Category

Best Startup

Product/Solution Name

CTPS1 Inhibitor

Date of Approval

N/A

Indications

T cell and B cell lymphomas
Solid tumors
Autoimmune diseases

Therapeutic Categories

Oncology and Autoimmune diseases

Background information and need for solution/product

Step Pharma is a privately held French biotechnology company developing a novel class of oral nucleotide synthesis inhibitors specifically targeting cytidine triphosphate synthase 1 (CTPS1) to treat cancer and autoimmune conditions.
Step Pharma is the world leader in the discovery and development of CTPS1 inhibitors. The company was incorporated in France in 2015 and has raised capital through seed, Series A and Series B rounds with top tier European investors. The leadership team has significant experience in oncology drug development, and we are privileged to be supported by world leading scientists and clinicians.
DNA and RNA synthesis are essential for cell growth and division in both normal and cancerous cells. Cancer cells have an elevated proliferation rate which brings with it a high demand for nucleotides to support DNA replication. Targeting nucleotide synthesis, either pyrimidine or purine, is not a new concept in designing and developing anti-cancer agents. Many chemotherapeutic drugs act on these pathways but with unacceptable toxicities and eventual resistance. All previous attempts to use targeted therapies to specifically inhibit the pyrimidine synthesis pathway in oncology have failed due to toxicity which is not unexpected if the pathway is blocked in all dividing cells in the body as this leads to inhibition of essential activities such as stem cell proliferation in the gastro-intestinal tract.
Every step in the pyrimidine synthesis pathway has a single enzyme that catalyses the conversion of substrate to product with one exception, the final and rate limiting step converting UTP to CTP. Two very closely related enzymes, CTP Synthase 1 and CTP Synthase 2, can catalyse this final step which provides a point of differentiation from other steps in the pathway.
Professor Alain Fischer and colleagues identified a rare group of patients deficient solely in CTPS1 and demonstrated that lack of CTPS1 has a restricted effect on lymphocytes with no effects on other cell types. T cells and B cells isolated from these patients are unable to synthesise CTP when activated and thus unable to proliferate. This demonstrates the non-redundant role of CTPS1 in lymphocytes, while in all other cell types CTPS2 is able to compensate for the loss of CTPS1.
Thus, inhibition of CTPS1 alone represents a targeted approach to block aberrant proliferation of T and B cells, as is seen in haematological malignancies, to deliver efficacy with a good therapeutic index.

In addition to the key role that CTPS1 plays in lymphocytes, and thus in haematological malignancies, we also believe that all cancers have developed an addiction to CTPS1 for the synthesis of CTP. This represents a therapeutic vulnerability that can be exploited in several ways. The most compelling is the concept of metabolic collateral lethality in which the loss of CTPS2 exposes a sensitivity to inhibition of CTPS1 alone. In ovarian, lung, bladder and several other solid tumours we have shown that greater than 15% of patients have genomic deletion of CTPS2. This creates the opportunity to use a CTPS2 biomarker approach to select patients that would be sensitive to CTPS1 inhibition.

