

Drug Development Plan

GROUP C - PRIYA BHUTADA

TRACK - DRUG

DATE 15/10/2022

Product Description -

Product name: Hertumig® / monoclonal antibody (mAb) VBT001

Company: VaudBiotech SA., Swiss Federal Institute of Technology Lausanne (EPFL), Station 19, CH-1015 Lausanne. <https://VaudBiotech SA.com>

Treatment: HER2- positive metastatic/non-metastatic breast cancer

Delivery: Intravenous (IV) administration.

Category: HER2 targeted drug

Product details – The supplement provides chemical name, molecular formula/molecular weight, amino acid sequences, composition, availability, etc.

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Table of Contents

1. Executive summary.....	3
2. Introduction	4
3. Developmental Plan.....	6
Part A. Preclinical Plan.....	6
Part B. Clinical Plan.....	9
Part C. Chemistry, Manufacturing and Controls	11
Part D: Pre-IND Meeting / Scientific Advice	13
Part E: Inspection Readiness	14
4. Overall strategy	15
5. Advice to Management	16
6. Conclusion	16
7. References.....	17
8. Supplement	19

1. Executive summary

Breast cancer has now seized the second position as one of the most significant causes of death by cancer in the world (Siegel et al., 2020). According to the American Cancer Society, it is the most prevalent and lethal type of cancer in women.

Approximately 20-25% of all breast cancer account for (HER2) positive breast cancer (Schlam & Swain, 2021). Hertumig®/mAb VBT001 is a humanized monoclonal antibody (mAb) proposed as a treatment for HER2-positive metastatic/non-metastatic breast cancer. Hertumig® participates in neoadjuvant therapy alone or combined with chemotherapy and targeted therapy. Hertumig® has efficiently prevented apoptosis and proliferation of breast cancer tumors in nude mice breast cancer xenograft models (rodent) and rhesus monkeys (non-rodent).

The phase 1 clinical trial will occur at Heidelberg University Hospital, Germany. Vitria Biotech Co. will manufacture mAb in Switzerland under GMP compliances.

2. Introduction

Breast cancer is one of the leading causes of death in women worldwide (Siegel et al., 2020)(Wilkinson & Gathani, 2022). The survival rates associated with the current anticancer treatment greatly vary with the stage of cancer development. In the present scenario, a major challenge with conventional anticancer drug treatment is multidrug resistance that results in tumor relapse (Goldhirsch et al., 2013) (Balocco et al., 2022). In addition, lack of selectivity for tumor cells, high systemic toxicity, and unrecognized long-term side effects remain critical issues(Hansel et al., 2010). Under these circumstances, discovering and developing new anticancer drugs is a necessity. Therefore, we have developed Hertumig[®], a mAb that targets a newly defined antigen of the HER2 receptor. Nomenclature of our Drug is according to New INN nomenclature for monoclonal antibodies (Balocco et al., 2022).

A transmembrane tyrosine kinase (TK) receptor HER2 (human epidermal growth factor receptor 2) is a member of the EGFR family(AK & TR, 2008). HER2 receptors are activated by the formation of homodimers and/or heterodimers with any member of the EGFR family (Graus-Porta et al., 1997). HER2 receptors are overexpressed in HER2-positive breast cancer. Dimerization of HER receptors inhibits apoptosis and promotes the proliferation of tumor cells. The HER2 receptor is one of breast cancer's most active and tumor-promoting receptors, making it an ideal candidate for targeted drug therapy alone or in combination with chemotherapy and/or other HER2-directed agents in breast cancer patients (Schlam & Swain, 2021) (Chiavenna et al., 2017) (Mitri et al., 2012).

