POOLBEG PHARMA LTD (LON:POLB)

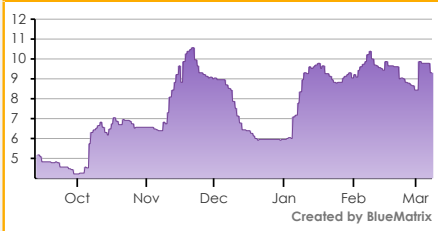
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proactive research

Pharmaceuticals, Biotechnology & Life Sciences

52-WEEK HIGH	**11.14p**
52-WEEK LOW	**4.00p**
PRICE	**9.35p**
MARKET CAP MLN	£46.80

Share Price



Major Shareholders

Shares in issue	500,000,000
Avg Three-month trading volume	1,428,727
Primary Index	AIM

Company Information

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Strong and clear POLB 001 trial data

Trial data shows clear control of inflammatory response

Poolbeg Pharma has disclosed selected data from its human volunteer LPS challenge trial (EudraCT N0: 2022-001458-48) with its lead molecule POLB 001, following its initial announcement of the study's success in January. POLB 001 is a small molecule immunomodulator which inhibits p38 MAP Kinase, a well-characterised intracellular signalling molecule associated with the inflammatory response. This pharmaceutical class is known from multiple prior clinical studies to cause reductions in the production of inflammatory cytokines by immune system cells. The POLB 001 data are from a volunteer LPS-challenge study (run in the Netherlands) and clearly show an effect with two dose levels of 70mg and 150mg with rapid responses following administration. Poolbeg also has access to full Phase 1 trial data conducted as part of an earlier development programme by a prior licensee. Together, these data should provide a comprehensive licensing package that will allow a future licensor to take the compound directly into efficacy studies in patients.

Poolbeg states that POLB 001 could be developed further for the treatment of severe influenza and holds use IP covering p38 MAP Kinase inhibitors (including a recently granted US patent) that confers potent protection until at least 2038. Based on WHO data, Poolbeg estimates there may be 3-5mln severe influenza cases a year globally. The main commercial protection will be regulatory (about 10 -12 years, depending on country/region) as POLB 001 could be the first p38 MAP Kinase inhibitor to gain approval. However, the exact indication pursued would be the decision of any future partner.

Although Poolbeg probably has sufficient cash to fund a Phase 2 study, its strategy is to seek an early, probably global partnering deal. A further indication envisaged could be in managing the cytokine release syndrome side effect of CAR T-cell therapies; a current niche, high-value oncology market served by approved products like the anti-IL-6 antibody tocilizumab.

The challenge study tested POLB 001 in 36 healthy volunteers at three dose levels. After repeat dosing over several days, volunteers were challenged with LPS (lipopolysaccharide), a bacterial molecule that triggers an immune response with rapid and diverse cytokine production. Cytokines are potent inflammatory mediator proteins made by immune cells and cause temperature rises, muscle aches and increased heart rates: 'flu symptoms.

POLB 001 showed that at the higher doses (over 70mg) it limited or removed cytokine responses by targeting p38 in immune cells. This worked for both localised and systemic LPS challenges. The oral drug was rapidly absorbed and widely distributed in vivo. Poolbeg did not report any safety issues although longer-term use side effects are known in this class from other studies although this would not be relevant for acute settings such as severe influenza.

EV very attractive currently

Poolbeg reported cash of £18.9mln at the end of June 2022; full-year results are expected soon. Based on the current market capitalisation (£47mln), we estimate it has an enterprise value currently of about £29mln. Poolbeg has a pipeline with a Phase 2 ready asset (POLB 001), now posed for partnering, and four preclinical programmes (plus two artificial intelligence data collaborations), all addressing unmet needs in infectious and other diseases.

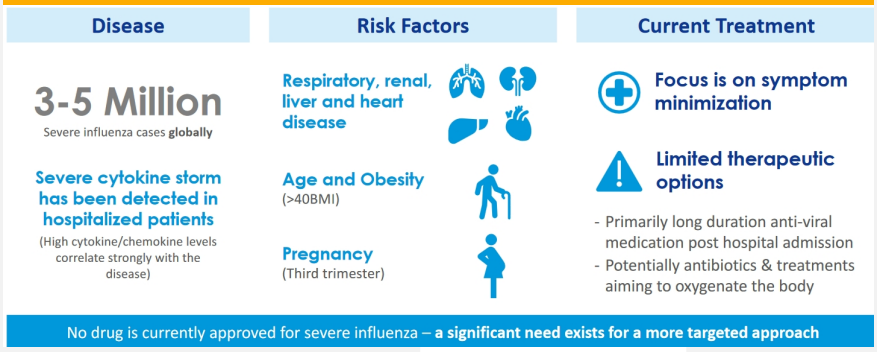
Chief executive officer: Jeremy Sklillington began his biotechnology career in the business development group of Genentech, where he was responsible for executing over 40 licensing, investment and collaboration transactions. He has also held senior roles at Opsona Therapeutics, TriMod Therapeutics. HS Lifesciences and Inflazome.