History of the development of the solution/product

Step Pharma is developing STP938, a first in class, potent, highly selective, orally bioavailable small molecular weight CTPS1 inhibitor with >1,000 selectivity for human CTPS1 over CTPS2.
Step Pharma conducted high throughput screens to identify novel compounds with weak activity against CTPS1. Medicinal chemistry was then applied to select and optimise the most promising molecules leading to the progression of STP938 as a clinical candidate. Additional compounds in the same compound series were identified to be developed for alternative indications beyond oncology.
Extensive preclinical studies have been undertaken to establish CTPS1 as a broad cancer therapeutic target, with haematological cancers, particularly T cell neoplasms, showing greatest sensitivity to CTPS1 inhibition. STP938 shows anti-tumour activity as monotherapy in vivo against human T cell and B cell tumours.
Lymphoma therapy, particularly for indolent disease, is moving away from chemotherapy towards chemo-free combinations of targeted drugs and antibodies. Key to the development of successful combination therapies is an understanding of how the combined agents interact mechanistically with each other and with the biology of the tumour. Preclinical studies have identified synergy between STP938 and BCL2 inhibition in models of myeloma and mantle cell lymphoma. Synergy between STP938 and the BCL2 inhibitor venetoclax was confirmed in an in vivo model of mantle cell lymphoma.
STP938 also shows synergy in vitro with drugs that inhibit the DNA damage response pathway, comprising inhibitors of ATR, CHEK1 and WEE1. Synergy between STP938 and ATR inhibition was confirmed in an in vivo solid tumour model.
STP938 will initially be developed as a monotherapy and combination options explored based upon our preclinical studies following positive clinical data.
STP938 has concluded all non-clinical development activities and has received approval to enter clinical development from FDA (US), MHRA (UK) and EMA (EU).
Step Pharma is currently conducting a phase I/II proof of concept study in relapsed/refractory B and T cell lymphoma. The dose escalation (phase I) study will conclude in 1Q24 and following approval of the recommended phase 2 dose (RP2D) and schedule will advance into a dose expansion (phase II) basket study where up to 150 patients will be recruited across five different lymphoma/leukaemia sub-types. Study centres are open in the US and UK with French sites expected to be open by 2H23. The phase II study follows a Simon-two stage design such that an interim stop/go analysis is conducted in each indication after approximately ten patients have been recruited and dosed for a sufficient duration to enable assessment of efficacy. The complete study is expected to conclude in 2025 but given the open label nature of oncology studies, efficacy data and interim analysis will be reported on an on-going basis based upon speed of recruitment.
Phase II solid tumour studies are planned to commence in 2H24 using CTPS2 biomarker selection to enrich for patients sensitive to CTPS1 inhibition.

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Nucleotide synthesis is a known therapeutic vulnerability in cancer yet all previous attempts to selectively target the pyrimidine synthesis pathway have failed due to dose limiting toxicities. Our approach of directly and selectively targeting CTPS1 will enable inhibition of the pathway without the toxicities seen with previous drugs.
Step Pharma has led the way in discovering and developing CTPS1 inhibitors and STP938 is the first, and currently the only, CTPS1 inhibitor in clinical development.
Despite the extensive efforts applied to drug development in oncology there still remains significant unmet need in many cancers.
The T cell malignancies represent a huge area of unmet need. Diseases like peripheral T cell lymphoma (PTCL) have been largely neglected with no improvement in the 5-year survival rate in the past 20 years. Standard of care for PTCL remains chemotherapy and approved second line agents have limited efficacy. In addition to PTCL there is significant unmet need in relapsed cutaneous T cell lymphoma where current therapies offer poor response rates. A novel effective agent is much needed for T cell malignancies.
The treatment of B cell malignancies has improved with the arrival of novel targeted and cellular therapies. However, relapse rates remain high even with the current range of second- and third-line drugs, and CAR-T therapy becoming more readily available demonstrates there is still significant unmet clinical need.
Selective targeting of CTPS1 offers a potential new therapeutic for haematological malignancies.
The identification of solid tumours that lack CTPS2 also opens an exciting opportunity to use STP938 as a targeted therapy in biomarker selected patients. Of the four tumour types with the highest prevalence of CTPS2 loss, clinical development will initially focus on ovarian cancer and non small cell lung cancer (NSCLC). There are 60,000 new cases of advanced ovarian cancer in US/EU per year and a significant unmet need in the platinum refractory/resistant population.
The broad applicability of CTPS1 inhibitors across cancer has the potential to transform the way haematological malignancies are treated and offer new alternatives to solid tumour patients whose tumours show enhanced sensitivity to CTPS1 inhibition

Please provide appropriate references (ie Pubmed links)

Human Genetics
JCI Insight - Impaired lymphocyte function and differentiation in CTPS1-deficient patients result from a hypomorphic homozygous mutation
CTP synthase 1 deficiency in humans reveals its central role in lymphocyte proliferation - PubMed (nih.gov)
Role in cancer
CTP Synthase 1 Is a Novel Therapeutic Target in Lymphoma : HemaSphere (lww.com)
Structural basis for isoform-specific inhibition of human CTPS1 | PNAS
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Combined Inactivation of CTPS1 and ATR Is Synthetically Lethal to MYC-Overexpressing Cancer Cells | Cancer Research | American Association for Cancer Research (aacrjournals.org)
P864: CTPS1 IS A NOVEL THERAPEUTIC TARGET IN MYELOMA - SELEC... : HemaSphere (lww.com)

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