 (11.1)
DIZZINESS	28 (9.4)	29 (9.8)
DYSGEUSIA	22 (7.4)	24 (8.1)
NEUROPATHY PERIPHERAL	18 (6.0)	24 (8.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts with at Least one AE	121 (40.6)	108 (36.4)
NEUTROPENIA	83 (27.9)	80 (26.9)
ANAEMIA	37 (12.4)	34 (11.4)
LEUKOPENIA	37 (12.4)	24 (8.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts with at Least one AE	88 (29.5)	107 (36.0)
RADIATION SKIN INJURY	32 (10.7)	40 (13.5)
INCISION SITE PAIN	23 (7.7)	33 (11.1)
PROCEDURAL PAIN	15 (5.0)	18 (6.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts with at Least one AE	90 (30.2)	89 (30.0)
COUGH	24 (8.1)	34 (11.4)
DYSPNOEA	22 (7.4)	21 (7.1)
OROPHARYNGEAL PAIN	19 (6.4)	19 (6.4)
EPISTAXIS	18 (6.0)	19 (6.4)
METABOLISM AND NUTRITION DISORDERS		
Total Pts with at Least one AE	82 (27.5)	69 (23.2)
DECREASED APPETITE	58 (19.5)	58 (19.5)
VASCULAR DISORDERS		
Total Pts with at Least one AE	66 (22.1)	81 (27.3)
HOT FLUSH	29 (9.7)	29 (9.8)
HYPERTENSION	12 (4.0)	20 (6.7)
PSYCHIATRIC DISORDERS		
Total Pts with at Least one AE	53 (17.8)	54 (18.2)
INSOMNIA	31 (10.4)	26 (8.8)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Total Pts with at Least one AE	45 (15.1)	52 (17.5)
INVESTIGATIONS		
Total Pts With at Least one AE	44 (14.8)	35 (11.8)
ALANINE AMINOTRANSFERASE INCREASED	16 (5.4)	14 (4.7)
EYE DISORDERS		
Total Pts with at Least one AE	35 (11.7)	42 (14.1)
CARDIAC DISORDERS		
Total Pts with at Least one AE	37 (12.4)	37 (12.5)

IMMUNE SYSTEM DISORDERS		
Total Pts with at Least one AE	20 (6.7)	18 (6.1)
RENAL AND URINARY DISORDERS		
Total Pts with at Least one AE	16 (5.4)	17 (5.7)
EAR AND LABYRINTH DISORDERS		
Total Pts with at Least one AE	9 (3.0)	9 (3.0)
HEPATOBILIARY DISORDERS		
Total Pts with at Least one AE	7 (2.3)	5 (1.7)
ENDOCRINE DISORDERS		
Total Pts with at Least one AE	4 (1.3)	4 (1.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts with at Least one AE	4 (1.3)	4 (1.3)
SURGICAL AND MEDICAL PROCEDURES		
Total Pts with at Least one AE	2 (0.7)	-
SOCIAL CIRCUMSTANCE		
Total Pts with at Least one AE S	-	1 (0.3)

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Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Summary of Severe (Grade>=3) Adverse Events By System Organ Class (Preferred Terms with Incidence Rate of at least 1%; Safety Population)

Body System/ Adverse Event	TRASTUZUMAB IV N = 298 No. (%)	TRASTUZUMAB SC N = 297 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	156 (52.3)	159 (53.5)
Total Number of AEs	261	249
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	112 (37.6)	106 (35.7)
NEUTROPENIA	99 (33.2)	87 (29.3)
FEBRILE NEUTROPENIA	13 (4.4)	17 (5.7)
LEUKOPENIA	18 (6.0)	12 (4.0)
GRANULOCYTOPENIA	6 (2.0)	4 (1.3)
ANAEMIA	3 (1.0)	1 (0.3)
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	15 (5.0)	21 (7.1)
CELLULITIS	-	3 (1.0)
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	18 (6.0)	17 (5.7)
DIARRHOEA	8 (2.7)	8 (2.7)
NAUSEA	4 (1.3)	4 (1.3)
VOMITING	5 (1.7)	3 (1.0)
REPRODUCTIVE SYSTEM AND BREAST		

