Individual Case Study Report

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# Abbreviations

EGFR, epidermal growth factor receptor;

FIH, first in human;

HER, human epidermal growth factor receptor;

IV, Intravenous;

MAPK, mitogen-activated protein kinase;

MEK, MAPK/extracellular signal–related kinase kinase;

MFD maximal feasible dose;

MSRD, maximum recommended starting dose;

MTD, maximum tolerated dose;

NOAEL, no-observed-adverse-effect level;

PI3K, phosphoinositide 3-kinase;

SOS, son of sevenless;

VEGF, vascular endothelial growth factor;

MABEL, minimal anticipated biological-effective level;

MED, minimum effective dose;

PAD, pharmacologically active dose;

# Overview

**Due date**: 2022/10/15

**Name**:Dylan Lawless

**Track**: Drugs

**Product Profile**: Our product is a monoclonal antibody to be used in a phase 1 clinical trial in oncology. The company is named VaudBioTech with headquarters located in Switzerland. This company is the discoverer of the product in question. The planned phase 1 clinical trial will be conducted in Germany.

**Group:** C

**Group members:** Priya Bhutada, Mouna Hadiji, Raluca Ganea, Dylan Lawless, Olivia-Augustina Colbea.

**Company:** VaudBioTech

**Product name**: Hertumig.

**Treatment**: Treatment of HER2 receptor positive breast cancer.

**Delivery**: Subcutaneous administration.

**Mechanism/target**: Similar to the mode of action from Pertuzumab and Herceptin (as illustrated in **Figure 1**), Hertumig targets a newly defined antigen of HER2 which inhibits the [dimerization](https://en.wikipedia.org/wiki/Protein_dimer) with other HER receptors, thereby preventing [signaling](https://en.wikipedia.org/wiki/HER2/neu#Signal_transduction) in ways that promote cell growth and proliferation. HER2 positive breast cancer is caused by *ERBB2* gene amplification that results in overexpression of HER2 in approximately 15-30% of breast cancer tumors. Stimulates cell proliferation and cell growth. It is a bispecific monoclonal antibody (BsMAb) which targets two epitopes.

**Discussion**: This drug is reminiscent of the classical mAb anticancer treatments; (i) similar to [Pertuzumab](https://en.wikipedia.org/wiki/Pertuzumab) (RG6264, Perjeta) from [Genentech](https://en.wikipedia.org/wiki/Genentech) which was first approved in 2012, Europe in 2013, etc. (ii) similar to [Trastuzumab](https://en.wikipedia.org/wiki/Trastuzumab), Herceptin from Genentech very well known, approval US 1998, EU 2000, WHO essential medicine.

Map

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Figure 1 Cryo-EM structure of HER2 bound by mAb

HER2 (cyan) extracellular domain, Trastuzumab Fab (Herceptin - red and pink), and Pertuzumab Fab complex (Perjeta - yellow and orange). Derived from PDB 6OGE <https://doi.org/10.1371/journal.pone.0216095>.

## Product details

Chemical Name: Immunoglobulin G1 (human-mouse monoclonal rhuMAb HER2γ1- chain anti-human P185c-erB2 receptor) disulphided with human-mouse monoclonal rhuMAb HER2 light chain, dimer. Molecular Formula/Molecular Weight: C6460H9972N1724O2014S44 / 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) that binds to 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 GQGTLVTVSS

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS

GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG

PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE

MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW

QQGNVFSCSV MHEALHNHYT QKSLSLSPG

>Hertumig\_Light\_Chain:

DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS

RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ GTKVEIKRTV AAPSVFIFPP

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT

LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

## Production

The old-fashioned way was by hybridoma (trastuzumab) but we will use a modern protocol. To be defined.

* See - carvalho2017\_Production Processes for Monoclonal Antibodies
* See example method: <https://www.nature.com/articles/s41598-020-59818-2#Sec11>.

# Part A: Preclinical Plan

*A preclinical plan will be completed summarizing the work that needs to be done and included in the application for the above mentioned Investigational Medicinal Product. This consists of a short description of the preclinical studies to cover the clinical trial, namely the animal studies, the duration of treatment, pharmacology and toxicology studies in the appropriate animal model.*

Timeline

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Figure 2 Nonclinical evaluation for small molecules.

