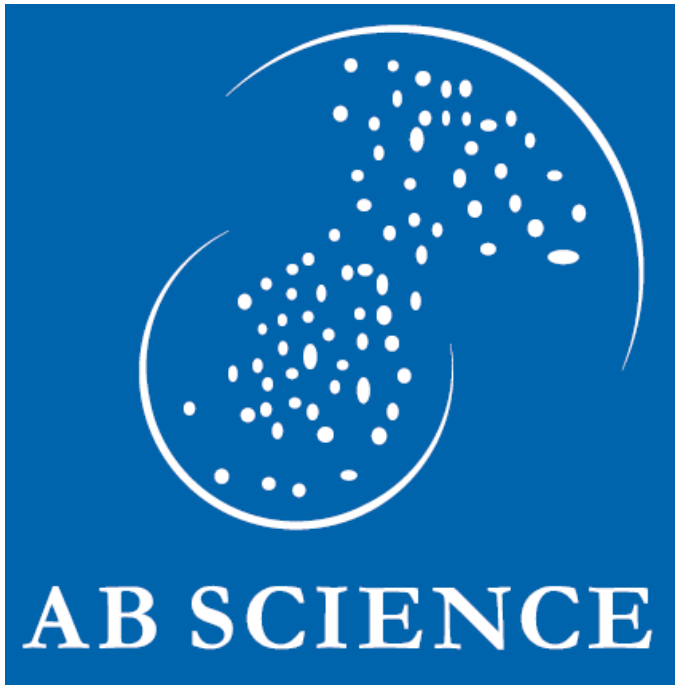

AB SCIENCE WEBCONFERENCE

MASITINIB + ISOQUERCETIN IN COVID-19

11 May 2020

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Speakers

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AGENDA

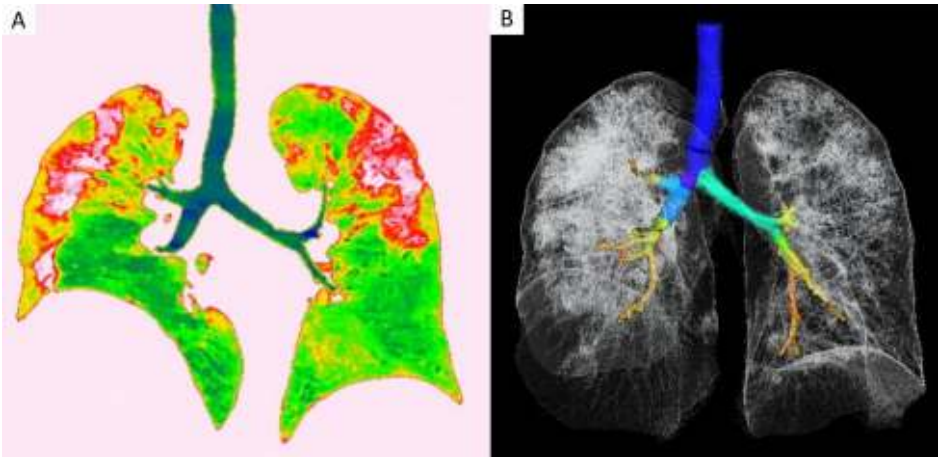
1. Scientific rationale for combining masitinib and IsoQ in Covid-19
2. Positioning and Key differentiating factors
3. Study Design

1. Scientific rationale for combining masitinib and IsoQ in Covid-19

Scientific Rationale

In moderate and severe forms of the disease, Covid-19 is triggering a “cytokine storm” leading to severe pulmonary inflammation and thrombosis associated with acute respiratory distress syndrome (ARDS) and potentially death.

- COVID-19 infection causes clusters of severe respiratory illness and is associated with intensive care unit admission and high mortality.
- COVID-2019 patients present pathological **inflammatory responses** leading to tissue necrosis, infiltration, and hyperplasia [1].
- COVID-19 patients often suffer from an excessive coagulation activation leading to an increased risk of venous and arterial **thrombosis** and a poor clinical course [2].



