Drug Development Plan for SBT001

[redacted]

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Executive Summary

Swiss BioTech (headquarters in Lausanne) is a spin-off from EPFL, which was founded in 2014 with the purpose to develop the humanized monoclonal antibody (mAb) SBT001, Swiss BioTech's lead candidate for advanced-stage prostate cancer. SBT001 targets TGF-β and was shown to be highly efficient in TGF-β-positive prostate cancer metastases in mice and non-human primates.

About 60% of biopsies of human prostate metastases were found to have high-expression levels of TGF-β, representing a new therapeutic target in patients with advanced stage prostate cancer for which chemotherapy and/or surgery failed.

SBT001 is manufactured by ExcellGene in Switzerland under cGMP in order to enter clinical development. It is expected to enter the EU market in 2028.

1. Introduction

SBT001 was developed by Swiss BioTech, a spin-off from EPFL, for the treatment of advanced-stage prostate cancer. If prostate cancer is diagnosed early, the 5-year survival is almost 100%. However, late diagnosis leads to metastases in 10 to 20% of the cases. Among those, approximately 60% of metastases biopsies show high-expression levels of transforming growth factor beta (TGF-β), representing a druggable target for advanced-stage patients for which chemotherapy and/or surgery failed.

The humanized mAb SBT001 targets TGF-β. It was shown to be highly efficient in TGF-β-positive prostate cancer metastases in mice and non-human primates. SBT001 targets a subset of life-threatening advanced-stage prostate cancers in patients lacking therapeutic options. Besides, with a prevalence of 1.12 cases of late stage prostate cancer per 10,000 EU inhabitants, SBT001 is below the upper prevalence limit for orphan drug designation of less than 5 cases per 10,000 inhabitants[1].

If the clinical trial phase I study succeeds, Swiss BioTech will apply for an orphan drug designation.

To ensure GMP compliance, Swiss BioTech will license the production of SBT001 to its partner Contract Development and Manufacturing Organization (CDMO) ExcellGene. ExcellGene will assess the strength and potency of SBT001, employ qualified personal, use qualified materials and optimize a stable formulation of the product.

2. Development Plan

Part A. Preclinical Plan

SBT001 is an IgG4 antagonist of TGF-β1. TGF-β1 is a cytokine with various roles in cell cycle control as well as regulation of early development, differentiation, migration and the extracellular matrix. TGF-β1 is involved in various diseases like cancer and fibrosis. Treatment options for prostate cancer – a life-threatening disease – are limited. We developed SBT001 to treat prostate cancer. Before entering clinical trials in humans, we collected substantial and valuable pre-clinical data to support the initiation of clinical development.

Lead mAb identification

In conventional discovery programs, antibody identification usually takes several months to years in order to find an ideal candidate. In order to speed up the hit identification, we performed high throughput screening in order to screen prospectively isolated panels against new pathogens and multiple viral strains. Thus, we rapidly identified our desired mAb for development. This helped us to lead the process development and manufacturing to the way of clinical evaluation.

Cell line development

In order to further accelerate the clinical development and associated processes, we chose Chinese Hamster Ovary (CHO) cell line as the primary production cell line[2]. As CHO bears ample clinical evidence, using a CHO cell line avoids any safety risk or potential negative impacts for patients that could arise from rare post-translational modifications. Next, we used molecular engineering tools to introduce novel variability into the complementarity determining regions (CDRs) of one or both IgG chains, followed by *in vitro* selection for improved target binding. Afterwards, we obtained single cell clones via fluorescence-

activated cell sorting. This allowed us to establish a clonally derived CHO cell line that is suitable for mAb production for clinical trial phase I.

Process and formulation development

In parallel to cell line development, we created transient expression cultures that allow us to produce material for downstream processes, formulation and analytical development. Following cell line selection, we continued with cGMP production. We took advantage of single-use bioreactors for rapid entry into clinical cGMP production[3]. We used three 1000-liter single-use bioreactors to produce thousands of doses and build up a launch supply of the drug substance.

