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Drug Development Plan

MABS - HERTUMIG

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Table of Contents

1. Executive summary

VaudBioTech – Lausanne/ Ecublens is a spin-off from EPFL which started its activity in the field of monoclonal antibodies (mAbs). One of the most promising candidates developed by VaudBioTech. Hertumig had been developed as treatment of HER2 receptor positive breast cancer. Similar to the mode of action from Pertuzumab and Herceptin, Hertumig targets a newly defined antigen of HER2 which inhibits the dimerization with other HER receptors, thereby preventing signalling 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 tumours. Stimulates cell proliferation and cell growth. It is a bispecific monoclonal antibody (BsMAb) which targets two epitopes.

Hertumig was reaching extremely relevant results based on non-clinical and Phase 1 studies results, therefore VaudBioTech will be considered for drug-approval process. To ensure GMP compliance, VaudBioTech will licence the production of Hertumig to a Contract Development and Manufacturing Organization in order to assess the potential of Hertumig.

2. Introduction

Monoclonal antibodies (mAb) are well established as cancer therapies. In 1980, human trials of mAb therapy for the treatment of lymphoma were performed and later this treatment strategy became a powerful tool for precision medicine [1]. Nowadays 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 [2]. The number of approvals of FDA is continuing to rising [3], starting with the first approval (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. The pharmacokinetics (PK) of monoclonal antibodies is generally well understood. The major drug disposition processes relevant for mAbs can be estimated starting to preclinical development phase. The product-specific and patient-specific factors that can impact PK behaviour can be considered for successful clinical therapy [4]. Each particular mAb has unique risks and efforts needs to be done in order to minimize potential adverse effects must be clear and accurate, therefore preclinical and clinical protocols must be established to avoid infusion reactions [5]. 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 pharma/biotech companies and those performing clinical studies [5]. 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 [6]. mAb are recognized as versatile platforms for cancer immunotherapy by directly stimulating or inhibiting immunological protein pathways [7]. The induction of antitumor immune responses can be used to develop new cancer treatment strategies based on tumours specific response of natural or engineered mAb [7]. The nomenclature for the drug is defined according to the WHO International Nonproprietary

Names (INN) (Programme and Classification of Medical Product) [8]. The current state of the art in anti-cancer monoclonal antibodies (mAbs) is overviewed by Chiavernna, et al. [9].

3. Development Plan:

Part A. Preclinical Plan

Toxico-pharmacological aspects

Hertumig is directed against HER2, which is part of a family of membrane-bound phosphoglycoproteins with tyrosine kinase activity. The proteins coded by the oncogens, the oncoproteins, are all involved in the signalling cascades that control cell proliferation and differentiation [12].

Pharmacodynamics

In vitro studies Hertumig inhibited proliferation of HER2 overexpressing cells and induced loss of intrinsic resistance of cells that overexpress HER2. Furthermore, reduction in synthesis of cellular components affecting cell adhesion and the metastatic potential of tumour cells in treatment with Hertumig.

Although Hertumig has been shown to bind to HER2 on several breast adenocarcinoma cell lines and activate the complement cascade [12].

In cross-reactivity studies with frozen human or Cynomolgus monkey's tissues, Hertumig and muMAb 4D5 showed similar patterns of immunoreactivity.

The nonlinear PK observed at lower doses of Hertumig in monkey is consistent with specific, saturable binding. The tissue cross reactivity and nonclinical PK studies and the demonstrated specificity for HER2, support the conclusion that Hertumig recognised monkey HER2 [12].

Several studies on the pharmacokinetic profiles of Hertumig after a single administration revealed a terminal half-life ranging from 8 to 15 days determined in mice, and cynomolgus monkeys. The presence of free extracellular domains (ECD) of HER-2 in the serum of cynomolgus resulted in an increased clearance and thus a shorter half life of Hertumig. ECD clearance was also decreased in the

presence of Hertumig in both the mouse and the monkey indicating that ECD can be maintained in circulation when complexed with Hertumig.

In single-dose studies in mice Cmax was 18, 2800, 2250 µg/ml for the doses of 1, 10, 100 mg/kg respectively. The dose response in terms of Cmax or AUC in the rhesus monkey was non-linear.

Toxicology Single Dose

Toxicity Single-dose acute studies were undertaken using iv bolus administration in mice (M+F) at 0, 9.5, 49 and 94 mg/kg and in rhesus monkeys (M+F) at 0, 4.7, 23.5 and 47 mg/kg. The absence of toxicity of several different preparations and formulations of Hertumig could be demonstrated.

Exploratory Clinical Trials

The draft revision of the ICH M3 (R2) guideline [10] describes five approaches, including two that use microdoses (objective: receptor occupancy and biodistribution) and three with pharmacological doses as a single dose or with up to 14 days of repeated dosing [objective: pharmacodynamic activity (PD) and/or pharmacokinetics (PK, PK/PD)].

Local Tolerance Clinical Trials

Pharmacodynamics

In alignment to ICH M3 (R2) [10], no specific pharmacodynamic study has been performed. The data gained from the exploratory pharmacodynamic analysis of the pivotal trial are too limited to draw any conclusion concerning trends between shed HER2 extracellular domain (ECD) and clinical response. It remains open whether ECD concentrations at baseline > 200 ng/mL are predictive of a worse clinical outcome.

Part B. Clinical Plan

In accordance with ICH E6 (R2) [11], there were three open-label, phase I clinical trials in patients with refractory (grade 4) HER2-positive meta-static breast cancer, which were primarily designed to determine the safety, maximum tolerated dose and pharmacokinetics of Hertumig. The weekly schedule of i.v. infusion was based on the expected clearance calculated from preclinical studies and was continued until disease progressed. As is usual in such studies, relatively low numbers of patients were recruited in these phase I clinical trials (n =15-18) and the enrolment was completed in short period of time. As a result, Hertumig was well tolerated at all doses from 10-450 mg i.v. and a maximum tolerated dose was not reached. In the single-agent trials, serious adverse events were recorded in four patients, but none were considered related to the administration of Hertumig.

Part C. Chemistry, Manufacturing and Controls

Overall, description of the upstream (cell expansion and main fermentation) and downstream process will be provided. The steps, control parameters, test methods used for control, and acceptance criteria to be indicated, in addition to information about buffer volumes, flow rates, in process controls, maximum target mass, and collection mode.

Each step in the filling, storage, and shipping steps will be described adequately, along with in-process controls and tests. The specifications for the raw materials used for purification, and the bulk formulation process will be provided.

4. References

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