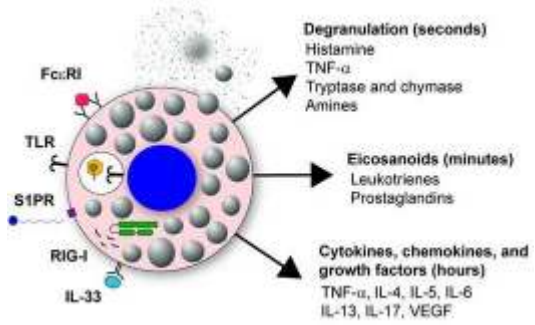
CT images in a 54-year-old woman with severe COVID-19 pneumonia. *A*, The color coronal image highlights the distribution of lung lesions (red areas) because software is used to automatically segment and render. *B*, On a three-dimensional volume-rendering image, trachea, bronchus, lung tissues, and lesions are differentiated by CT values and automatically segmented.
Tang L. Published Online: March 06, 2020

[1 Sarzi-Puttini P, Giorgi V, Sirotti S et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol 202; 38: 337-42.
[2] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7. doi:. http://dx.doi.org/10.1111/jth.14768

Scientific Rationale

Cytokine Storm Syndrome may be avoided by Mast cells activity inhibition

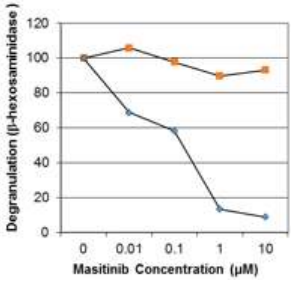
- Mast cells contribute to COVID19-induced inflammation by activating the early release of inflammatory compounds (IL-6, IL-1, TNFα) (Kritas 2020)



- Mast Cell degranulation, promote lung lesions during viral infection (Hu Y, 2012)
- Altered Mast Cell activity, in response to respiratory viruses, contribute to pulmonary disorders such as allergic asthma exacerbations or pulmonary edema (Jin, 2018)

- Masitinib inhibits c-Kit (IC50=100-300nM). c-Kit is highly expressed in mast cells and controls many essential cell functions. Thus, Masitinib inhibits mast cells activity.
- Masitinib inhibits LYN, FYN (225-240nM). These proteins are involved in the degranulation of mast cells (i.e. mast cell mediator release). Thus, Masitinib inhibits degranulation of mast cells

Masitinib inhibits mast cells degranulation (Dubreuil 2009)

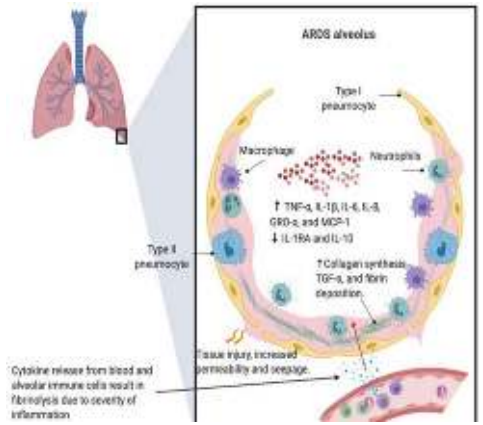


- Masitinib showed efficacy in patients with severe mastocytosis in a phase 3. The primary objective was met. The cumulative response (ie 75% of improvement in at least 1 of 4 severe symptoms of mast cell mediator release (pruritus, flushes, depression, or asthenia)) was 18·7% versus 7·4% for placebo (p=0·0076). Masitinib also demonstrated significant activity on objective markers of mast cell activation and burden (Lortholary Lancet 2018)
- Quercetin inhibits the production and release of histamine and other allergic and inflammatory substances, (Mlcek 2016, Wheng Z, 2012)

Scientific Rationale

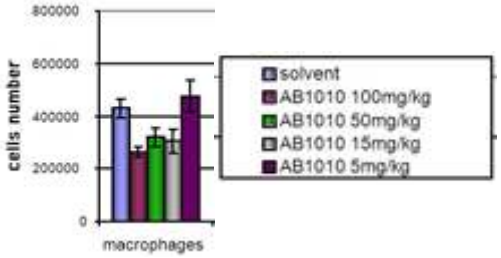
Cytokine Storm Syndrome may be avoided by Macrophage activity inhibition

- There is evidence for Macrophage Activation Syndrome emerging in the COVID-19 setting that is supported by the abnormal laboratory parameters (McGonagle D, 2020)



