Fibrogen and Blade Therapeutics' antifibrotic drug evaluations with COVID-19 endpoints draw expert support over trials for Roche and Boehringer Ingelheim's drugs using standard IPF measures, experts say

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- Acute illness warrants short-term use with endpoints on clinical parameters
- Impact on fibrosis needs to be assessed with longer trial follow-ups

Fibrogen (NASDAQ:FGEN) and **Blade Therapeutics'** focus on COVID-19-specific endpoints for their idiopathic pulmonary fibrosis (IPF) drugs is favorable over traditional IPF measures, experts said. However, the drugs' impact on lung function and fibrosis will remain unclear since the ongoing Phase II trials are short-term studies.

However, investigator-led studies with **Boehringer Ingelheim's** Ofev (nintedanib) and **Roche's** (SIX:ROG) Esbriet (pirfenidone) have opted to use the standard fibrosis surrogate measure of forced vital capacity (FVC) over a longer period of time. Considering the acute setting of COVID-19, experts said the best way to judge the drugs' efficacy was to use parameters specific to the infectious disease. Still, pathological changes in fibrosis will likely take longer than the 28-day period used to measure the primary endpoint in Fibrogen and Blade's trials**.** Still, some experts did not dismiss the potential of an efficacy impact in the shorter acute COVID-19 setting, partly due to historical Ofev data, even though IPF drugs have been judged on the basis of long-term studies.

It is unclear what would be the ideal duration of treatment and when to start therapy, but experts noted at least a two-week course and initiation before the need for intubation arises would likely be needed for best results. Fibrogen's Phase II pamrevlumab trial (NCT04432298) and South San Francisco-based Blade Therapeutics' Phase II study (NCT04334460) of oral calpain inhibitor BLD-2660 have primary completion dates in December 2020 and September 2020, respectively. Topline BLD-2660 data is expected in 4Q20, said CEO Wendye Robbins. Ofev and Esbriet are in investigator-led Phase II (NCT04338802) and Phase III (NCT04282902) studies scheduled to complete in August 2020 and June 2020, respectively. There is rationale for evaluating antifibrotics in COVID-19 given the SARS-CoV-2 virus' impact on the lungs, but several unknowns persist on the overlap between IPF and COVID-19-related fibrosis, making the therapeutic impact of antifibrotics unclear, this news service reported earlier today (22 July).

Fibrogen and Boehringer Ingelheim did not respond to a request for comment by press time. A Roche spokesperson said the company was aware of investigator-led studies of Esbriet in COVID-19, but noted there is no clinical evidence of its efficacy and safety in treating COVID-19 patients and it is not approved for this use by any health authority.

However, Roche is actively involved in understanding the potential of some drugs in its existing portfolio for use in COVID-19 patients, he added.

Acute versus chronic use of antifibrotics

FVC is used in IPF studies as a surrogate endpoint for survival mainly because it would be too expensive to conduct survival endpoint-driven trials, said Dr Daniel Kass, associate professor of Medicine, Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, Pennsylvania. If antifibrotics improve survival or the hard endpoints used in the pamrevlumab and BLD-2660 COVID-19 studies, their impact on lung capacity or fibrosis may not matter, he added. The primary endpoint in the pamrevlumab trial is proportion of patients who never received mechanical ventilation and or extracorporeal membrane oxygenation (ECMO) and are alive from baseline to 28 days, while the primary endpoint in the BLD-2660 trial is time to recovery at 28 days and the change in oxygenation at 10 days.

It is also difficult to conduct pulmonary function tests in COVID-19 patients given the high risk of generating viral aerosols, said Kass. Moreover, it is not known if a change in lung function would result in a mortality benefit, said Dr Gordon Yung, professor of Medicine, University of California San Diego, adding these drugs are unlikely to stop fibrosis altogether. The investigator-led Ofev trial hinges on an FVC change over eight weeks, while Esbriet's impact is being measured via chest computed tomography (CT) scan, and an absolute change from baseline in parameters like pulse oxygen, blood gas and King's brief questionnaire for interstitial pulmonary disease over a four-week time frame.

If a drug is meant to modify the acute phase of illness, the design would mirror the design of other COVID-19 studies and consider mortality, oxygen requirements and deterioration over a 28 day period, said Dr Toby Maher, professor of Clinical Medicine, University of Southern California, Los Angeles. Assessing hospital discharge or time on ventilator and FVC as secondary endpoints would also be rational COVID-19 trials, added a US-based pulmonologist.

However, considering these antifibrotics are designed to protect against long-term fibrosis as a complication of acute respiratory distress syndrome (ARDS), a benefit on fibrosis would be seen three to six months later, so these COVID-19 studies should have an appropriate follow-up period, said Maher. It is important to monitor long-term remodeling or impact on lung injury, he explained. The BLD-2660 study includes a poststudy 60-day assessment of FVC as a secondary endpoint, Robbins noted.

