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Therapeutic areas in focus

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EXCLUSIVE INTERVIEW

Polyphor CEO Gökhan Batur discusses how COVID-19 can be an opportunity for infectious disease research

In affiliation with

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Rare diseases in 2021 and beyond

Why there is hope for rare disease patients in a post-COVID world

Understanding respiratory disease in today's world

How to seize the opportunities just over the horizon

Triple action to effectively treat COVID-19 patients

Abivax's ABX464 has shown antiviral, anti-inflammatory, and tissue repair properties in clinical trials. As Founder and Chairman Philippe Pouletty and CEO Hartmut J Ehrlich explain, this makes it a unique candidate to treat COVID-19

Abivax's lead product – the small molecule drug ABX464 – has already demonstrated safety as well as antiviral, anti-inflammatory and tissue repair properties in clinical trials in HIV and ulcerative colitis (UC).

So, when COVID-19 swept across the world this year, and hyperinflammation or "cytokine storm" was observed to cause acute respiratory distress syndrome (ARDS), the company believed ABX464 could be effective in treating these patients, based on the potent anti-inflammatory effects and tissue repair properties observed in UC patients. But the company also postulated that ABX464 could have an antiviral effect, since the drug candidate was originally designed and shown to be effective at reducing HIV viral load in humans. It was during the HIV trials that ABX464 was shown to have potent anti-inflammatory action and the company's development strategy shifted to focus on UC, Crohn's disease (CD), rheumatoid arthritis (RA), and other auto-immune disorders.

Early during the COVID-19 outbreak, newly gathered data showed that ABX464 does in fact inhibit replication of SARS-CoV-2 in an *in vitro* reconstituted human respiratory epithelium model. Thus, ABX464 has a highly differentiated triple mechanism of action against COVID-19, featuring antiviral effects specific to SARS-CoV-2; potent anti-inflammatory effects; tissue repair properties.

Given the current pandemic and patients' excessive inflammatory response to the virus as the primary cause of ARDS and consequently death in COVID-19 patients, ABX464 – with its convenient once-daily oral administration and triple action – is now being tested in an international, randomised, double-blind, placebo-controlled Phase IIb/III clinical trial in 1,034 high-risk patients as a potential new treatment to:

- Prevent and reduce inflammation, as already demonstrated in another severe inflammatory disease, UC. ABX464 has been shown to upregulate miR-124, which is a natural brake in inflammatory pathways and to down-regulate the multiple chemo- and cytokines involved in the COVID-19 cytokine storm
- Reduce viral replication, likely mediated by RNA quality control, and miR-124 induced inhibition of dynamin 2, a key component necessary for viral replication
- Promote tissue repair and decrease pulmonary fibrosis observed in ARDS

Moving at speed in COVID-19

There have been unprecedented efforts to develop a vaccine against COVID-19, and this is undoubtedly something we urgently need. But even with a vaccine or vaccines approved, effective treatments will still be needed during the many months or even years while sufficient quantities are manufactured, distributed, and administered to billions of people around the globe. Even then, treatments may be needed for people who refuse vaccines or for whom vaccines are not effective. So far, no prophylactic or therapeutic treatment has shown much efficacy in any rigorous trial to treat the severe form of COVID-19.

While they are more predictive in infectious diseases than many other indications, *in vitro* results cannot predict clinical benefits in patients; nevertheless, ABX464's antiviral effect and protection of tissue integrity are significant as they are based on a physiologic *in vitro* reconstituted human pulmonary epithelium model and not on the more basic monkey kidney Vero E6 cells model.

In July, the first patient in the COVID-19 study was treated at the University Hospital Center in Nice, France (CHU Nice) in our Phase IIb/III trial, named miR-AGE, which investigates the effect of early treatment (at point of diagnosis) in elderly or otherwise high-risk COVID-19 patients. The main goal is to measure the potential of ABX464 to limit viral replication and, more importantly, to prevent the severe inflammation that leads to the potentially fatal ARDS.

ABX464's easy, once-daily oral administration means it can be taken outside a hospital setting, so hospitalised as well as non-hospitalised COVID-19 patients can be enrolled in the trial. If ABX464 proves to be an effective treatment, this oral administration could facilitate out-patient treatment and limit future demand – and risk of further infections – in hospitals and intensive care units, while allowing patients to quarantine at home during treatment.

Abivax has already received clearance for the study from regulatory authorities in France, Germany, UK, Italy, Spain, Belgium, Brazil, and Mexico and authorisations are expected in additional Latin American countries with high infection rates, namely Chile and Peru, in due course. An interim analysis will be performed after the treatment of 300 patients and, subject to the evolution of the pandemic, Abivax envisages to complete recruitment in Q4 2020.

If successful, this trial could bring us one step closer to a potent preventive treatment for this disease to protect especially high-risk patients who are more vulnerable to developing the severe form.