Pharmacokinetics

Our systemically administered mAb exhibited a biphasic pharmacokinetics profile in circulation, indicating a relatively fast distribution phase which was followed by a slower elimination phase. Due to the large molecular size of the mAb, the absorption occurred by lymphatic uptake. The distribution was primarily limited to vascular and interstitial fluids, whereas metabolism took place through proteolysis to small peptides and amino acids. We measured a long half-life of 12 days for our product and found a dose dependent nonlinear clearance of 590 ml per day.

For the most of our bioanalytical studies, we used ligand-based assays (ELISA) and LC-MS for high-throughput quantification. Our ELISA assays detected a binding affinity for TGF-β that was comparable to the one determined in our rodent preclinical animal models. Moreover, we measured the binding affinity of SBT001 to TGF-β through surface plasmon resonance where we observed a 10-fold higher affinity to human TGF-β. Due to these immunological differences, we performed a safety assessment.

Immunotoxicity and safety assessment

SBT001 showed cross-reactivity in both rodents and cynomolgus monkeys. We carried out 6-month repeat dose toxicology studies, as was reviewed earlier in cynomolgus monkeys and rodent models to determine the nature and extent of immunological effects of SBT001[4]. The long half-life of SBT001 necessitated a long recovery to allow clearance of the mAb in cynomolgus monkeys. We also included primary endpoints including hematological assessment, clinical chemistry, pathological characteristics, organ weight and extended histopathology of lymphoid organs. SBT001 showed desirable immunopharmacological effects, including activation of T cell population. We also found expected effects including epithelial hyperplasia in multiple tissues, renal tubular inflammation and tubular injury. Furthermore, we successfully demonstrated that SBT001 could be drugged safely as we did not identify any potential human-translatable toxicity in the rodent and cynomolgus monkey models.

Dosage, storage and profitability

For phase I production we used a platform process. This allowed us to quickly produce hundreds of thousands of doses (>150 kg). We then prepared high-concentration liquid formulations (>150 mg per ml) and stored the stock solutions cold or frozen. Next, we used a pre-formulation screen in order to evaluate proven formulations and excipients. This limited any risk that would be associated with poor stability of the formulated drug product. This production mechanism will ensure a profitable return compared to other manufacturing facilities, as identified earlier[5].

Next, we conducted a 9-month study in non-human primates (NHP)[6] in order to test if a less frequent dosing regimen (1-month dosing) could further enhance the margin of safety. Our study demonstrated that pathological changes were limited to very mild epithelial

proliferation in specific tissues, which were later considered as non-adverse. We also showed that certain hazards seen in knockout mice models could be avoided through careful application of the mAb dose regimen. Our animal and NHP pharmacology, toxicology and safety data for SBT001 identified a defined clinical dosing frequency and supports initiation of the clinical study.

Part B. Clinical Plan[7]

The clinical trials will be conducted in Germany and therefore need to be approved by the federal institute for vaccines and biomedicines Paul Ehrlich Institute (PEI).

Clinical trial phase I, which we estimate to take around one year, needs to be conducted on cancer patients since the treatment is likely to harm healthy subjects. Only patients with advanced/metastatic solid tumors, who are resistant to standard therapy are included (inclusion criteria). Exclusion criteria are the history of adverse reactions, presence of autoimmune diseases and ongoing viral infections.

The cohort size will be 50 patients. After receiving the IMP, participants will remain under medical supervision for the following 24 h. The first safe dose was calculated based on MABEL of the pre-clinical data. A 10-fold safety factor will be applied, considering the 10-fold higher affinity of SBT001 to human TGF-β.

The purpose of the phase I trial is to assess safety and dosage, uncover side effects and establish the maximal dose. In phase Ia, a single ascending dose (SAD) will be administered, whereas multiple ascending doses (MAD) will be applied in phase Ib.

