Category

Best Startup

Product/Solution Name

O2L-001

Date of Approval

N/A

Indications

Spontaneous Intracerebral hemorrhage

Therapeutic Categories

Biotechnologies, cardiovascular, cerebrovascular/neurovascular, acute care in hospital

Attached Files:

- 1701Op2lysis introduction Q2 23 Series A pitch 230405.pdf

Background information and need for solution/product

Spontaneous Intracerebral hemorrhage (ICH) is an unmet medical need that affects >325 000 patients yearly in the European Union, USA and in Japan. It results from the rupture of small arteries leading to the formation of a solid and massive intracerebral hematoma outside of the vessels. The mass-effect of the hematoma (sizing at least like a golf ball) plays a central role in the primary (mass-effect and mechanical injury) and secondary injuries (edema formation). ICH is associated with the highest mortality rate among all forms of strokes. Mortality rate for ICH is >50% at one year. Although ICH accounts for only 20% of all strokes, its overall global burden accounts for almost 50% of all stroke burden.

Up to now, there is no approved therapeutic solution for ICH. Three main therapeutic strategies have been explored so far, targeting ICH at various stages:
- Stopping (re)bleeding at a very early stage. While hemostatic treatment to stop bleeding with factor VIIa failed so far, intensive blood pressure lowering treatment showed very recently (INTERACT 3 study) the first positive results in this indication.

- Reducing long-term neurotoxicity but no treatment has demonstrated efficacy with this approach.

- Evacuating intracerebral hematoma once formed:
Evacuation of the intracerebral or intraventricular hematoma is necessary due to its deleterious mass-effect and appears as the most promising approach to reduce burden. Medical devices (Artemis system or Brainpath), are being investigated in ICH, however, the demonstration of clinical benefit has not yet been proven with this surgical approach.

The ”hematoma evacuation” strategy has been reinforced by encouraging results of the MISTIE III and CLEAR III studies, which used an old thrombolytic agent (alteplase) administered through a catheter

positioned inside the clot through a minimally invasive surgery technique.
Alteplase is the first recombinant human tissue plasminogen activator (rtPA), marketed for ischemic stroke since 1996. Published results of these two large clinical trials have demonstrated the feasibility and safety of the procedure (minimally invasive surgery) and of blood clot lysis and drainage by alteplase. However, both trials did not achieve statistically significant benefit in their primary analyses of functional change on the disability modified Rankin scale (mRS), essentially due to the limited efficacy of alteplase. Nonetheless, they offer a clinical proof-of-concept with a clear demonstration of clinical benefit – reduction in disability and mortality – when a sufficient blood hematoma reduction was achieved, an important surrogate marker for future development.

The engineering and selection of O2L-001 were driven on the ground of these previous experiences, to optimize the extent of clot lysis albeit limiting the risk of re-bleeding and the pro-neurotoxicity properties associated with available recombinant tPAs.

In summary, intracerebral hemorrhage is an unmet medical need, associated with high dependency and mortality rates. The MisTIE program highlighted for the first time a strong relationship between the volume of hematoma evacuated with such technology and the level of handicap one year after treatment. Thus, data from the real-world needs (patients) help us in designing our therapeutic solution, O2L-001, to promote higher efficacy and safety.

History of the development of the solution/product

O2L-001 is a patented therapeutic solution derived from the NANOp2Lysis® platform, and using on our innovative thrombolytic agent, OptPA. OptPA has been shown to have less pro-bleeding activity and less neurotoxicity capabilities than rtPA/alteplase thanks to its two point-mutations (Parcq et al., 2013; Goulay et al., 2018).

O2L-001 is an injectable suspension, consisting of nanoprecipitated OptPA entrapped into thermosensitive poloxamer 407 (P407) to enable the extended release of OptPA. The goal being to enhance the local duration of action and to optimize intracerebral hematoma lysis, albeit limiting the need for repeated administrations.

The engineering and selection of O2L-001 were driven on the ground of the previous experiences of CLEAR and MISTIE clinical trials. The main characteristics of O2L-001 are thus the following:

EFFICACY, better thrombolytic effect on best translational model (vs alteplase)
While OptPA and rtPA share the same thrombolytic activity, O2L-001 allows increased thrombolytic efficacy (+44% more hematoma liquefaction in a model of human blood hematoma when compared to rtPA (alteplase) - data submitted to publication).

SAFE, reduced side effects (bleeding and neurotoxicity vs alteplase).
The MISTIE phase 3 highlighted a high rebleeding risk (+24% vs medical treatment) following rtPA treatment, attributed to undesirable off-target plasmin activation. rtPA has also potential neurotoxic effect due to the interaction with NMDA receptors (NMDAR) leading to the increased of peri-hematoma volume and neuronal death as demonstrated in large animal with intracerebral hemorrhage. O2L-001 has -80% off target plasmin-generation capacity and cannot activate NMDAR.