DISORDERS		
Total Pts With at Least one AE	12 (4.0)	11 (3.7)
MENSTRUATION IRREGULAR	6 (2.0)	5 (1.7)
AMENORRHOEA	5 (1.7)	3 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	9 (3.0)	10 (3.4)
FATIGUE	4 (1.3)	1 (0.3)
ASTHENIA	3 (1.0)	1 (0.3)
VASCULAR DISORDERS		
Total Pts With at Least one AE	5 (1.7)	13 (4.4)
HYPERTENSION	1 (0.3)	6 (2.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	9 (3.0)	6 (2.0)
ALOPECIA	5 (1.7)	4 (1.3)
INVESTIGATIONS		
Total Pts With at Least one AE	6 (2.0)	6 (2.0)
ALANINE AMINOTRANSFERASE INCREASED	3 (1.0)	2 (0.7)
ASPARTATE AMINOTRANSFERASE INCREASED	3 (1.0)	-
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	9 (3.0)	3 (1.0)
HYPERGLYCAEMIA	3 (1.0)	2 (0.7)
HYPOKALAEMIA	4 (1.3)	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	8 (2.7)	3 (1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	5 (1.7)	5 (1.7)
BACK PAIN	3 (1.0)	1 (0.3)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	7 (2.3)	3 (1.0)
CARDIAC DISORDERS		
Total Pts With at Least one AE	3 (1.0)	5 (1.7)
IMMUNE SYSTEM DISORDERS		
Total Pts With at Least one AE	4 (1.3)	3 (1.0)
HYPERSENSITIVITY	3 (1.0)	1 (0.3)
HEPATOBILIARY DISORDERS		
Total Pts With at Least one AE	2 (0.7)	2 (0.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	1 (0.3)	3 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	-	4 (1.3)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS		
Total Pts With at Least one AE	-	2 (0.7)

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PSYCHIATRIC DISORDERS
  Total Pts With at Least one AE       -               2 (  0.7)

ENDOCRINE DISORDERS
  Total Pts With at Least one AE       1 (  0.3)       -

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Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Serious adverse event / deaths / other significant events

The proportion of patients for whom at least one SAE was recorded was higher in the trastuzumab SC arm. SAEs were more frequently reported in the SOCs blood and lymphatic system disorders and infections and infestations. Although the number of events was small, there was also a higher incidence of SAEs in the SOC cardiac disorders. Most of the overall difference in SAEs between the two treatment arms was due to events in the SOC infections and infestations; the remaining difference was due to a higher number of sporadic events in the trastuzumab SC arm reported across SOCs.

The reporting rate of SAEs varied widely across countries and regions, e.g. in the SC arm, from 41.2% in South Africa down to 10.5% in Eastern Europe, where the latter contributed for 38% of the patient population (clinical cut-off date of 9 july 2012).

For the adjuvant treatment phase a higher rate of serious AEs and AEs leading to withdrawals were reported for the trastuzumab SC arm (3.4% vs. 8.1% and 1.3% vs. 3.7% for the trastuzumab IV vs. trastuzumab SC respectively). Events in the SOC infections and infestations largely accounted for the SAE imbalance (1.7% vs. 4.4%)in the adjuvant treatment phase. An imbalance in administration-related reactions was also reported for the adjuvant treatment phase (12.1% of patients in the trastuzumab IV arm and 18.5% of patients in the trastuzumab SC arm), however most administration related reactions in either treatment phase were non-severe (Grade <3).

The cumulative exposure of trastuzumab over the full treatment period neo- + adjuvant for i.v. and s.c. administered trastuzumab was estimated.