In our phase II trial, efficacy and further side effects of SBT001 will be assessed using a cohort size of 100 patients. The progression/regression state of the prostate cancer will be assessed. The data of the phase II trial will be used to refine the phase III protocols.

For clinical trial phase III, hundreds to thousands of cancer patients will be recruited. Its purpose is to determine SBT001's efficacy and to compare it to already-approved similar drugs. Besides, less common side effects will be monitored. After finalization and review of phase III, the report will be submitted to PEI for market approval.

Post market approval, long-term monitoring of benefits and side effects on a larger population will take place (phase IV).

Part C. Chemistry, Manufacturing and Controls[8,9,10,11,12,13]

Initially, detailed analytical methods to characterize the mAb have to be developed in order to ensure that the mAb is safe and has the desired functional properties, meaning that it inhibits TGF-β. These assays also include assessment of structure and glycosylation of the mAb. Secondly, a suitable genetically-modified engineered production cell line with sufficiently high productivity of the mAb has to be developed and tested. Next, the manufacturing process has to be established. This includes for example the testing of the composition of cell culture media, development of the bioreactor process (e.g. bioreactor size and optimization of bioreactor conditions for optimal growth, viability, specific productivity, mAb yield, product consistency and impurity levels) and purification of the mAb. In addition, CMC includes formulation development (for mAb typically infusion with intravenous route of administration) and stability studies of the bulk drug substance and final drug product (including establishment of storage and shipping conditions). The product used for the clinical trial has to be produced under cGMP, sterilized and filled aseptically.

The total CMC development of a mAb before submission of a CTA is estimated to cost around 6 Mio € and takes around 1.5 years. The CMC activities will be performed by the CDMO ExcellGene (located in Switzerland) because Swiss BioTech is a young and small

company and therefore has neither sufficient experience in development and manufacturing nor suitable facilities. Compliance will be ensured by quality controls and checking documentation that has to be very detailed.

Part D: Pre-IND Meeting / Scientific Advice[4]

Summary: SBT001 showed encouraging results in murine and non-human primate models. We developed a CMC plan and a clinical plan in order to demonstrate its safety and efficacy in humans.

The objective of the meeting is to evaluate the preclinical data, CMC plan, timelines and clinical trial design.

Proposed agenda:

1. Introduction by the sponsor [5 min]
2. Level of confidence on preclinical data, relevance of animal model [10 min]
3. Validation of the indication, discussion about the FiH dose [5 min]
4. Appropriateness of studies in patients, recruitment criteria, PK/PD, endpoint [5 min]
5. Is SBT001 being compared with an appropriate alternative?
6. Dosing and dose escalation schemes [5 min]
7. Results analysis methods [5 min]
8. Discussion about the estimated times of the different phases [10 min]
9. CMC: Validation of the proposed CDMO and Quality acceptance criteria [10 min]

List of Sponsor participants:

Xavier Pierrat, Chief Executive Officer, Swiss BioTech
Nilabh Ghosh, Chief Research Officer, Swiss BioTech
Alessia De Masi, Chief Medical Officer, Swiss BioTech
Anna Näger, Chief Scientific Officer, Swiss BioTech
Dr. Intel, Chief Executive Officer, ExcellGene (CDMO)

List of requested participants from Scientific advice:

Experts in mAb development

Experts in prostate cancer or solid tumors

Proposed meeting dates:

Friday, 15th of October

Tuesday, 19th of October

Wednesday, 20th of October

Friday, 22nd of October

Part E: Inspection Readiness

A suitable quality management system (QMS) needs to be build and maintained. The quality system should include a summary of all the proofs that the equipment used is certified, regularly controlled and maintained. In addition, it contains instructions on how to operate machines and records of the activities performed.