EASY, simplified model of administration (unique injection)

Thanks to the extended-release formulation, O2L-001 is effective with a single administration versus up to three injection per day, up to three consecutive days with rtPA. This clinical set up is manageable in small hospital with only one neurosurgeon.

In addition, the pharmacokinetic investigation of O2L-001 in rodents has shown a minimal systemic exposure and no accumulation over time after an intraparenchymal or intraventricular injection of O2L-001.
These features will be confirmed during a future GLP nonclinical toxicology program to demonstrate the drug availability, to identify undesirable effects, to address the toxicity of the compound and to support the selection of doses for the clinical study.
The preclinical path to reach clinical stage of development and the proposed clinical study design have been validated during pre-IND meeting and Protocol Assistance consultations, respectively with the FDA and EMA. The objective of these first consultations with health agencies was mainly to make our programme known and to de-risk our business, by validating some of our hypotheses.
In addition, as intracerebral hemorrhage is a life-threatening disease and an unmet medical need (no approved treatment), an Orphan Drug Designation (ODD) has been granted in USA and Europe to OptPA for the treatment of intracerebral hemorrhage.

In summary, our product is a best-in-class game-changing opportunity for patients with intracerebral hemorrhage. O2L-001 is a drug product allowing extended release of OptPA to favor hematoma liquefaction and extraction. The potential benefit of O2L-001 (safe, efficacy and easy) has been established using in vitro, ex vivo and in vivo experimental models.

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

The NANOp2Lysis® platform offers the opportunity to produce active drug product, in a drug-delivery system, with high concentration and clinical grade quality, by converting biological molecule to solid particles prior to suspension into polymeric systems. The NANOp2Lysis® platform allows the formulation of active biological molecules to ensure high protection of active biological molecule during its vectorization in the human body.

A critical problem with thrombolytic agents is that most thrombolytic drugs are currently administered by frequent injections due to their short half-life in the bloodstream. Vectorization and extended-release technology offers the promise for reducing dosing frequency, maximizing the efficacy–dose relationship, and decreasing adverse side effects. However, developing extended-release dosage forms of thrombolytic agents is a challenge as most of manufacturing process cause proteins to denature. The patented NANOp2Lysis® technology solves this issue.

O2L-001 is a brand-new, patented product, composed of a new biological entity (OptPA) protected by a family of patent, expressed by a patented cell line expression system. OptPA is nanoprecipitated using the NANOp2lysis® technology and incorporated into a thermosensitive polymer, designed to be injected locally into brain hematoma of patients with intracerebral hematoma, to facilitate hematoma liquefaction and evacuation over a few hours. Four families of patents protect our groundbreaking technology based on a well-known mechanism of action.

Intracerebral hemorrhage is an acute life-threatening disease with no specific treatment approved so far. An interest in fighting ICH has been raising since 2010. A Stroke Action Plan 2018-2030 for Europe

and number of clinical trials targeting ICH in the USA were initiated these last years. One of the priorities is to develop by 2030 treatment strategies that can improve outcomes in patients with ICH, increasing the rate of good functional outcomes to >50%. Up to now, no clinical trial succeeded to improve the outcome of ICH patients. Based on the demonstration of MISTIE and of the surrogate marker that is the reduction of the hematoma volume, we can expect O2L-001, the first safe and effective treatment to remove intracerebral hematoma, to reduce death and long-term severe disability.

The strength of our technology stands also in the NANOp2Lysis® platform, which allows to develop new drug products on the basis of the same drug substance, OptPA to develop tailored product for the main intracerebral hemorrhage's subtypes, to treat all of them. Indeed, our ambition is to adapt the vectorization system (and thus to develop new products) for small infratentorial hemorrhage, that needs lower drug product quantity and faster hematoma removal.

Moreover, the NANOp2lysis platform being a game changing deep-tech to facilitate loading at high concentration of active enzyme in carrier without loss of activity, is the corner stone of innovative delivery strategies, and has been demonstrated with several enzymes and large proteins (Giteau et al., 2008; Giteau et al., 2008; Paillard-Giteau et al., 2010), opening the way to innovation in partnership (reduction of immunogenicity, reduction of injected doses, reduction of toxicity).

Please provide appropriate references (ie Pubmed links)

OptPA
Description and characterization of OptPA :
https://pubmed.ncbi.nlm.nih.gov/28741405/
Molecular requirements for safer generation of thrombolytics and basics of OptPA:
https://pubmed.ncbi.nlm.nih.gov/23301636/
https://pubmed.ncbi.nlm.nih.gov/18334994/

OptPA patents: WO2013034710

O2L-001
O2L-001 patents: WO-2021228800-A1
our results about our drug product O2L-001 and its highest efficacy versus rtPA is currently being reviewed (First round of review resend the 20th of May - minor revision ; publication expected in July)

Clinical surrogate marker for O2L-001
https://pubmed.ncbi.nlm.nih.gov/30739747/