At the clinical cut-off date of 09 July 2012, six SAEs with fatal outcome had been reported for reasons other than progressive disease. Two of these (myeloid leukemia in the treatment free follow up more than 6 months after last study drug administration; pneumonia in the neoadjuvant phase) occurred in the IV arm of the BO22227 study and four (septic shock in the neoadjuvant phase; sudden death in the neoadjuvant phase; myocardial infarction in the neoadjuvant phase; endometrial cancer in the treatment free follow-up phase) in the SC arm. Despite pre-existing cardiac risk factors of hypertension and overweight in the patients with sudden death and myocardial infarction and additional elderly age and diabetes in one of the patients, a relation to the treatment with trastuzumab could not be ruled out.

Table 1 Summary of Serious Adverse Events: All Treatment Phases

Body System / Adverse Event	Trastuzumab IV N=298	Trastuzumab SC N=297
ALL BODY SYSTEMS		
Total Pts with at least one AE	42 (14.1)	64 (21.5)
Total Number of AEs	52	87
Blood and lymphatic system disorders		
Total Pts with at least one AE	20 (6.7)	21 (7.1)
Total Number of AEs	20	22
Infections and infestations		
Total Pts with at least one AE	13 (4.4)	24 (8.1)
Total Number of AEs	13	26
Cardiac disorders		
Total Pts with at least one AE	2 (0.7)	5 (1.7)
Total Number of AEs	2	6
Injury, poisoning and procedural complications		
Total Pts with at least one AE	4 (1.3)	3 (1.0)
Total Number of AEs	5	3
Gastrointestinal Disorders		
Total Pts with at least one AE	4 (1.3)	2 (0.7)
Total Number of AEs	4	2
Respiratory, thoracic and mediastinal disorders		
Total Pts with at least one AE	1 (0.3)	4 (1.3)
Total Number of AEs	1	4
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Total Pts with at least one AE	1 (0.3)	3 (1.0)
Total Number of AEs	1	3
Reproductive system and breast disorders		
Total Pts with at least one AE	1 (0.3)	3 (1.0)
Total Number of AEs	1	3
Vascular disorders		
Total Pts with at least one AE	1 (0.3)	3 (1.0)
Total Number of AEs	1	3
General disorders and administration site conditions		
Total Pts with at least one AE	-	3 (1.0)
Total Number of AEs	-	4
Psychiatric disorders		
Total Pts with at least one AE	1 (0.3)	2 (0.7)
Total Number of AEs	1	2
Immune system disorders		
Total Pts with at least one AE	2 (0.7)	-
Total Number of AEs	2	-
Musculoskeletal and connective tissue disorders		
Total Pts with at least one AE	-	2 (0.7)
Total Number of AEs	-	2
Nervous system disorders		

Body System / Adverse Event	Trastuzumab IV N=298	Trastuzumab SC N=297
Total Pts with at least one AE	-	2 (0.7)
Total Number of AEs	-	2
Pregnancy, puerperium and perinatal conditions		
Total Pts with at least one AE	-	2 (0.7)
Total Number of AEs	-	2
Endocrine disorders		
Total Pts with at least one AE	1 (0.3)	-
Total Number of AEs	1	-
Investigations		
Total Pts with at least one AE	-	1 (0.3)
Total Number of AEs	-	1
Renal and urinary disorders		
Total Pts with at least one AE	-	1 (0.3)
Total Number of AEs	-	1
Skin and subcutaneous tissue disorders		
Total Pts with at least one AE	-	1 (0.3)
Total Number of AEs	-	1

AE = adverse event; IV = intravenous; N, No. = number; Pts = patients; SC = subcutaneous.
J22227O outputs: Investigator text for Adverse Events encoded using MedDRA version 16.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Table 12 Summary of Serious and Severe Infections