However, even though Ofev was approved based on a 52-week primary endpoint, it showed rapid action in its IPF study, so antifibrotics can show an effect quickly, noted Dr Athol Wells, consultant chest physician, Royal Brompton Hospital, London. In the IPF Phase III Ofev studies (NCT00287729 and NCT00287716), an effect on FVC was seen

starting at 24 weeks (p=0.0007) (Noble et al. [2011] *The Lancet*, 377[9779] p. 1760–1769).

However, Dr Katerina Antoniou, associate professor in Respiratory Medicine, University of Crete, Heraklion, Greece, said it will be difficult to see the impact on fibrosis in COVID-19 patients through an outcome like FVC in less than six months. Antifibrotic drugs are different from anti-inflammatories or anticoagulants, which can be studied in shorter periods, she added. It is likely 28 days will be too short to assess the antifibrotics' impact on lung fibrosis specifically, said Kass. The pamrevlumab and BLD-2660 trials include secondary measures on oxygen requirements but do not measure FVC.

Trial caveats with patient selection and timing

Knowing when to treat COVID-19 patients and the duration of treatment are still difficult questions, said Kass. While a two-week treatment is the minimum, using antifibrotic drugs for three months would be ideal, said Yung. Pamrevlumab is given in four infusions over a 28-day period. In the investigator-led studies, Ofev is continuously dosed twice daily for eight weeks, while Esbriet is given thrice daily for four weeks or longer. BLD-2660 is dosed twice daily for 10 days in the COVID-19 study, said Robbins.

Whatever the treatment duration is, antifibrotics should come after anti-inflammatories, antivirals and anticoagulants have been used in the early stages of COVID-19, said Antoniou. After ARDS has set in, changes on CT scans are accompanied by pulmonary dysfunction and fibrosis, which is when antifibrotics would be evaluated, she added. The investigator-initiated Ofev study is enrolling patients with multiple fibrotic shadows in both lungs on CT scans, while the pamrevlumab and BLD-2660 trials also use radiographic criteria as inclusion criteria. CT imaging is used in addition to symptom history in the Esbriet study to determine inclusion into the trial.

The right duration of BLD-2660 treatment is unknown, but in animal models, good cytokine-downregulating activity was seen at seven days, which informed the trial design, said Robbins. BLD-2660 was found to safe and well-tolerated as per unpublished results from a Phase I healthy volunteer study, Robbins added.

These antifibrotics are not suitable when a patient is in the intensive care unit (ICU) or on a ventilator, because then there is overwhelming lung injury, said Wells. It is unclear whether this drug class, which prevents lung damage, has a role once there is substantial lung damage, he explained. The pulmonologist agreed it may be too late to intervene after a patient is intubated, but noted antifibrotics could be considered for patients who have evidence of fibrosis on CT scans while on a ventilator for multiple days. The pamrevlumab and BLD-2660 studies are excluding mechanically ventilated patients, while this information is not outlined for the Ofev and Esbriet trials. While it is being tested in hospitalized patients, BLD-2660 could also have potential for at-risk healthcare workers or nursing home patients, said Robbins.

Moreover, since patients are on multiple drugs for COVID-19, it will be challenging to conduct a study directly correlating a drug's use with the trial outcome, said Yung. Even if patients are not receiving concomitant antiviral therapies, they may have some kidney or liver issues due to prior treatment, he added.

Patients will likely be treated with dexamethasone and **Gilead Sciences'** (NASDAQ:GILD) Veklury (remdesivir), and it is not known if those therapies would interfere with the normal healing process, said Kass. However, steroids are commonly used in IPF, Yung said, adding potential drug interactions with approved IPF drugs was of less concern with dexamethasone. Veklury currently has an emergency use authorization, and several treatment guidelines recommend dexamethasone. The 130-patient pamrevlumab study allows concomitant medications. The 120-patient BLD-2660 study allows Veklury treatment and is recording the drug's impact on duration of Veklury use as a secondary endpoint, said Robbins. The company does not expect BLD-2660 to be synergistic with Veklury, she added.

by Manasi Vaidya in New York

Experts:	Athol Wells; Daniel Kass; Gordon Yung; Katerina Antoniou; Toby Maher	1 Undisclosed Expert
Country:	United States	
Topic:	Product Development - Experts	
Company Name:	Blade Therapeutics Inc; Boehringer Ingelheim Biopharmaceuticals GmbH; F. Hoffmann-La Roche Ltd; FibroGen Inc	
Indication:	Coronavirus Disease 2019 (COVID-19)	
Drug(s)/Molecule(s):	pirfenidone; pamrevlumab; nintedanib; BLD-2660	

Trial Identifier	Trial Phase	Trial Status
GDCT0058181	Phase III	Completed
GDCT0061271	Phase III	Completed
GDCT0380495	Phase III	Ongoing, recruiting
GDCT0384125	Phase II	Ongoing, recruiting

GDCT0384418	Phase II	Planned
GDCT0390244	Phase II	Ongoing, recruiting