Figure reproduced from Nürnberg and Pierre 2017 [1]. Biologics may require fewer nonclinical studies than small molecules but can be complicated due to novelty and lack of relevant model species. Often the rodent species by be omitted if they are not representative of the expected human response. However, transgenic murine models may be required. Immunogenicity can produce both a lack of efficacy or severe adverse outcomes (PD and PK). Extensive immunogenicity testing may be required. Only major steps are illustrated; e.g. carcinogenicity may require dose testing and subsequent two-year rodent study and six-month transgenic mouse study.

## Acute toxicity

In accordance with ICH M3 R2 [2] (cite and specific other), acute toxicity will be assessed using single-dose toxicity studies in two mammalian species (one non-rodent):

1. Intravenous (IV) bolus administration in mice (M+F) at 0, 9.4, 47 and 94 mg/kg [*H0030\_preclinical\_acute\_toxicity\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*
2. Intravenous (IV) bolus administration in rhesus monkeys (M+F) at 0, 4.7, 23.5 and 47 mg/kg [*H0031\_preclinical\_acute\_toxicity\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*

[ *Note to self: we could use subcut instead of IV, and therefore need to adjust the realworld dosages to those expected – according to FDA “The recommended Herceptin Hylecta dose is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks.”* ]

[*Note to self: the dosage for subcut will probably be something like human; IV 6mg/kg = 360mg mg subcut (6mg\*60kg) and mouse; IV 6mg/kg = 0.12 mg subcut (6mg\*0.02kg)*]

The presence or absence of toxicity of several different preparations and formulations of hertumig will be measured based on standard parameters including food consumption, body weight, antibody formation, clinical chemistry and macro- and microscopic examination of standard organs/tissues. The no-observable-effect-level (NOEL) will be obtained which, based on other similar products, is expected to be 94 and 47 mg/kg in mice and monkeys, respectively. In these studies (H0030, H0031), both the clinical and parenteral route of administration will be (IB bolus). The minimum and maximum dosages (4.7 - 47 mg/kg) to be administered over 90 minutes without short-term adverse effects. Each study will be conducted under GLP (cite). All subjects will be evaluated for antibody production (cite). Any subjects with detected anti-hertumig antibodies will be subsequently assessed for allergic manifestations to quantify risks in further clinical testing. Acute toxicity results will be used in combination with the known toxicity for other mAbs to assess the potential consequences of human overdose and will be available to support Phase III (cite).

Table 1Treatment Schedules for Hertumig preclinical trials

Table

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## Dosage

* Reasons why dosage will vary: CPTpham2017ryman\_Pharmacokinetics of Monoclonal Antibodies.
* Considerations: NatRevDrugDis2010hansel\_The safety and side effects of monoclonal antibodies
* Risk (clinical trial): nejm2006Suntharalingam\_Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412
* Main summary: nejm2011\_Trastuzumab
* Main summary: trastuzumab\_2011
* One Nature/NEJM review on mAb dosage.

Two regulatory documents that provide guidance on selecting the FIH dose are:

• FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005

• EMEA/CHMP Draft Guideline on Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products, March 22, 2007.

Labels of dosage

* minimal anticipated biological-effective level (MABEL)
* minimum effective dose (MED)
* pharmacologically active dose (PAD)
* no-observed-adverse-effect level (NOAEL)
* maximum recommended starting dose (MSRD)
* maximum tolerated dose (MTD)
* maximal feasible dose (MFD)

The maximum recommended starting dose (MSRD) is required as the first step in FIH. This determination is based on in vitro and in vivo pharmacological, pharmacodynamic, pharmacokinetic, physiological, and toxicological data. The no-observed-adverse-effect level (NOAEL) dose will be determined from the GLP toxicology study. Pharmacologically active dose (PAD) will be quantified in the preclinical trials and based on other similar mAb, defined for the FIH clinical trials. MSRD is calculated from the NOAEL and needs to be compared with the PAD and the minimal anticipated biological-effective level (MABEL). Lastly, based on the multiple measurements (MABEL, PAD, NOAEL) the lowest estimate will be used [3]. After IV administration the initial plasma concentration is typically approximately 50mL/kg. The mAb is initially confined to circulation in the vasculature with eventual extravasation into tissue [3]–[5].

