**Oncamine: Repositioning F14512, a deprioritized clinical stage oncology drug**

## Background

Despite the major progress ongoing in the treatment of cancer with immunotherapy and targeted therapies, chemotherapy (cytotoxic agents) will remain a cornerstone of cancer treatment, and better drugs with improved efficacy and safety are badly needed. This is especially true for "orphan" indications where immunotherapy and targeted therapies are struggling to demonstrate their clinical relevance, such as Acute Myeloid Leukemia (AML), Small Cell Lung Cancer (SCLC), Pancreatic cancer, and pediatric solid tumors.

The concept of vectorization of cytotoxic agents, i.e., linking a toxin to a ligand targeting receptors that are overexpressed in cancer cells to increase the specificity of the drug for the tumor cells, has been a popular avenue and has translated into several successes in terms of development. The most well-known examples are Antibody Drug Conjugates (ADC), such as Kadcyla® and Mylotarg®.

F14512 is a next generation vectorized cytotoxic agent developed by Pierre Fabre. It is a conjugate between a toxin (epipodophyllotoxin) and a polyamine (spermine). Polyamines are very important cellular metabolites that enter cells through an active transport system called the Polyamine Transport System (PTS). The PTS is very often over-expressed in tumor cells, therefore F14512 has a high specificity for tumor cells, which has been demonstrated by a very high potency *in vitro* compared to the benchmark etoposide.

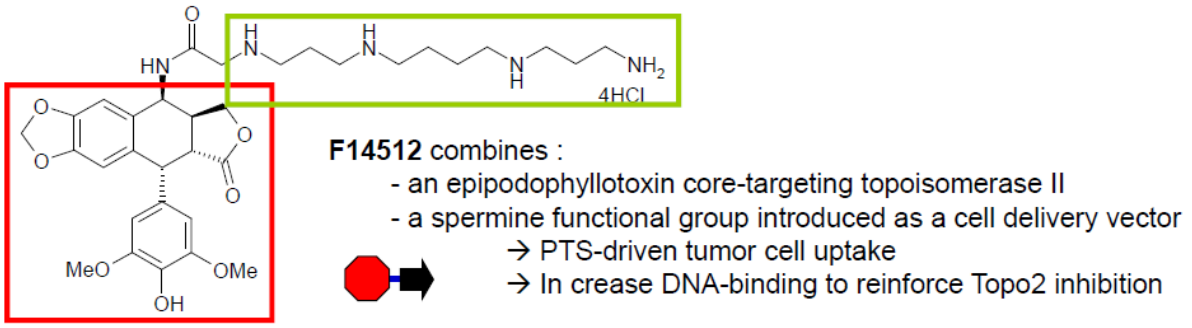


Figure 1: F14512 chemical structure (extracted from Bahleda et al., 2014)

F14512 has been developed in the treatment of elderly (>60y) patients with relapsed or refractory acute myeloid leukemia. In this very difficult indication (median survival time is 5 months, the standard of care has not evolved in the last 20 years), F14512 has demonstrated an encouraging anti-tumoral activity, combined with a very favorable safety profile. In phase 2, the objective response rate for F14512 combined with cytarabine (Ara-C) was nearly 40%, to be compared with less than 20% for cytarabine alone. Despite those encouraging results, Pierre Fabre has discontinued the development of the product.

During the last 12 months, we have been discussing with Pierre Fabre regarding the in-licensing of F14512 in a NewCo. As of today, Oncamine Pharmaceuticals is incorporated, and we have secured our rights on the product. We are now seeking investors to fund this drug repositioning project.

## Our project

The cellular uptake mechanism of F14512 through the PTS is at the same time a strength (because the PTS is often overexpressed in tumor cells) and a weakness, because tumor cells can down-regulate the expression of the PTS and thus become resistant to the drug.

However, this mechanism can be exploited to optimize the efficacy of the product. Indeed, it is well known that the administration of a polyamine synthesis inhibitor, such as Eflornithine (DFMO), a drug that is already registered on the market for the treatment of sickness disease, induces an upregulation of the PTS activity, especially in tumors, which are highly dependent upon polyamines.