- Macrophages could contribute to viral spread, excessive inflammation and activation-induced lymphocytic cell death during COVID-19 infection (Park MD, 2020)

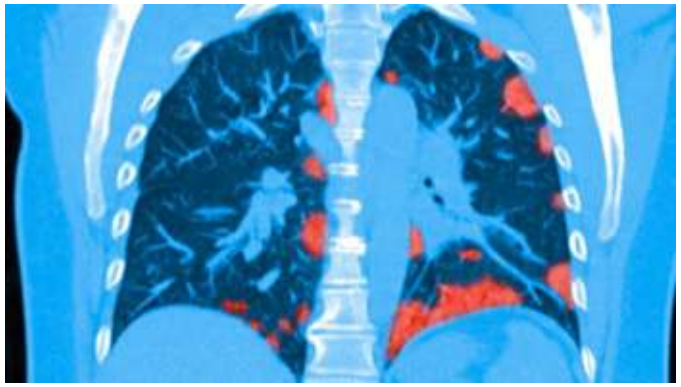
- Masitinib inhibits macrophage colony-stimulating factor 1 receptor MCSF1R with an IC50=90nM.
- MCSF1 receptor is crucial for the differentiation and survival of the macrophages (Stanley ER, 2014)
- In a asthma mouse model of airway inflammation, Masitinib inhibited of 40% the infiltration of macrophages



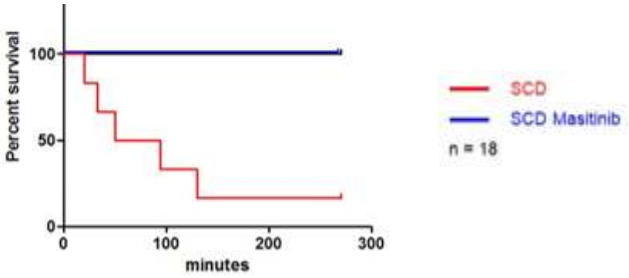
Scientific Rationale

Masitinib may prevent lung injuries by decreasing mast cells and macrophages lung infiltration

- Lung injuries in COVID-19 are life-threatening symptoms
- Among patients who have recovered from COVID-19 some may suffer long-term damage from the disease



- Masitinib showed prevention against acute chest syndrome in an animal model of sickle cell disease (SCD). Masitinib prevented mast cell infiltration and edema in lungs. None of the mice died on the contrary to the control (figure below).



- In a asthma model of airway inflammation in mice, Masitinib decreased the lung inflammation. Lung Infiltration of macrophages was decreased by about 40%.
- Masitinib has showed efficacy in pneumology in severe persistent asthma. A phase 3 clinical study of 355 patients has been successfully completed. The primary criteria was met with a statistically significant reduction (-35%, p=0.0103) of severe asthma exacerbations over a long period of time (about 60 weeks) compared to placebo

Scientific Rationale

Cytokine Storm Syndrome may be avoided by Neutrophils inhibition with Isoquercetin

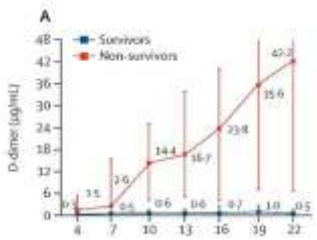
- Neutrophilia predicts poor outcomes in patients with COVID-19 (Wang, 2020)
- Neutrophil-to-Lymphocyte ratio is a marker of severe illness in COVID-19 patients (Liu J, 2020; Zhang, 2020)
- In dead COVID-19 patients, accumulation of networks of extracellular fibers, composed of DNA from neutrophils was identified. Excessive amount of this network can trigger a cascade of inflammatory reactions that destroys surrounding tissues, and induce permanent organ damage to the pulmonary, cardiovascular, and renal systems (Barnes, 2020).