## Guidance documents used

* [An introduction to little-known aspects of nonclinical regulatory writing](https://journal.emwa.org/preclinical-studies/an-introduction-to-little-known-aspects-of-nonclinical-regulatory-writing/); Nürnberg and Pierre [1].
* European Comission: ***EudraLex Volume 10 clinical trials guidelines*** (<https://ec.europa.eu/health/documents/eudralex/vol-10_en>) [6].
* European Comission: ***EudraLex Volume 10 clinical trials guidelines***: ***Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states; To guidance for the conduct of good clinical practice inspections 2008***. (see chapter 4 <https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en>) [6].
* EMA committee for medicinal products for human use (chmp): ***Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials*** (<https://health.ec.europa.eu/system/files/2016-11/18540104en_en_0.pdf>).
* ICH harmonised tripartite guideline*:* ***Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2) version step 4 2009*** (<https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf>) [2].
* ICH harmonised tripartite guideline: (<https://www.ich.org/page/safety-guidelines>), specifically section ***S9 Nonclinical evaluation for anticancer pharmaceuticals version step 4 2009*** (<https://database.ich.org/sites/default/files/S9_Guideline.pdf>) [7].
* ICH harmonised guideline: ***Integrated addendum to ICH e6(r1): guideline for good clinical practice*** ***E6(r2)step 4 version 2016*** (<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>) [8].
* EMA Committee for medicinal products for human use (chmp): ***Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials 2022***
* (<https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal>) [9].

# Part B: Clinical Plan

* Clinical Trial Protocol will be drafted for inclusion in the application for the above-mentioned Investigational Medicinal Product. In this we define the main points of the clinical trial protocol and consider a master protocol.[Ledford 2013](http://www.nature.com/news/master-protocol-aims-to-revamp-cancer-trials-1.13176) reports on “‘Master protocol’ aims to revamp cancer trials” [10] and [Woodcock and LaVange 2017](http://www.nejm.org/doi/full/10.1056/NEJMra1510062#t=article) on requirements to “Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both” [11]. Consider[*PRIME*](https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines)and[*Breakthrough Designations*](https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-breakthrough-therapies) (for comparison see FAQ 24. [here](https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies)).
* Guidance and reference is found in the ICH harmonised guideline: ***Integrated addendum to ICH e6(r1): guideline for good clinical practice*** ***E6(r2)step 4 version 2016*** (<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>) [8].
* See husid2011nejm\_Trastuzumab - Table 1. Results of Studies of Trastuzumab as Monotherapy for Metastatic Breast Cancer.
* See husid2011nejm\_Trastuzumab - Table 2. Randomized Trials Comparing Chemotherapy Alone with Chemotherapy plus Trastuzumab for Metastatic Disease.

# Part C: Chemistry, Manufacturing and Controls, CMC

Here we will write a clear CMC plan on the work that needs to be done and included in the application for the above mentioned Investigational Medicinal Product. Emphasize the level of detail required.

Guidance and reference can be found at

* European Commission: ***EudraLex Volume 10 clinical trials guidelines*** (<https://ec.europa.eu/health/documents/eudralex/vol-10_en>) [6].
* European Commission ***EudraLex Volume 10 clinical trials guidelines***: ***Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states; To guidance for the conduct of good clinical practice inspections 2008***. (see chapter 4 <https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en> or PDF <https://health.ec.europa.eu/system/files/2016-11/18540104en_en_0.pdf>) [6].

# Part D: Pre-IND Meeting / Scientific Advice

Here we will include a summary of the project background, the questions with the opinion of the company, number of attendees, and the time for the meeting (ideally).

Advice can be found at

* Paul-Ehrlich-Institute, Federal Institute for Vaccines and Biomedicines webpage (<https://www.pei.de/EN/information/license-applicants/advice/scientific-advice/scientific-advice-node.html>).
* EMA Human Regulatory webpage for Scientific advice and protocol assistance (<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance>).

# Part E: Inspection Readiness

Here we will write a summary of the work that a company needs to have ready before the inspection to ensure compliance to GxP. Extract some details from the Week 3 presentation. Important is to know the points the inspector normally go through during an inspection.

Guidance can be found at

* European Commission ***EudraLex Volume 10 clinical trials guidelines***: ***Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states; To guidance for the conduct of good clinical practice inspections 2008***. (see chapter 4 <https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en>) [6].
* European Commission: Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states. ***Guidance for the conduct of good clinical practice inspections*** (<https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2008_11/vpl10_an5_10-2008_en.pdf>).

# Overall strategy

Hints – With the above plans on the domains of preclinical, clinical and CMC, how would you accelerate submission process in Germany, with minimum questions from the health authorities and EC/IRB, and obtain rapid HA and EC/IRB approvals?

# Advice to Management

Hints – A short cover letter to the management on the Development Plan.

# Conclusion

Hints – A very short (two paragraphs) on why you think the regulatory strategy is well thought through and has the maximum chance of success.