Overall and by Treatment phase, total patients with at least one AE

	Trastuzumab IV (N=298) n (%)	Trastuzumab SC (N=297) n (%)
Serious Infections	13 (**4.4**)	24 (**8.1**)
Neoadjuvant phase	8 (2.7)	10 (3.4)
Adjuvant phase	5 (**1.7**)	13 (**4.4**)
Treatment free follow-up	0	1 (0.3)
Severe Infections	15 (**5**)	21 (**7.1**)
Neoadjuvant phase	9 (3)	10 (3.4)
Adjuvant phase	6 (**2**)	11 (**3.7**)
Treatment free follow-up	0	1(0.3)

Serious or severe postoperative **wound infection**	5(**1.7**)	9 (**3**)

Laboratory findings

The pattern of laboratory abnormalities was generally similar for the 2 treatment arms, with neutropenia reported as the most common Grade 3/4 change in a haematological laboratory parameter. The blood chemistry parameters (ASAT, ALAT, total bilirubin, lactate dehydrogenase, serum creatinine) were also similar (data not shown). No effect on proteinuria and haematuria was observed (data not shown).

stlb23hem_se Summary of Hematology Laboratory Data and Worst Grade (Safety Population)
Protocol(s): J22227O
Analysis: SAFETY Center: ALL CENTERS
Class: HEMATOLOGY
Time Window: from study day 2 to 999 and 9999 days after end of treatment. WORST value selected.

Parameter	TRASTUZUMAB IV N = 298	TRASTUZUMAB SC N = 297
Hemoglobin g/L (HYPO)		
n	297	296
Grade 0	34 (11%)	42 (14%)
Grade 1	189 (64%)	185 (63%)
Grade 2	69 (23%)	64 (22%)
Grade 3	4 (1%)	3 (1%)
Grade 4	1 (<1%)	2 (<1%)
White blood cell (WBC) 10**9/L (HYPO)		
n	297	296
Grade 0	94 (32%)	95 (32%)
Grade 1	73 (25%)	81 (27%)
Grade 2	74 (25%)	52 (18%)
Grade 3	53 (18%)	57 (19%)
Grade 4	3 (1%)	11 (4%)
Platelets 10**9/L (HYPO)		
n	297	296
Grade 0	241 (81%)	230 (78%)
Grade 1	52 (18%)	64 (22%)
Grade 2	2 (<1%)	-
Grade 3	-	2 (<1%)
Grade 4	2 (<1%)	-

n represents number of patients with at least one valid value within the given time window.
Missing and non-numeric values are excluded from the analysis!
Percentages are based on n. Percentages not calculated if n < 10.
LB23 28JUN2013:15:39:27 (1 of 2)

2.6.1. Discussion on clinical safety

A higher docetaxel dose used in clinical practice could lead to an increased toxicity in combination with trastuzumab SC. To address this issue the Applicant included annual comparisons on the combined use of trastuzumab SC with docetaxel 75 m/m^2 and 100 mg/m^2 to the post-marketing activity.

A slight increased toxicity of the SC regimen in comparison with the standard intravenous regimen was observed. This was most evident in higher incidence rates of SAEs with a relatively larger difference in the adjuvant treatment phase. Most SAEs were identified by in-patient hospitalisation or prolongation of existing hospitalisation. The difference between arms was mainly driven by infectious events and is

also noted for cardiac events though the numbers are smaller. In addition more hypertensive events and a higher immunogenicity (which did not induce adverse reactions) were reported for the trastuzumab SC formulation in the pivotal study. Overall, the difference in SAE rates is not reflected by a difference in severe adverse events.