Hertumig[®] is a bispecific monoclonal antibody (BsmAb) that targets two novel epitopes of the HER2 receptor (Figure 1). Currently, the HER-targeted mAb Trastuzumab (Herceptin[®], Genentech) and Pertuzumab (Perjeta[®], Genentech) alone or in combination with

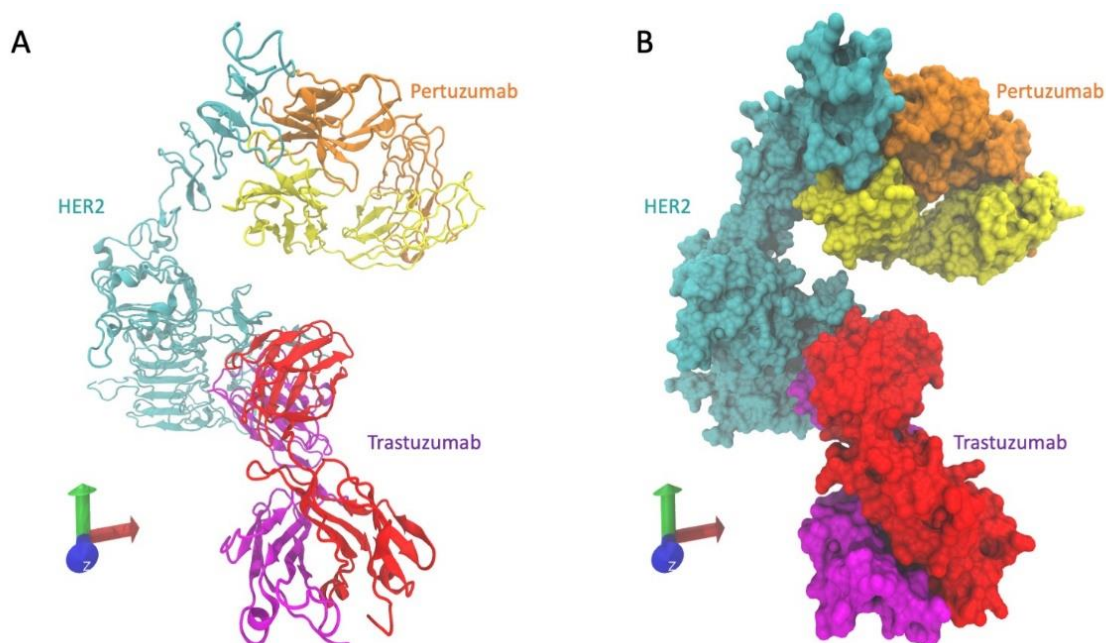


Figure 1. Cryo-EM structure of HER2 bound by mAbs – HER2 (cyan) extracellular domain, Trastuzumab Fab (Herceptin - red and pink), and Pertuzumab Fab complex (Perjeta - yellow and orange). Modified from PDB 6OGE

chemotherapy are approved as a therapy for HER2-positive breast cancer (Tarantino et al., 2021) (Balduzzi et al., 2014) (Amiri-Kordestani et al., 2014).

In our preclinical studies, Hertumig[®] has shown promising antitumor and antiproliferative activity alone and in combination with Herceptin and Perjeta. Besides, Hertumig[®], in combination with docetaxel (Taxotere[®]), also showed promising results in our preclinical studies. The preclinical studies were performed under GLP compliance.

VaudBiotech SA. will apply for biologics-anticancer therapeutic drug designation after completing the Hertumig[®] clinical trial phase 1 study. As per the Drug development plan, VaudBiotech SA. will launch Hertumig[®] in the European Union (EU) by 2030. Vitria Biotech SA. will manufacture it considering GMP compliances.

3. Development Plan:

Part A. Preclinical Plan / Non-clinical Plan –

Targeted therapy using mAb Trastuzumab (Herceptin[®], Genentech) and Pertuzumab (Perjeta[®], Genentech) in combination with chemotherapy significantly improved overall survival in HER2-positive breast cancer patients (Mitri et al., 2012) (Spector & Blackwell, 2009) (Schlam & Swain, 2021). Due to the high susceptibility for developing resistance against existing HER2-targeted drugs, there is a constant need for developing novel therapeutic agents such as HER-2 targeting mAbs.

Screening for lead antibodies was performed under GLP compliance. Multiparameter high-throughput screening (HTS) platforms are applied to speed up the process of antibody lead selection. This strategy allowed the selection of lead antibodies that bind strongly and specifically to target antigens. Humanized mAbs were produced in HER2 surface-expressing Balb/c mice by hybridoma technology. Antibody humanization was carried out by standard protocol. In the following steps, recombinant Chinese hamster ovary (CHO) cells were used to produce mAb for the phase I clinical trial.