Chairman: Cathal Friel is founder and executive chairman of hVIVO; also co-founder of Amryt Pharma; founder of Fastnet Oil & Gas; co-founder of Merrion Stockbrokers, which was sold in 2006.

Market opportunity

Influenza is a prevalent infection that is estimated to have 3-5mln severe cases globally (Exhibit 1). Cytokine storms generated by the immune reaction against the virus become damaging to patients (Liu *et al* 2016). Current guidance relies on anti-viral medicines, the best being baloxavir (Xofluza, Roche), to control the infection thought limited to 48 hours post symptoms. Immune suppression using steroids (as was found useful in Covid-19) is not recommended in influenza as it may increase mortality although a Cochrane review found low-quality evidence from mainly observational studies (Lansbury *et at* 2019). Liu *et al* (2019) also noted that no other supportive interventions had robust (or any) clinical data. Hence, if POLB 001, as an anti-inflammatory agent, can demonstrate a survival advantage in these severe influenza patients, probably combined with anti-viral drugs, it could have a good market opportunity. Use would be short-term, possibly 10-14 days, while the patient recovers from the infection. It is important to recognise that the current volunteer study mimics the hyper-inflammatory response and is cannot be considered a model for ongoing viral infection (indeed it uses protein from a bacterial source).

Exhibit 1 - Major Severe influenza opportunity



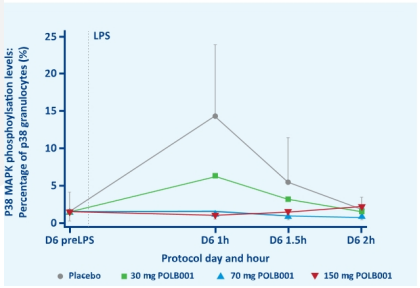
Source: Poolbeg

Clinical results

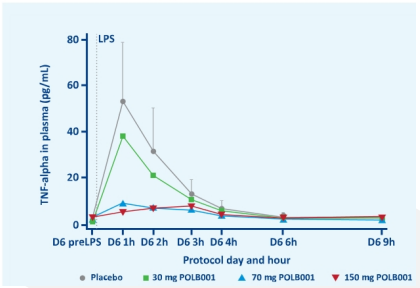
The study, Exhibit 2 (discussed in more detail below), confirmed several key aspects. We are now clear that POLB 001 does inhibit p38MAPK inside immune cells and that this dampens or removes the immune response to a direct acute challenge like LPS. Exhibit 2 shows some key data. The drug has a fast absorption rate but is eliminated apparently within 12 hours. Regular dosing in clinical use might be required, perhaps twice daily. There were clear effects in limiting localised skin inflammation in the localised LPS challenge (on Day 4). In the systemic challenge on Day 6, mimicking an infection, cytokine release was limited. As these were healthy volunteers, it is not possible to predict the profile in patients with high levels of viral infection and/or those most susceptible to severe influenza (eg the elderly). It is recognised that p38 levels increase with age (De Meyer et al, 2020) suggesting the approach is well suited to the elderly.

Exhibit 2 - POLB 001 clinical activity

POLB 001 Engages with its Target
p38 MAPK phosphorylation levels



Blunts Blood Cytokine Storm
TNF-α in plasma (pg/ml)



Source: Poolbeg

Little competition

There is very little (if any) pharmaceutical competition addressing the hyper-inflammatory response in influenza, although there has been some trials using approved biological agents against the same phenomenon arising from Covid-19 infection and in acute respiratory distress syndrome. A medical device (Cytosorb) is CE marked and was given emergency use authorisation in the US for use in the treatment of cytokine storm arising from Covid infection.

Patent cover on POLB 001

Poolbeg has reported the grant of a US patent on POLB 001: 11,339,207. This covers the use of certain p38 MAP kinase inhibitors, including POLB 001, for the treatment or prevention of severe influenza and its associated hypercytokinaemia (cytokine storm) through modulation of the immune response. The US patent expires on 26 June 2037. A European patent has been granted and other patents are pending. Poolbeg has just been granted a second US patent application, US20200360351A1, which covers a specific claim for POLB 001 against cytokine storms and also on in combination with anti-viral agents.

p38 MAPK background

This class of therapy: p38 Mitogen Activated Protein Kinase inhibitors target the internal cell signalling protein p38. In humans, there are four p38 versions and p38 is ubiquitous in many tissues including the brain. The version most relevant to the immune response appears to be alpha with POLB 001 targeting both alpha and beta forms. p38 is an internal signalling molecule that links several possible cell stimuli to various response mechanisms. Stress stimuli, including infection, cause cell receptors to activate p38 (by adding a phosphate) and it in turn activates a wide variety of other proteins and then genes. More recent research shows that it is a fast response system (O'Neil *et al* (2018)) leading to rapid synthesis and release of potent blood signalling. When overexpressed, cytokines can sweep throughout the body re-programming white blood cells causing tissue damage, shutting down circulation and other essential organs leading to death; a process called septic shock and in certain circumstances cytokine storm or cytokine release syndrome (CRS). Such excessive cytokine responses can be seen in diseases such as severe influenza and other acute inflammatory diseases. These cause temperature rises, drive heart rate and stimulate other immune cells.