- Quercetin reduces neutrophil (Souto FO, 2011)
- Quercetin diminish neutrophil oxidative metabolism and lipid peroxidation (Zielinska M, 2001)
- Quercetin inhibits neutrophil degranulation, superoxide production, and the phosphorylation of specific neutrophil proteins (Blackburn WD, 1987)

Scientific Rationale

Decreasing D-Dimer by Isoquercetin may prevent death and injuries due to thrombosis

- Increase in D-dimer is a predictor of in-hospital mortality in patients with Covid-19 (Wu C 2020; Gao Y, 2020; Zhou F., 2020; Han H., 2020; Tang N., 2020, Lippi, 2020)



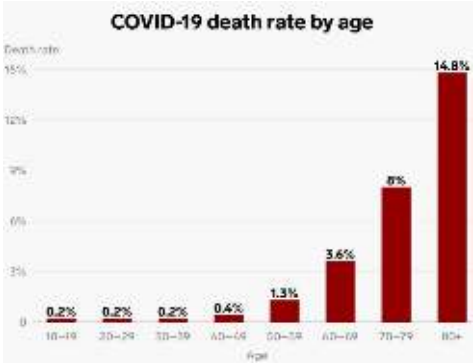
- D-dimer is the most validated and commonly utilized laboratory biomarker to predict hypercoagulability (Zhou, 2020).
- Covid-19 virus induces changes in coagulation that lead to the development of thrombi. Autopsies have shown that thrombi were evident in the veins and microcirculation of soft tissues surrounding the lungs, spleen, pancreas, kidneys, adrenal glands, and mesenteric lymph nodes.
- Deep vein thrombosis and/or pulmonary embolism and pulmonary artery thrombosis have also been reported in COVID 19 patients is probably leading to death in 20% of cases (Su et al, 2020).

- Isoquercetin has been shown recently in a phase II clinical trial decreased D-Dimer by inhibiting disulfide isomerase (PDI), an enzyme directly involved in the formation of clots, and prevent thrombosis in metastatic late stage cancer patients (Zwicker, 2019). PDI is involved in viral-mediated thrombosis.
- The administration of 1000 mg isoquercetin decreased D-dimer plasma concentrations by a median of -21.9% ($P = 0.0002$). Isoquercetin increased PDI inhibitory activity in plasma (73.3% , $P < 0.001$). Corroborating the antithrombotic efficacy, a significant decrease in platelet-dependent thrombin generation (-57.2%, $P = 0.004$) was observed (Zwicker,2019)
- Isoquercetin is under evaluation in Phase III clinical study in USA for thrombosis prevention in pancreatic cancer (NCT02195232).

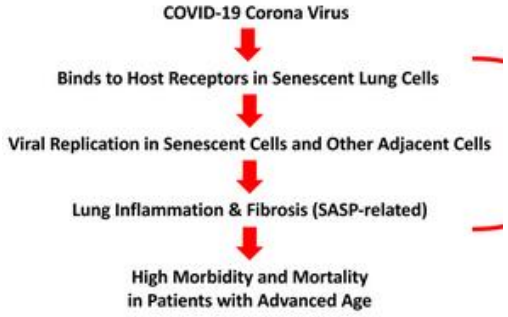
Scientific Rationale

Masitinib and Isoquercetin is suited to treat aged people which are the most exposed to death.

- Deadly pulmonary inflammation occurs more frequently in aged people.



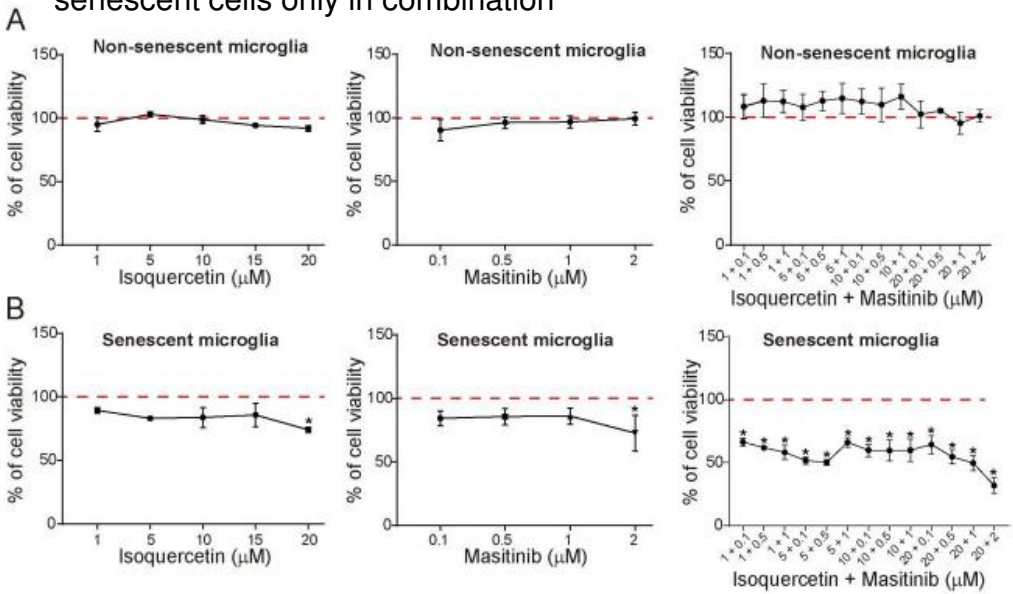
- Senescent cells accumulate with age in humans in many tissues due to cell damage. Their accumulation causes chronic inflammation and increases the risk of many age-related diseases (Karin O, 2019)