Preclinical studies were planned to ensure the safety and efficacy of mAbs and to determine the Hertumig phase I regimen, as shown in Figure 2. Breast carcinoma cell lines (SK-BR-3, MCF7) were used for preclinical in vivo studies. Per guidelines, in vivo studies were performed in nude mice breast cancer xenograft models (rodent) and rhesus monkeys (non-rodent). All preclinical safety studies were conducted with appropriate guidelines and in compliance with GLP.

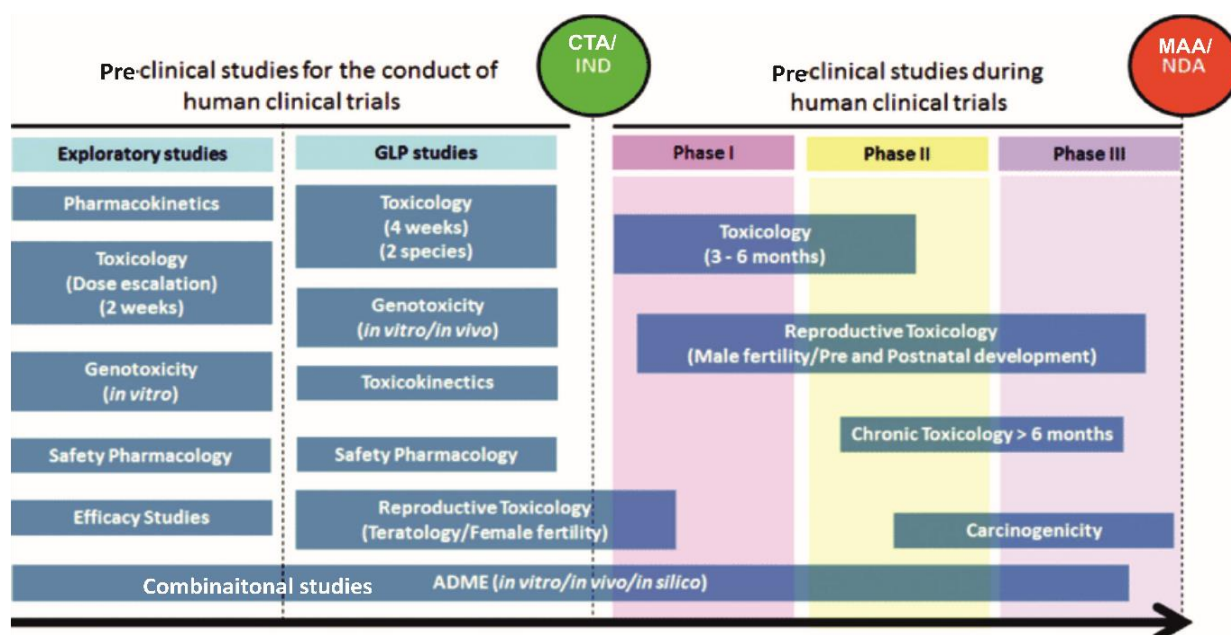


Figure 2 – Preclinical studies in the drug development pipeline. Figure modified (Andrade et al., 2016)

1. Combinational Study -

ICH M3 R2, ICH S9, and guidelines for fixed combination medicinal products suggest combination studies are usually not warranted for oncology drugs unless there is a significant toxicological concern. However, preclinical combination study enhances the confidence of combinational clinical trial. In addition to patient safety, the combined efficacy of the drug combination was also evaluated in the studies. Therefore, preclinical general toxicity and pharmacology studies were systematically designed for Hertumig combined therapy. Existing mAbs Herceptin® and Perjeta® and chemotherapeutic with Taxotere® were selected to evaluate the efficacy of the Hertumig combined therapy.

In vitro combination studies were conducted in SK-BR-3, HER2-transfected MCF7, and BT-474 cell lines. Molecular assays were developed to analyze the antitumor and antiproliferative activity of Hertumig (HT1 to HT15). In vitro cytokine stimulation assay was performed to

assess immune stimulation in the case of the mAb combination. In vivo combinational studies were performed for 90 days in the rhesus monkey that evaluated efficacy with safety endpoints.

In combination studies, synergistic effects were observed in cell culture with Herceptin® and Perjeta®, whereas a combination with Taxotere® has shown additive interactions. Combinations with Perjeta® and Taxotere® were most effective *in vivo*. The combination with Taxotere® has the most significant tumor regression in vivo with the BT-474 cell line.