As a class, p38 inhibitors were developed against long-term chronic disease like rheumatoid arthritis. They generally showed an excellent short-term (one week) control of the disease but were ineffective long-term (Genovese, M., (2009)). This means that a short-term acute indication for POLB 001 looks feasible. The other aspect was that as p38 is ubiquitous, chronic side effects were common. This is probably less likely for short-term acute use but might be a question to resolve for severe flu patients. Doses used in RA were higher than Poolbeg tested in its trial. Further dose ranging might be needed in an acute viral infection indication.

Detailed trial analysis

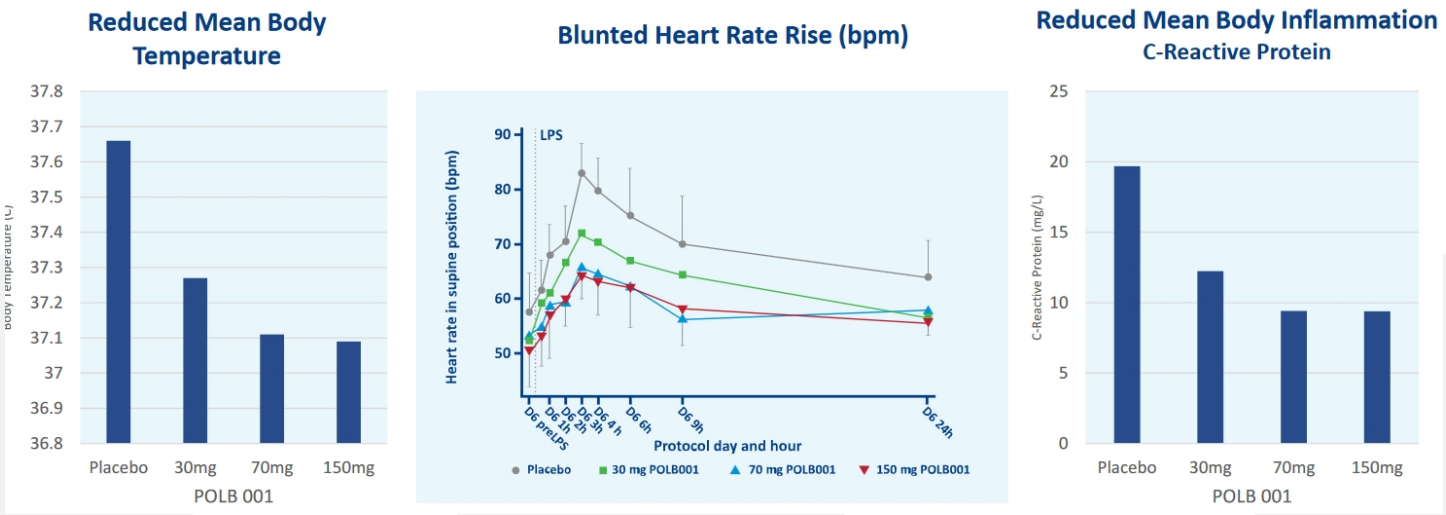
The trial enrolled 36 volunteers in three cohorts of 12 (9 active, 3 placebo); one cohort for each dose level (30mg, 70mg, 150mg). POLB 001 was given orally and showed fast absorption peaking in a few hours with clearance within 12 hours. In our view, twice daily dosing might be needed or a slow-release formulation is required, though an IV formulation should be feasible in the ICU setting.

Volunteers were challenged with LPS under the skin on Day 4 and then systemically challenged with an LPS injection (Day 6). This mimics local infection (Day4) and then general bacterial infection (Day 6); by analogy, this can be extrapolated to viral infection but anti-viral immune responses do differ from antibacterial - they tend to be based more on T-cell responses which take several days to develop whereas bacterial infections trigger the rapid innate response immune system before mounting a longer term antibody-based response.

On Day 4 POLB 001 at 70 and 150mg was locally effective at markedly reducing local skin inflammatory responses demonstrating that the drug administered orally is widely distributed and is active at the site of inflammation (note this is not the expected indication). On Day 6, against systemic LPS challenge at 70mg and 150mg doses, POLB 001 cut p38 MAP Kinase activity and stopped increases in blood cytokine levels. Physiological changes (Exhibit 3) like increased heart rate were reduced and volunteer body temperatures remained at normal levels. If on placebo or at 30mg dose, these were both raised.

No safety issues were noted in the study but this may need further investigation since this class of drug is known to have widespread side effects in long-term chronic use, though this may not be relevant in the acute dosing scenario.

Exhibit 3 - Physiological responses to LPS challenge with POLB 001



Source: Poolbeg

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