Project files to present to the health authorities have to be ready before going to human trials, as well as after phase I, phase II, and before going to the market. In addition, compliance with GMP during drug production, GCP during the clinical trials and GLP throughout every step has to be demonstrated. Besides, the facility in which SBT001 is manufactured needs to be approved by the health authorities.

In conclusion, we need approval for the facility and for the project to have the final authorization.

3. Overall Strategy[1,15,16]

Due to the nature of the diseases – prostate cancer – the clinical trials will be performed with male subjects only. This will facilitate the establishment of the clinical trial protocol and the submission process.

Furthermore, we want to apply for orphan designation for disseminated/recurrent prostate cancer. Once approved safe, we plan to extend our objectives to trials for testing other types of cancers, too. SBT001 fulfils all criteria that need to be met for an orphan drug designation:

1. SBT001 is intended to treat a life-threatening condition (prostate cancer).
2. The prevalence of the disease is below the EU threshold of 5 cases in 10,000 inhabitants.
3. No satisfactory treatment method is available.

If SBT001 receives orphan drug designation, we would obtain protocol assistance – scientific advice specific for designated orphan medicines. Besides, we would have access to the centralized authorization procedure, which allows us to make a single application to the European Medicines Agency that would be valid in all EU member states. Moreover, we would obtain ten years of market exclusivity once SBT001 is approved. In addition, small companies (like Swiss BioTech) receive administrative and procedural assistance from the Agency's SME office and fee reductions if they obtain orphan drug designation.

4. Advice to Management

Dear Senior Management,

We hereby provide you the details of our product development strategy concerning SBT001.

Our drug discovery began with the identification of a medical need. This included a thorough judgement and patent analysis on the adequacy of existing therapies for prostate cancer. From

our initial analysis – in combination with an appraisal of the current knowledge – we hypothesized the development of a potential monoclonal-antibody-driven therapeutic strategy for late-stage prostate cancer. Based on our hypothesis and the disease area, we set specific objectives for the project.

Initially, we performed various pre-clinical studies at the *in vitro* and *in vivo* level for lead optimization.

In vitro:

- Generation of cell line and safety studies (cytokine release assays)
- Binding affinity and functional activity studies
- Immunohistochemistry in human and animal tissues to determine target protein expression pattern

In vivo:

- PK/PD profile and dose escalation studies (to determine the clinical dose)
- Toxicology studies (incorporating safety and immunotoxicity endpoints)

We strictly adhered to the following regulatory guidelines in order to further support our pre-clinical development of SBT001:

- ICH S6: Preclinical safety evaluation
- ICH S8: Immunotoxicity studies
- ICH S9: Nonclinical evaluation for anticancer pharmaceuticals
- ICH S5a: Toxicity to medicinal products on human reproduction cycle

Our studies further helped us to make certain important considerations regarding our product, SBT001:

- We observed a significantly upregulated TGF-β expression in cancer tissues.
- SBT001 showed sufficient potency in rodent models.
- SBT001 showed sufficient potency in NHP models.

Consequently, our team decided to opt for intravenous administration for the primary indication. The on-target binding of SBT001 did not induce any toxicity and is therefore aptly applicable for therapeutic functions. These findings along with our phase I clinical trial results further highlight the strong benefits of SBT001 when targeting prostate cancer. For a life-threatening condition, our benefit/risk assessment favours the administration of SBT001 in patients with prostate cancer beyond phase I. I thus believe that our company will achieve a high profitability from SBT001.

5. Conclusion

SBT001 is being produced under GMP compliance for use in the clinical investigations. It targets a subset of late-stage prostate cancer patients that are lacking therapeutic options. Besides, due to the prevalence of 1.12 late stage prostate cancer patients per 10000 inhabitants in the EU, SBT001 is eligible for orphan drug designation

Based on pre-clinical data, we determined a first-in-human dose that is expected to be safe. Furthermore, the proposed dose escalation scheme will allow us to determine the therapeutic window of SBT001.

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