Our plan is to exploit this specific cellular uptake mechanism to optimize **F14512** efficacy, by combining it in vivo with DMO. DFMO administration, concomitantly to F14512, will block polyamine synthesis in tumor cells, thereby inducing an upregulation of the PTS, and an increase of F14512 uptake into tumor cells, leading to increased anti-tumor efficacy and preventing the emergence of resistances associated to a down-regulation of the PTS.

Additionally, DFMO is known to have anti-tumor effects per se and is currently investigated in the treatment of neuroblastoma, as well as in the prevention of colon cancer in high-risk individuals. DFMO is free of rights, is available for clinical trials (iv formulation). It is a safe drug with very limited toxicity. We aim to combine DFMO with F14512 in a single coformulation for iv administration. F14512+DFMO will provide improved efficacy vs F14512 alone, with little or no cost in terms of additional toxicity. It could make a major difference in terms of clinical benefit, in AML and in other indications.

### Development and business strategy

We plan to test the DFMO+F14512 combination, with the addition of Ara-C, in the same indication where F14512 has been evaluated until now, i.e., elderly patients with relapsed & refractory acute myeloid leukemia. A Proof of Concept Ph2 trial will demonstrate the benefit of adding DFMO to F14512 compared to F14512 alone, and the benefit in terms of response rate and overall survival provided by the triplet combination will provide sufficient basis to file for conditional approval, enabling fast access to the market in this first indication, in a 5-year time frame.

The size of the envisaged market for the first indication is ~100-200M€. Although there is high competition regarding new drug development in the field of oncology, Acute Myeloid Leukemia remains an indication of very high medical need where the standard of care, essentially relying upon chemotherapy, hasn't changed in the last 30 years. Recent approvals of targeted therapies only impact marginally the situation, and current drugs in late-stage development do not have a game changing potential.

We plan to commercialize ourselves the product in Europe, while finding partners and distributors for the US. Indeed, the hematology market is a niche market with a small number of excellence centers (~20 in France) and is within reach of a small organization.

Clinical trial success in AML will trigger an expansion of the development of DFMO+F14512 in other indications, both in hematology and in solid tumors such as small cell lung cancer, pancreas cancer and pediatric tumors, where the need for improved cytotoxic agents is high. This will fuel the long-term growth of product sales and company valuation.

### Intellectual property and other market protections

We have secured rights on Pierre Fabre IP on F14512 (composition of matter and synthesis), and we have also filed our own patent, a method of use patent covering the combination of F14512 and a polyamine depletion strategy to increase its efficacy (filed in 2017). We will also rely upon regulatory market protections, such as orphan drug protection (AML is an eligible indication), and data protection (10 years). This will provide a good protection securing the return on investment. Additional IP can be sought in the months to come (formulation).

### Business plan and financials

We plan to raise ~6M€ in Series A to fund the PoC trial. In case of success in the PoC, additional 10M€ will be raised to generate additional data (more patients, longer follow-up) within the same protocol. An IPO is planned in 2023 to raise additional 40M€ required for phase 3 and product launch in 2024. Target annual revenues exceed 150M€. Short term, we are looking for a seed financing round of ~500k€ that would help accelerate the project.

### Status, next steps and calendar

We already have experimental preclinical data demonstrating the validity of our concept of F14512 potentiation by DFMO in cancer cell lines, and *in vivo* studies are in progress. We have agreed on a terms sheet for F14512 license with Pierre Fabre and have an LOI for exclusive negotiation. Our plan is to have the first patient included in the Proof of Concept trial by Q3 2019. The next year will be allocated to fund raising, manufacturing clinical batches, generating a limited amount of preclinical data needed to support our dossier, and file for clinical trial approval. Initial clinical results needed for Series B will be available by End 2020 and targeted market entry

### Team

Our team is composed of senior professionals with high expertise built upon past experience in oncology drug development, preclinical development and regulatory affairs, legal affairs and licensing. We have all the skills needed to succeed in the execution of the plan, as well as a strong support from KOLs in AML.