2. Genotoxicity –

As per guidelines ICH M3 (R2) and ICH S9, for oncology studies genotoxicity not warranted by health regulatory unless any significant health concerns. Like combination therapy, Antibody-drug conjugates (ADC) are proven more efficient for treating HER2-overexpressing breast cancer. A classic example of ADC is Herceptin/Trastuzumab emtansine (Kadcyla™), effectively used in the HER2-positive breast cancer regimen. Genotoxicity studies for Hertumig alone and conjugated to DM1 were performed. DM1 is a cytotoxic derivative of maytansine, a highly potent microtubule inhibitory drug. Genotoxicity for Hertumig was evaluated under the ICH S6(R1) guideline ('Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals' 1997, later complemented by an addendum ICH S6 R1, 2011)

The genotoxicity of Hertumig (HT1 to HT15) has been investigated by *in vitro* and *in vivo* preclinical studies. Hertumig (HT1 to HT15) concentrations up to 5 mg/ml were used in both *in vitro* and *in vivo* assays. No significant genotoxic effects were observed for Hertumig alone, whereas conjugation to DM1 makes it genotoxic.

In vitro studies:

1. Ames test in *Salmonella typhimurium* (strains TA 98, 100, 1535, and 1537),
2. *E. coli* assays (strains WP2pKM101 and WP2uvrApKM101),
3. Chromosome aberration assay in human peripheral lymphocytes.

In vivo test was a mouse micronucleus assay involving a single iv injection of Hertumig (HT1 to HT15) at 29.5, 59, and 118 mg/kg.

Part B. Clinical Plan

Preclinical studies have demonstrated the efficacy and safety of Hertumig. A multifactorial preclinical study provides a stronger foundation for establishing phase I clinical trials in the Hertumig drug development program. Phase I clinical studies' main objectives are evaluating safety and tolerability, determining biomarkers, proof of concept, and the first human-safe dose. Further details about the trial are mentioned below -

- Site - Heidelberg University Hospital, Germany.
- Duration - 15 months
- Cohort size - 24
- Inclusion criteria –
 - Advanced refractory HER2-positive metastatic breast cancer
 - HER2 overexpression at a 3+ level (determined by immunohistochemistry)
 - No chemotherapy treatment in the last 30 days
- Exclusion criteria –
 - History of adverse reactions, cardiac dysfunction, or symptomatic and asymptomatic cardiotoxicity, autoimmune diseases
 - Ongoing viral infection
 - Pregnancy and breastfeeding
- Study design - two open labeled
 - Phase I A - SAD (single ascending dose)
 - Phase I B - MAD (multiple ascending doses) weekly repeated
- Concentration for dose escalation study- 10/50/100/ 250/500 mg

- Safety factor for dose - 10
- Medical supervision - 24 hours after administration
- Endpoints- Safety and PK (Pharmacokinetics)

Clinical studies are designed in agreement with (ICH M3) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (R2) and (ICH E6: Guideline for good clinical practice (R2).

Part C. Chemistry, Manufacturing, and Controls –

Drug discovery has identified the lead compound Hertumig. We aim to produce the Hertumig required for the consecutive clinical trial phases under GMP compliance.

Control of Drug substances and Drug products – Characterization

As shown in the following table, the structural and functional characterization (also termed an analytical assessment) of Hertumig was carried out. We have determined physicochemical properties of the Hertumig (e.g., size, charge, isoelectric point, amino acid sequence, hydrophobicity, post-translational modifications -glycosylation).

Table 1. Analytical items and analytical methods for the analysis of mAb characterization.

Characteristics	Items	Analytical methods
Primary structure	Intact mass analysis	Mass spectrometric analysis
	Peptide mapping	Enzyme digestion and HPLC
	N-terminal sequence	Edman degradation
	C-terminal sequence	Peptide mapping and intact molecular mass analysis
	Disulfide bond bridge analysis	Peptide mapping under nonreduced condition
	Glycosylation site	Peptide mapping with mass spectrometric analysis
Higher order structure	Structure analysis	Circular dichroism
Post-translational modification	Glycan profiles	Enzyme digestion and mass spectrometric analysis
	Sialic acid content	HPAEC-PAD
Heterogeneity	Isoforms	cIEF
Immunological activity	Binding affinity	Enzyme immunoassay
Biological activity	Potency	Cell-based assay
Purity/impurity	Product-related impurity	HPLC
Process-related impurity	Host cell protein	ELISA
	Residual DNA	PCR
	Residual protein A	ELISA
	Endotoxin	LAL