Building on robust clinical data

Development of ABX464 in COVID-19 can be based on already existing, robust clinical data in hundreds of patients on its use against UC and HIV. In particular, ABX464 has already demonstrated impressive long-term safety and efficacy in a Phase IIa clinical trial in UC, for which Abivax recently reported two-year open label maintenance data. Of the 16 patients who remained in the open label trial for 2 years, 69% were in clinical remission and 94% were showing a clinical response to ABX464.

Potent anti-inflammatory effects were observed in this trial and maintained or improved upon during the open label maintenance trial, along with a good safety profile. These results, together with the unique molecular mechanism action of ABX464, support the rationale to use it to treat the cytokine storm and hyper-inflammation syndrome observed in COVID-19 patients.

Unlike other potent anti-inflammatory agents that specifically target single cytokines, ABX464 has not been associated with increased vulnerability to opportunistic infections or a damping down of the immune system. This is because it does not completely block specific critical actors like TNFa, IL-6, IL-17 or MCP-1 in the immune system; instead it acts as a brake on the immune system by targeting the cap binding complex (CBC), which is located on the 5' end of every cellular non-coding RNA molecule. ABX464 binding CBC results in upregulating the splicing of a long, non-coding RNA, that induces the overexpression of a single micro-RNA product, miR-124. miR-124 initiates a cascade which is believed to propagate the anti-inflammatory effect that has been observed in preclinical models.[1]

Abivax hopes that ABX464 will have a positive impact by reducing the severity of COVID-19 sequelae but remains prudent on expectations for the miR-AGE trial given the complexities surrounding treatment of COVID-19 patients and the speed of the disease evolution. While we felt the necessity to test ABX464 in COVID-19 due to its potentially beneficial triple effect, progressing ABX464 development in chronic inflammatory diseases, especially in inflammatory bowel diseases, remains Abivax's corporate priority.

Exciting results in ulcerative colitis

Our recently reported two-year Phase IIa maintenance data in UC confirm the favourable durable safety and efficacy results of ABX464 during the second year of treatment, which were already observed during the eight-week induction trial and first year of the maintenance study.

These are very exciting results that reinforce the potential of ABX464 as a well-tolerated and efficacious once-daily oral therapy for patients with moderate-to-severe UC, and provide further momentum to Abivax's clinical development efforts to address this high unmet medical need.

A 232-patient randomized, double-blind, placebo-controlled Phase 2b induction study in moderate-to-severe UC patients is currently ongoing in 15 European countries, Canada, and the US. Enrolment is on track, with completion of patient recruitment expected by the end of this year and top-line results in Q2 2021. This clinical programme in UC is our first priority and Abivax is already working on all necessary steps to further progress into Phase III studies in UC.

At the same time, enrolment in Phase IIb/III trials in RA, the largest market opportunity in inflammatory disease, is progressing well and the completion of recruitment also is anticipated by the end of 2020. The sustained efficacy in UC and broad efficacy in a preclinical RA model suggest ABX464 could have potential as a novel, highly differentiated anti-inflammatory agent in RA.

Abivax's key opinion leaders (KOLs) are confident that ABX464 will also show beneficial effects in CD, based on the clinical similarities with UC and the predictability of the dextran sodium sulfate (DSS) model for both diseases. Based on the KOL recommendation, the good safety data and promising long-term efficacy results obtained for ABX464 in UC, Abivax plans to enter ABX464 directly into a pivotal Phase IIb/III trial for the treatment of CD and expects to start recruiting patients at the beginning of 2021.

An agile response

In 2013, our initial focus was viral diseases but, as the data made clear, ABX464 had a much more important impact on inflammatory conditions; and this led us to focus on inflammation and adapt our strategy for the therapeutic-candidate. Abivax believes that inflammatory conditions, many of which remain poorly addressed by marketed therapeutics, are the area ABX464 will have the greatest impact.

The emergence of COVID-19 has reinforced the importance of the healthcare industry and, more specifically the biotechnology industry's ability to produce efficacious treatments for diseases that threaten our society. It has also reinforced the inability to predict the future and the need for us to maintain readiness and vigilance.

What can be said is that both the biotech industry as a whole can be proud of the way we have reacted to this crisis. Although it is not yet clear whether ABX464 will make a meaningful difference to patients with severe COVID-19, we are hopeful to be able to contribute overcoming this unprecedented challenge.

Reference:
1 miRNA-124 in immune system and immune disorders, *Front Immunol*, 2016

Professor Hartmut J Ehrlich, MD is a physician with 35 years of experience in academia and the biopharmaceutical industry, 25 of which were spent in research and product development at Baxter, Lilly and Sandoz. He has been CEO of Abivax since 2013.

Philippe Pouletty, MD, is Founder and Chairman of the board at Abivax. He is also the Managing Partner of Truffle Capital and an entrepreneur and pioneer in the biotechnology and medical devices sector.