# Supplemental

## Introduction on therapeutic mAb

Monoclonal antibodies (mAb) are well established as cancer therapies. As early as 1890, the neutralizing effect on diphtheria was known [12]. In 1980, human trials of mAb therapy for the treatment of lymphoma were performed and with the advent of antibody humanization later that decade, this treatment strategy became a powerful tool for precision medicine [12].

The advent and rise of mAb is a triumph for clinical medicine. Since the beginning of their modern understanding, the applications for mAb have been recognized; “a 1975 Nature paper reported how cell lines could be made that produce an antibody of known specificity” [13]. While these early days of antibody production - relying on hybridoma technology - were challenging, today mAb are often produced by isolation or transformation of Ab-producing cells taken directly from immunized animals or humans. The immunoglobulin genes responsible for the Ab of interest are subsequently transplanted into cell lines [13].

Recently (2021), the FDA approved the 100th mAb product [14]. The timeline starts in 1986 with the majority of products consisting of canonical antibodies, and a small number of alternative constructs including antibody–drug conjugates, bispecific Abs, fragment Abs, and others. While a high potential exists, the hurdles for biological drug approvals limit the number of products available thus far. “Just ten targets… account for 42% of the approvals to date”: PD1/PDL1, CD20, TNF, HER2, CGRP/CGRPR, VEGF/VEGFR, IL-6/IL-6R, IL-23 p19, EGFR, and CD19 [14].

The pharmacokinetics (PK) of monoclonal antibodies is generally well understood. The major drug disposition processes relevant for mAbs can be estimated in preclinical development. The product-specific and patient-specific factors that can affect PK behavior can be considered for successful clinical therapy [15].

Each particular mAb has unique risks. The steps to identify and minimize potential adverse effects must be clear and accurate. preclinical and clinical protocols must be established to avoid infusion reactions [16]. Preclinical validation of in vitro safety using human tissues is necessary to predict potential outcome for administration to humans. For clinical trial volunteer safety, communication must be maintained between scientists and clinicians both in phama/biotech companies and those performing clinical studies [16].

The serious risks of off-target antigen binding are well-known, particularly after the adverse outcome seen during the phase 1 trial of anti-CD28 mAb TGN1412 resulting in systemic inflammatory response in all six volunteers [17].

Despite the known potential for first-in-human studies there is no current robust way to ensure complete safety. Therefore, adherence to guidance and regulatory protocols are vital for safe and successful trials.

mAb are recognized as versatile platforms for cancer immunotherapy by directly stimulating or inhibiting immunological protein pathways [18]. The induction of antitumor immune responses can be exploited to develop new cancer treatment strategies based on tumor-specific response of natural or engineered mAb [18].

The nomenclature for our drug is defined according to the WHO International Nonproprietary Names (INN) (Programme and Classification of Medical Product) [19]. The current state of the art in anti-cancer monoclonal antibodies (mAbs) is overviewed by [Chiavernna, et al](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5319201/). [20].

Diagram

Description automatically generated

Figure 1. Signal transduction by the HER family and potential mechanisms of action of trastuzumab. Abbreviations: EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase kinase; PI3K, phosphoinositide 3-kinase; SOS, son of sevenless; VEGF, vascular endothelial growth factor. Reprinted from Hudis CA. Trastuzumab—Mechanism of action and use in clinical practice. N Engl J Med 2007; 357:39-51 DOI: 10.1056/NEJMra043186.

## Open access

* The protocol, study design, specific aims
* The raw data collected (as appropriate) and analysable data
* The data sharing plan
* Statistical analysis methods
* An overall study report summarising the key findings and next steps

## Guidelines (remove in final version)

*The Individual Case Study Report (ICSR) should be based on the case study description linked above and written using the provided template.*

*Requirements:*

*• 4 pages in length*

*• double-spaced (not including references)*

*• minimum two obligatory EU Health Authority requirements (following, among other references, the EU and ICH guidelines, as referenced in the required readings) for the each of the following five sections*

*• and write a short executive summary and a conclusion by himself or herself.*

*Required sections for ICSR-Track on Drugs:*

*1. Preclinical Plan*

*2. Clinical Plan*

*3. Chemistry, Manufacturing and Controls (CMC)*

*4. Pre-IND Meeting / Scientific Advice*

*5. Inspection Readiness*

*Medical device requires comparison of EU and US (MDR, IVDR) are more complex than drug and therefore more critical comparison of FDA/EMA.*

# References

[1] A. Nürnberg and H. Pierre, “An introduction to little-known aspects of nonclinical regulatory writing,” *Medical Writing*, vol. 26, pp. 9–19, 2017.

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