Manufacturing process - Purification

For the large-scale production of the Hertumig, we have developed (optimized) a manufacturing process to yield drug substances and products per specifications needed for human use. During the manufacturing process, product-related and process-related impurities are generated. These impurities are host-cell-derived proteins, nucleic acid, viruses, and other impurities, including media-derived compounds and undesirable chemicals introduced by the purification process itself. A combination of orthogonal methods generates the Hertumig purity/impurity profile. These methods generally include determining physicochemical properties such as molecular weight or size, isoform pattern, extinction coefficient, electrophoretic profiles, chromatographic data, and spectroscopic profiles. Further validation of the Hertumig purification process was performed, and a reduction factor at each stage of purification was established.

The following guidelines are used for Hertumig

- European Commission: (EudraLex Volume 10 clinical trials guidelines),
- Eudralex Volume 3 PRODUCTION AND QUALITY CONTROL OF MEDICINAL PRODUCTS DERIVED BY RECOMBINANT DNA TECHNOLOGY
- Production and Quality Control of medicinal products derived by recombinant DNA technology” (3AB1A),
- ICH guidelines - ICH Q6B “Test Procedures and Acceptance Criteria for Biotechnological/Biological Products” (CPMP/ICH/365/96) Good manufacturing practice (ICH GMP).
- Guideline on development, production, characterization, and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008

Part D: Pre-IND Meeting –

VaudBiotech SA. considers the pre-IND (investigational new drug) meeting an excellent opportunity to meet representatives of the regulatory bodies.

Pre-IND meeting objectives –

- ✓ Purpose of the study /unmet medical need
- ✓ Represent preclinical data
- ✓ Represent the proposed plan for the clinical phase and CMC
- ✓ Drug development timeline
- ✓ Guidance and advice on the IND application

In the following steps of drug development, we aim to get approval to evaluating the efficacy and safety of Hertumig in humans.

Scientific Advice -

Getting advice and guidance at the early stage of drug development significantly improves the chances of success in drug approval. CHMP (Committee for Medicinal Products for Human Use) on SAWP (the Scientific Advice Working Party) provides scientific advice and protocol assistance to the Hertumig Drug development process. EMA guidance for applicants is a one-stop solution for regulatory and procedural guidelines. A brief progress report and milestones of the drug development process are summarized in the application.

Parallel scientific advice –

Convincing datasets from preclinical studies encouraged us to introduce Hertumig in the US market. We plan to get approval for the drug in the EU first. Additionally, we would like to initiate the FDA approved process in parallel. We are in the process of getting joint scientific advice (PSA).

Part E: Inspection Readiness (IR)

Health authorities (HA), ethical committees (EC), and institutional review boards (IRB) closely follow the process of drug development. Inspection from the regulatory authorities ensures that the drug development process is being conducted as per guidelines, regulations, and compliances. Inspections are an integral part of the drug development process and are carried out for numerous reasons regularly and might be without any intimation. For the preparation of European Commission EudraLex Volume 10 clinical trials Guidelines, Guidance for the conduct of good clinical practice inspections were used.

We have an internal quality management system (QMS) that manages change control, risk management, and corrective action preventive action (CAPA) processes. We also run an inspection readiness program that consists of cross-functional subject matter experts.

- Keep updated with current regulations, guidance, and compliances
- It organizes mock inspections, audits
- Provide unbiased reviews
- Provide formal training to make competent to handle inspections

In VaudBiotech SA, inspection readiness is considered the state of the operation. We are confident and fully equipped to welcome inspectors and satisfactorily answer their questions.

4. Overall strategy –

We aim to provide safe, effective, and quality drugs to patients. We have strictly and stringently monitored the drug development process to ensure the study is carried out under the regulations, guidance, and compliance. Therefore, we have designed well defined, robust regulatory strategy to ensure Hertumig gets approval to treat HER2+ breast cancer.