From Sargiacomo, 2020

- In a model of Amyotrophic Lateral Sclerosis (Maladie de Charcot), Masitinib and Isoquercetin kills senescent cells but not non senescent cells

- Interestingly, Masitinib and Isoquercetin are able to kill senescent cells only in combination



- This synergy of masitinib and isoquercetin against senescent cells higlights the potential efficacy of this combination for improving the severe pulmonary disorder specifically in old people with COVID-19.

Scientific Rationale

Severe and persistent neurological symptoms are the new challenge in COVID-19 and Masitinib could control them.

- Covid19 virus infect nervous system and skeletal muscle as well as the respiratory tract. In those with severe infection, neurologic involvement is greater, which includes acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury
- More than 30% of patients had neurological symptoms (Mao L, 2020). Estimations ranging from 46% to 84% of severe cases showing neurological symptoms and they are found to persist after recovery
- SARS-CoV-2 infection which results in a very strong response by the immune system may directly cause neurological disorders in the form of Guillain–Barré syndrome. Brain inflammation might also indirectly cause neurological damage

- Masitinib inhibits proliferation and migration of microglia by targeting CSF1/CSF-1R. Proliferation and accumulation of microglial cells is a major neuropathological feature of neurodegenerative disease (Trias,2013). As macrophage cells, microglia act as the first and main form of active immune defense in the nervous system.
- In a model of Amyotrophic Lateral Sclerosis, Masitinib slowed microglia proliferation and migration, with decreased mast cells infiltration while improving motor neuron pathology.
- Masitinib has shown efficacy in patients with Amyotrophic Lateral Sclerosis in a phase 2b clinical trials of 394 patients (Mora JS, 2018). Masitinib showed significant benefit over placebo with a ΔALSFRS-R between-group difference of 3.4 ($p = 0.016$), corresponding to a 27% slowing in rate of functional decline.
- Masitinib has also shown positive results in patients with progressive multiple sclerosis in a phase2b clinical trials of 611 patients. Masitinib showed significant improvement ($p=0.0256$) in a disability score (EDSS) with a masitinib dose of 4.5mg/kg/day. Additionally, masitinib significantly delayed disease progression.
- Depression and asthenia are potential psychiatric manifestations of mast cell activation. In an international phase 3 clinical trial, indication that Masitinib decreases depression in patients with severe mastocytosis was observed (Lortholary O, 2018)

Scientific Rationale

Isoquercetin has an anti-viral activity in-vitro and may have activity against COVID-19 virus in human

- Isoquercetin has a broad antiviral spectrum. It inhibits Hepatitis C Virus, Human Respiratory Syncytial Virus, Influenza A virus, Dengue virus, Enterovirus 71, Rhinovirus cell entry and replication in vitro and in vivo (Ganesan, 2012 and Wu, 2016)
- Isoquercetin inhibits 3C-like protease, an enzyme which is vital to COVID-19 virus replication with an IC50 of about 70µM (Yi L, 2004, Jo S, 2019)
- By molecular modeling, Isoquercetin was identified as one of the molecules that appear to have the highest potential to inhibit Mpro inhibitor which is essential to the maturation of the COVID-19 virus (Khaerunnisa et al., 2020)
- Furthermore, Isoquercetin is able to limit COVID-19 virus recognition of host cells and/or disrupt host-virus interactions by binding to 2 important proteins, Viral Spike Protein and Viral Spike Protein-Human ACE2 , namely (Smith 2020).