In the trastuzumab SC arm there was a higher incidence AEs suggestive of administration-related reactions (37.2% vs. 47.8% in the trastuzumab IV vs. trastuzumab SC arm, respectively; clinical cut-off date of July 2012) mainly due to erythema and cough. Taking the different pharmacokinetics into account, a later onset of ARRs could be theoretically hypothesized for the SC formulation, thus possibly requiring a longer observation period. To clarify this issue, the time to onset of administration-related reactions will be evaluated in the ongoing SC SID cohort of study SafeHer (see RMP).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Study B022227 demonstrated a safety profile for Trastuzumab SC consistent with the known safety profile for trastuzumab IV with no new safety findings, but higher rates of some AEs were observed in the trastuzumab SC arm compared to the trastuzumab IV arm, however no definite conclusions were made as to whether this is a true safety difference between the formulations and more information will be provided through additional follow-up as agreed in the RMP. All the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC agreed by consensus that the risk management system for trastuzumab (Herceptin) is acceptable. The following points should be considered in the next revision of the RMP to be submitted together with the next PSUR:

- The PRAC recommendation for a Phase IV clinical trial concerning safety of 100 mg/m^2 docetaxel and sc Herceptin in patients with metastatic breast cancer with specific focus on active cardiac monitoring.
- The RMP needs to be revised with the presentation of data on overdose for trastuzumab IV versus trastuzumab SC.
- To allow more comprehensive comparison with clinical trial data post-marketing data should be presented as reporting rate, using the frequency from number of concerned events and the number of total events as numerator and denominator.
- Clear milestones should be provided by the company for some studies mentioned in the Pharmacovigilance Plan of the RMP. At the moment there are unclear dates present (e.g. H4613g (HER-Q-Les) 'circa 2013', and for ML20529 no dates at all)

In future PSURs the following should be taken into account:

- The analyses of safety of docetacel 75mg/m2 versus 100mg/m2 should be presented with each PSUR.
- Metastatic dissemination should undergo further close monitoring and evaluation with comparison of the data for IV and SC formulation administered

Trastuzumab is currently licensed for use in HER2-positive:

- Early breast cancer (EBC):
  - As neoadjuvant-adjuvant therapy (in combination with neoadjuvant chemotherapy, followed by trastuzumab monotherapy for a total duration of 1 year).
  - In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
  - Following surgery, neoadjuvant or adjuvant chemotherapy and radiotherapy, if applicable.
- Metastatic breast cancer (MBC)
  - As monotherapy or
  - In combination with paclitaxel, docetaxel or an aromatase inhibitor.
- Metastatic gastric cancer
  - In combination with chemotherapy.

This advice is based on the following content of the Risk Management Plan:

- Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Cardiac dysfunction - Administration-related reactions - Haematological toxicity - Oligohydramnios - Pulmonary disorder
Important potential risks	- Infections - Medication errors - Immunogenicity/Hypersensitivity and Anaphylaxis (subcutaneous formulation) - Relative short-term safety of higher absolute dose intensity (subcutaneous formulation compared to IV formulation)
missing information	- Treatment in male patients - Relative long-term safety of safety of higher absolute dose intensity (subcutaneous formulation compared to IV formulation) - Safety of 75 mg/m^2 vs. 100 mg/m^2 docetaxel dose

The PRAC agreed.