The regulatory strategy for Hertumig consists of the following components -

- Literature review for critically and carefully designing studies
- Learn from the past submission in the same category
- Consistent, clear, and precise datasets generated from studies
- Practical and feasible timeline for deliverables
- Timely crosstalk among stakeholders
- Dedicated team for handling documentation, submission
- Dedicated team for CMC and manufacturing (most critical)
- Dedicated IP- patenting team
- Consultation from an expert in the field
- Organize a pre-submission meeting with health agencies for feedback and guidance
- Update on global regulatory requirements
- Streamline strategy
- Strategic and operational outsourcing
- Scientific advice and Protocol assistance from the Scientific Advice Working Party (SWAP)

A robust regulatory strategy will assist in a smooth and swift transition from the preclinical to the clinical phase. We will choose a centralized marketing authorization application (MAA). A single application to EMA is valid for all the members of the EU. We have filed a patent application and aim to get market exclusivity rights for ten years.

5. Advice to Management

A Hertumig drug development process has been planned considering the limitations of the currently available treatment for breast cancer. Per current regulations and guidelines, the Hertumig drug discovery and development plan has been carefully and critically drafted by our team.

In a preclinical and clinical phase I studies, safety and efficacy were evaluated in the first place. Convincing robust datasets from our preclinical studies established a reliable platform for clinical phase I studies. Simultaneous optimization of the manufacturing design process prepared us for the large-scale production of the drug. Regulatory guidelines were followed strictly and stringently for the large-scale production of Hertumig. In addition, the necessary documentation supporting our studies has been completed and submitted on time.

In summary, we will deliver a safe, efficacious, quality drug, Hertumig, which can be a crucial player in HER2+ breast cancer treatment. Datasets from our preclinical and phase I clinical study give us the impression that we will complete subsequent phases of the drug development process in time.

6. Conclusion –

In this study, we are explicitly targeting the HER+ positive subtype of breast cancer. Hertumig drug discovery, development, and production were planned and executed according to current regulatory guidelines and compliances. So far, we have completed preclinical studies in time without any adverse events. We have determined the First- in- human dose and evaluated the safety and efficacy of the Hertumig by *in vivo* and *in vitro* assays. In addition, a combinational study with existing therapies was carried out. We are confident to enter the next stage of the drug development process.

References –

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Suppliment –

Hertumig® / monoclonal antibody (mAb) VBT001

Product details

Chemical Name: Immunoglobulin G1 (human-mouse monoclonal rhuMAb HER2y1- chain anti-human P185c-erbB2 receptor) disulfide with human-mouse monoclonal rhuMAb HER2 light chain, dimer. Molecular Formula/Molecular Weight: C₆₄H₉₉N₁₇O₂₁S₄ / 148 kDa (without the N-glycan moiety). Structure or Biochemical Description: SB3 (hertumig) contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) modified to bind to two epitopes of HER2. SB3 consists of 1,328 amino acids. The amino acid sequences for the heavy and light chains of SB3 are listed in the following FASTA format:

>Hertumig_Heavy_Chain

```
EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR IYPTNGYTRY  
ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG GDGFYAMDYW GQGTLTVTVSS  
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPTVS WNSGALTSGV HTFPAVLQSS  
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG  
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN  
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAIEKTIS KAKGQPREPQ VYTLPPSREE  
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW  
QQGNVFSCSV MHEALHNHYT QKSLSLSPG
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>Hertumig_Light_Chain:

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DIQMTQSPSS LSASVGDRTV ITCRASQDVN TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS  
RFGSGRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ GTKVEIKRTV AAPSVFIFPP  
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSLSTLT  
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEK
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Composition: Hertumig is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial contains 440 mg of Hertumig, 6.4 mg L-histidine, 9.9 mg L-histidine HCl, 1.8 mg polysorbate 20, and 400 mg α,α -trehalose dihydrate. Reconstitution with 20 mL of the supplied BWFI, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL Hertumig, at a pH of approximately 6.

Availability: Hertumig is supplied as a lyophilized, sterile powder containing 440 mg Hertumig per vial under vacuum. BWFI is supplied as a 20 mL vial of sterile solution containing 1.1% benzyl alcohol as an antimicrobial preservative. Each carton contains one vial of 440 mg Hertumig and one 20 mL vial of BWFI containing 1.1% benzyl alcohol.