Treatment of Joint Pain in Hemophilia

Hemophilia

Hemophilia is a mostly inherited genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. This results in people bleeding longer after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. Those with a mild case of the disease may have symptoms only after an accident or during surgery. Bleeding into a joint can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of consciousness.

There are two main types of hemophilia: hemophilia A, which occurs due to low amounts of clotting factor VIII, and hemophilia B, which occurs due to low levels of clotting factor IX. They are typically inherited from one's parents through an X chromosome with a nonfunctional gene.

Hemophilia A affects about 1 in 5,000–10,000, while hemophilia B affects about 1 in 40,000 males at birth. As hemophilia A and B are both X-linked recessive disorders, females are rarely severely affected. Thus, males represent about 90% of the total.

Among the countries that collect data, a total of 210,000 cases of hemophilia were reported in 2018, including 18,000 in the U.S., 30,000 in 5 major Europe countries, 21,000 in India, 18,000 in China, 2,000 in Korea and about 121,000 in the rest of the reporting countries (World Federation of Hemophilia 2018 report). There is no cure for Hemophilia; treatment consists of administration of Factor VIII or Factor IX.

Common Complications of Hemophilia

Hemarthrosis is a bleeding into joints and a common problem of hemophilia. Joint bleeding accounts for 70 – 80% of all bleeding cases in patients with severe hemophilia and causes extreme pain (hemophilic arthropathy). It can repeat to a cycle of bleeding, synovitis, and more bleeding. Pain in one or more joints is a common problem up to two-thirds of patients with severe hemophilia. Pain is therefore a critical aspect of hemophilia and adds to the burden of the disease.

Methods of Treatment

RICE Therapy

Rest, Ice, Compression and Elevation (RICE) can be used in acute hemarthrosis generally but provides little relief from pain.

Pain Management

There is no effective pain management method currently available for these patients except opioids, which expose them to the risk of addiction.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been considered as an alternative. They inhibit cyclo-oxygenase (COX), the enzyme that converts arachidonic acids to prostaglandins. Prostaglandins are produced in response to injury or infection and cause inflammation, which is associated with the symptoms of redness, swelling, pain and fever. Two isozymes, COX-1 and COX-2, are found in humans. Traditional NSAIDs inhibit both COX-1 and COX-2 enzymes. However, their use is associated with the side effects such as gastrointestinal and renal toxicity. The anti-inflammatory action of NSAIDs and reduction of pain are produced by the inhibition of COX-2 activity, while the undesired side effects are caused by the inhibition of COX-1 activity. Thus, it was thought that inhibitors more selective to COX-2 ("COX-2 inhibitors") would have reduced side effects. Indeed, some of COX-2 inhibitors ("coxibs") were proven in clinical studies to reduce the gastrointestinal adverse effects of the traditional NSAIDs. However, all COX-2 inhibitors cause adverse cardiovascular effects, celecoxib less than others. The adverse cardiovascular effects led to withdrawal of all COX-2 inhibitors from the U.S. market except celecoxib, which is not recommended for long term use.

Our Approach

Most NSAIDs, including COX-2 inhibitors, are taken orally and are subject to systemic exposure. As described above, the systemic exposure of COX-2 inhibitors has shown to cause adverse cardiovascular effects. Postsurgical Therapeutics, Inc. ("PTI") is developing injectable formulations of celecoxib encapsulated in PLGA microspheres (described below), which are suspended in a non-viscous aqueous solution. The product will be administered by intra-articular injection to the painful joints with a user-friendly syringe. We believe this simple, convenient drug delivery system will significantly reduce the amount of the drug in the systemic circulation, minimizing the possibility of adverse cardiovascular effects while significantly reducing the joint pain associated with hemophilic arthropathy.

Product Development

Polylactic glycolic acid (PLGA) and its derivatives are biodegradable polymers that are widely used in many FDA-approved drug products. There are at least 19 FDA-approved PLGA-based drug products available on the U.S. market. These products are designed to reduce dosing frequency and potential drug toxicity. Less frequent dosing improve compliance, providing a better treatment option for regimens that require frequent oral or injectable medications.

PTI and its partner for this project have extensive experience in the development of formulations/products based on PLGA technology. We developed formulations of celecoxib encapsulated in PLGA microspheres designed to release celecoxib for periods between seven days and two months and compared the ***in vitro*** release profiles to select the candidate for animal testing.

We selected the 14-day formulation and completed a pharmacokinetic ("PK") study in beagle dogs and subsequently an efficacy study in rats.

PK Study in Beagle Dogs

Celecoxib encapsulated in PLGA microspheres suspended in an aqueous CMC solution with a 14-day release profile was delivered by intra-articular injection into the knee at 1.5 mg/kg dose on day 0. The concentrations of celecoxib in plasma and synovial fluid were monitored at several time points during the 14 days. The Cmax in synovial fluid (1,360 ng/mL) was 65-fold higher than that in plasma (20.8 ng/mL), showing that very little celecoxib was absorbed into the systemic circulation after intra-articular injection while high concentration was maintained locally. The duration of release was 11 days in the PK study similar to 14 days in the ***in vitro*** study.

Efficacy Study in Rats

We investigated efficacy using the hemophilic arthropathy model of pain. We compared swelling rate and gait score for the test and control groups. The test group was injected with celecoxib-PLGA microspheres suspended in aqueous CMC solution at 1.5 mg/kg dose in the knee area of the hind leg and the control group with the same vehicle. Both groups were injected with autologous whole blood into the hind knee joint on days 0, 5 and 10 to induce hemophilic arthropathy and monitored for 14 days. The swelling rates and gait scores during 14 days were significantly lower in the test group. PTI believes that the benefits demonstrated in the rat model justify initiation of clinical trials.

Regulatory Approval in the U.S.

PTI believes the product will be eligible for the FDA's 505(b)(2) NDA approval path in the U.S. ("repurposed drug") rather than the 505(b)(1) NDA approval path required for new drugs. The 505(b)(2) NDA approval path allows the developer of a new formulation of an approved therapeutic agent to reference the safety and efficacy data on which the therapeutic agent was approved. Depending on clinical requirements, product development and approval by the 505(b)(2) NDA approval can take substantially less than five years from the date of IND approval.

Orphan Drug Designation

Because Hemophilia is a rare disease in the U.S. (approximately 18,000 individuals), we expect to receive Orphan Drug Designation ("ODD") from the FDA for our product. ODD can provide incentives in the U.S., including potential exemption from the requirement for Phase I and Phase II clinical trials, expedited regulatory review, extended duration of exclusivity, tax benefits and higher price for treatment compared to branded drugs. The tax credits of up to 50% of R&D costs, R&D grants, waived FDA fees, protocol assistance and may get clinical trial tax incentives.

We filed the application for ODD on May 5, 2020 and received the ODD from the FDA on July 30, 2020. The regulatory path for Orphan Drugs along with 505(b)(2) NDA regulatory path can

lead to approval in a fraction of the time and cost expected with the 505(b)(1) NDA regulatory path.

Intellectual Property

PTI filed a PCT application in April, 2019 worldwide including the U.S. We also filed a continuation-in-part (CIP) to strengthen the original application in June, 2020 and obtained the issuance of the CIP on October 24, 2023 (US #11,793,762). PTI sold the intellectual property of this project to Upex-Med in 2019 by transfer by Kossen. Currently PTI and Upex-Med are co-developing this project.

Commercialization Strategy

Currently PTI intends to establish corporate collaboration(s) to complete development, obtain regulatory approvals and commercialize the product worldwide.