- Pharmacovigilance plans

Table 2.2: Ongoing and planned studies in the PhV development plan

Actions	Milestones / Exposure	Milestones / Calendar Time	Study Status
Annual analysis of BO20652 (OHERA)	N/A/est. 3800	With the PSUR – data lock point 24 September.	Ongoing
H4613g (HER-Q-Les)	N/A/est. 55	Final study report circa 2013. No interim analyses planned.	Ongoing
ML20529	Interim analysis after 10 cardiac failures/est. 200	First interim analysis completed. DSMB recommends protocol continuation with no amendments.	Ongoing
Annual analysis of H4621g (MotHER)	N/A	With the PSUR/PBRER – DLP 24 March.	Ongoing
WO17299	Interim analysis 6 months after LPI	The snapshot of closing the database is 22 Oct 2010	Ongoing
BO22227 (HannaH)	Cardiac safety follow up 5 years post treatment.	Annual report with the PSUR – DLP 24 March. Final clinical study report – Sept 2017	Ongoing.
Potential for off-label use – Annual analysis of oxaliplatin vs cisplatin and SC formulation usage in GC indication.	N/A	Annual report with the PSUR – DLP 24 March.	Ongoing
Annual analysis of SC + docetaxel 75 mg/m^2 versus docetaxel 100 mg/m^2.	N/A	Annual report with the PSUR – DLP 24 March (2014 – 2017).	Ongoing
Annual analysis of data received from guided questionnaire for ARRs	N/A	Annual report with the PSUR – DLP 24 September.	Ongoing
Annual analysis of data received from guided questionnaire for medication errors	Following launch of the new SC formulation	Annual report with the PSUR – DLP 24 September.	Ongoing
6-monthly aggregate review of all medication error cases.	Following launch of the new SC formulation	6-monthly review submitted with scheduled PSURs	Ongoing
SafeHER	planned enrolment is 2,500 patients	Annual reports starting 2014 Final analysis estimated Q4 2019	Ongoing
PrefHER (MO22982)	planned enrolment is 200 patients	Final analysis estimated Q1 2016	Ongoing

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC advises to request a Phase IV clinical trial concerning safety of 100 mg/m2 docetaxel and sc Herceptin in patients with metastatic breast cancer with specific focus on active cardiac monitoring.

- Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardiac dysfunction	*Section 4.4 of the SmPC*	*Clinical Recommendation Algorithm*
Administration-related reactions	*Sections 4.2 and 4.4 of the SmPC.*	*None*
Haematological toxicity	*Section 4.8 of the SmPC*	*None*
Oligohydramnios	*Section 4.6 of the SmPC*	*None*
Pulmonary disorder	*Sections 4.3 and 4.4 of the SmPC*	*None*
Infections	*Section 4.8 of the SmPC*	*None*
Medication errors	*Section 4.2 of the SmPC*	*None*
Immunogenicity/Hypersensitivity and Anaphylaxis (subcutaneous formulation)	*Section 4.8 of the SmPC*	*None*
Relative short-term safety of higher absolute dose intensity (subcutaneous formulation compared to IV formulation)	*Section 4.2 of the SmPC*	*None*
Treatment in male patients	*Section 5.3 of the SmPC*	*None*
Relative long-term safety of safety of higher absolute dose intensity (subcutaneous formulation compared to IV formulation)	*Section 4.2 of the SmPC*	*None*
Safety of 75 mg/m^2 vs. 100 mg/m^2 docetaxel dose	*Section 4.2 of the SmPC*	*None*
HER2 Overexpression	*Section 4.2 of the SmPC*	*HER2 testing website for pathologists*

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice, however it was considered that the requested Phase IV clinical trial with specific focus on active cardiac monitoring should be uncontrolled with an open choice of the dose of docetaxel. The protocol of the trial will be discussed with the MAH and agreed in the next RMP update.

2.8. User consultation

The applicant will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use* prior to placing the product on the market.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The present application provides data to support the license extension of the trastuzumab SC (vial) formulation (Herceptin SC) as a fixed dose (600 mg) for three-weekly assisted administration via a handheld syringe. The SC administration of trastuzumab is enabled by the use of recombinant human hyaluronidase (rHuPH20), a key excipient in the trastuzumab SC formulation which acts as a permeation enhancer. This application is based on data from one phase I pharmacokinetic (PK) dose-finding and dose-confirmation study (BP22023) and one pivotal, phase III clinical study (BO22227) in patients with EBC in the neoadjuvant-adjuvant setting.

The phase I study aimed at identifying a SC trastuzumab dose for a q3w regimen which allowed for drug exposure comparable to the licensed q3w IV regimen (loading dose of 8 mg/kg, maintenance dose 6 mg/kg q3w). Based on modeling and simulation of data from study BP22023, the fixed dose of 600 mg q3w was determined for the trastuzumab SC formulation that subsequently was investigated in the phase III pivotal study.

The primary analysis of the phase III study (EPP analysis set) allows to conclude non-inferiority of trastuzumab SC compared to trastuzumab IV in terms of the primary endpoints pCR, which was 45.4% (95% CI: 39.2%, 51.7%) vs. 40.7% (95% CI: 34.7%, 46.9%), and the co-primary endpoint Ctrough pre-dose Cycle 8, which was 78.7 µg/mL *vs.* 57.8 µg/mL for trastuzumab SC *vs*. trastuzumab IV respectively. The results were consistent with secondary analyses of secondary endpoints (tpCR, EFS, AUC) and analyses based on the ITT set.

The study was conducted in the neoadjuvant-adjuvant treatment setting in patients with early breast cancer with the efficacy assessment after the end of the neoadjuvant treatment. Extrapolation of efficacy is considered acceptable (regarding *safety* in MBC see Risks, below). The treatment of patients with gastric cancer is not within the scope of this line extension.

Uncertainty in the knowledge about the beneficial effects.

The choice of pCR as primary efficacy endpoint is generally acceptable but pCR can only be considered a surrogate parameter and non-inferiority in terms of pCR should be supported by long-term outcome data. The 2-year EFS of .82 (.76; .87) in the trastuzumab IV arm and .83 (.78; .89) in the

trastuzumab SC arm (EPP) provide support to the conclusion of non-inferiority in efficacy (median follow-up of about 20.7 months; clinical cut-off date of 9 July 2012). As set out in the pharmacovigilance plan, the Applicant will submit more complete follow-up data on EFS and OS once the last patient has completed the 24 months follow-up period and will present the final analysis including efficacy once the last patient has completed the 60 months follow-up period, to further confirm long-term outcome.

A higher rate of anti-drug antibodies against trastuzumab was observed for the SC formulation compared to trastuzumab IV. However, a very low incidence of neutralizing antibodies is reassuring (one patient treated with the IV formulation and two patients treated with the SC formulation). In addition antibodies were not associated with adverse reactions. The applicant will provide follow-up data from immunogenicity analyses on anti-trastuzumab and anti-rHuPH2 antibodies as part of the BO22227 Annual Report to be submitted with the March Data Lock Point (DLP) Herceptin PSUR.

The Applicant will submit the final study reports data for the clinical studies B022227, PrefHer and SafeHer, including immunogenicity, when available.

Risks

Unfavourable effects

Trastuzumab SC safety profile was consistent with the known safety profile for trastuzumab IV with no new safety findings, but higher rates of some AEs were observed in the trastuzumab SC arm compared to the trastuzumab IV arm. This included higher rate of SAEs (14.1% vs. 21.5%), SAEs not completely resolved (7.3% vs. 17.2% of SAEs in 1.3% vs 3.7% of patients); higher rate of treatment withdrawals for safety reasons (2.7% vs. 5.7%), higher rate of events in SOCs infections, higher rate of AE leading to death (2 vs. 4 patients), and higher incidence of Grade $\geq$ 3 cardiac AEs (1.0% vs. 1.7%), cardiac SAEs (0.7% vs. 1.7%), and higher withdrawals due to symptomatic LVEF decrease (0 vs. 2 patients). The difference in the safety profile of both trastuzumab formulations was more pronounced in the adjuvant treatment phase. It cannot be concluded with certainty whether the difference in the SAE profile between both treatment arms is due to a true safety difference between the formulations or is rather a bias due to the open-label study or mainly due to chance. All the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

A higher rate of cardiac toxicity has been reported in MBC compared with EBC patients receiving trastuzumab IV (most likely due to prior exposure to anthracyclines). In this context it was discussed whether the safety data of trastuzumab SC in the neoadjuvant setting are completely transferable to the metastastic breast cancer setting. The Applicant will provide a proposal for a phase IV safety clinical trial with prospective cardiac monitoring in patients with MBC to address this issue.

Uncertainty in the knowledge about the unfavourable effects

The follow-up-period for Study B022227 has been extended to 5 years and Annual Reports of Study BO22227 will be provided.

The MAH selected a lower docetaxel dose of 75m/m² in view of patient tolerability, as higher doses are associated with increased rates of neutropenic fever. No data have been provided for the treatment of trastuzumab SC with standard dose of chemotherapy, so a further increase in toxicity can be expected in combination with a higher dose chemotherapy backbone. To address this issue Annual Reports comparing trastuzumab SC plus 75 mg/m² docetaxel with trastuzumab SC plus 100 mg/m² docetaxel have been included as a pharmacovigilance measure for this Missing Information in the Risk Management Plan.

A higher rate of cardiac toxicity has been reported in MBC compared with EBC patients receiving trastuzumab IV (most likely due to prior exposure to anthracyclines). In this context it could be discussed whether the safety data of trastuzumab SC in the neoadjuvant setting are completely transferable to the metastastic breast cancer setting. The Applicant will provide a proposal for a phase IV clinical safety study with prospective cardiac monitoring in patients with MBC to address this issue.

The applicant will provide follow-up data from immunogenicity analyses on anti-trastuzumab and anti-rHuPH2 antibodies as part of the BO22227 Annual Report to be submitted with the March Data Lock Point (DLP) Herceptin PSUR.

Limited information is available regarding switching patients between both trastuzumab formulations. A further risk associated with the switch from SC to IV application is related to the higher Ctrough levels reached during SC administration. Subsequent IV infusion will lead to a very high Cmax level resulting from addition to the high pre-dose Ctrough. However limited safety data from the first interim analysis of Study M0222982 PrefHER did not reveal a clinical safety signal so far (data not shown). The lack of sufficient data is reflected in section 4.2 of the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

Compared to IV administration, SC administration may have advantages in terms of shorter administration time (2-5 minutes) and alternative route of administration, particularly for trastuzumab monotherapy (e.g., during adjuvant treatment). A fixed subcutaneous dose independent of the patient´s weight and without a loading dose simplifies the dose regimen. The risk of medication errors relating to accidentally wrong doses is expected to be reduced compared to a weight-based dosing.

Trastuzumab SC was associated with a slightly higher incidence of AE for some adverse events like SAEs, infections, AE leading to death, cardiac AEs and AEs leading to treatment withdrawals for safety reasons in the trastuzumab SC arm. However, the differences were small, often based on rare events, and may be at least in part due to bias and chance. Exploratory analyses did not reveal an association between toxicity and exposure. Although the incidence of SAEs was higher for trastuzumab SC, the incidence of severe (Grade 3 or higher) AEs was similar in both treatment groups.

Benefit-risk balance

Efficacy in term of antitumor response (pCR) was considered at least non-inferior to the trastuzumab IV formulation. The expected benefit of the greater convenience of the SC treatment has to be weighed against the risk of exposing the patients to a drug with a potentially worse safety profile. The benefit is particularly relevant in the adjuvant treatment phase, when the patients are not bound any longer to the burden of chemotherapy, and counter-balances the slightly higher toxicity observed with the SC regimen.

Discussion on the benefit-risk balance

The study was conducted in the neoadjuvant-adjuvant treatment setting in patients with early breast cancer with the efficacy assessment after the end of the neoadjuvant treatment. This is a licensed indication for trastuzumab IV and the rationale for the choice of this patient population is considered acceptable. Extrapolation of efficacy to the metastatic breast cancer setting is considered acceptable.

The treatment of patients with gastric cancer is not within the scope of this line extension.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of trastuzumab 600mgsolution for subcutaneous use in the treatment of:

patients with HER2 positive metastatic breast cancer:

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

patients with HER2 positive early breast cancer.

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin monotherapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.>

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.