Scientific Rationale

The safety profiles of Masitinib and IsoQuercetin are well defined.

- **Masitinib**
  - Over 7500 patients randomized
  - Evaluated in patients wit various diseases, age and comorbidities (Alzheimer, Multiple sclerosis, Amyotrophic lateral sclerosis, Asthma, Mastocytosis
  - Safety recognized as acceptable (FDA IND in ALS, ANSM IND in Mastocytosis)
  - Risk Management Plan in place and validated by Health Authorities
- **IsoQuercetin**
  - Isoquercetin is safe in human clinicals up to 1,000 mg/day (FDA IND)
  - GRAS dossier for Quercetin and FDA documents IB / IMPD available now

2. Positioning and Key differentiating factors

Overview of strategies pursued

The combination Masitinib + IsoQuercetin is one of the treatment candidates in the immunomodulation strategy.

Strategy	Severity	Target	Agent	Company
Anti-viral	Mild Moderate Severe	Inhibiting glycosylation of host receptors	Hydroxychloroquine	generic
		3CL protease	Lopinavir/Ritonavir	generic
		S protein/ACE2, membrane fusion inhibitor	Umifenovir	generic
		RNA polymerase inhibitor	Ribavirin	generic
		RNA polymerase inhibitor	Remdesivir	Gilead
		RNA polymerase inhibitor	Favipiravir	Fujifilm
Other strategy against virus	Moderate Severe	Stimulation of immune system	Interferon-α and -β	generic
		Stimulation of immune system	Plasmapheresis	Not applicable
		Antihelminthic agent	Nitazoxanide	generic
Anti-inflammatory or Immunomodulation	Mild / Mod. / Severe		corticosteroids	generic
	Moderate Severe	**Antibody IL-6 receptor antagonist**	**Tocilizumab**	**Roche**
		Antibody IL-6 receptor antagonist	Sarilumab	Regeneron
		Antibody IL-1 receptor antagonist	Anakinra	Sobi
		Antibody inhibiting IL-17A	Secukinumab	Novartis
		Anti–vascular endothelial growth factor	Bevacizumab	Roche
		Sphingosine-1P receptor modulator	Fingolimod	Novartis
		Antibody inhibiting complement C5	Eculizumab / Avdoralimab	Alexion / Innate Pharma
		Jak Kinase	Ruxolitinib / Baricitinib	Novartis / Lilly
		Mast cell / Macrophages / Neutrophils /D-Dimer	**Masitinib + IsoQ**	**AB Science / Quercegen**

Positioning

Masitinib combined with Isoquercetin is positioned in moderate and severe form of COVID-19.

Disease severity	Signs and symptoms	Scope	%
Mild	No supplemental oxygen therapy requirement or evidence of pneumonia	No	81%
Moderate	Meeting of the following criteria: • Showing fever and respiratory symptoms with radiological findings of pneumonia. • Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97%	Yes	14%
Severe	Meeting any of the following criteria: • Respiratory distress (≧30 breaths/ min); • Oxygen saturation≤93% at rest in ambient air; or Oxygen saturation ≤97 % with O2 > 5L/min. • PaO2/FiO2≦300mmHg	Yes	
Critical	At least one of the following: ▪ Respiratory failure that needs to receive mechanical ventilation ▪ Shock (septic shock) ▪ Multiple organ failure (extra pulmonary organ failure) that needs to be transferred to the intensive care unit (ICU)	No	5%

Key Differentiating Factors

The combination Masitinib + IsoQuercetin differentiates from other strategies on key points.

- Targets the innate immune system cells upstream rather than the released interleukins downstream
- Can potentially prevent thrombosis (ICU and death)
- Can potentially treat the neurological symptoms
- Can treat patients above 80 years old

3. Study Design

AB20001 Phase 2 study design

Study AB20001 will enroll 200 patients with moderate and severe forms of the disease without limitation of age (i.e. patients above 80 will be enrolled).

- **Randomized, Open-label, Multicentre, Comparative Phase 2 study**
- **Main Inclusion Criteria**
  - Moderate cases
    - Showing fever and respiratory symptoms with radiological findings of pneumonia.
    - Requiring between 3L/min and 5L/min of oxygen to maintain SpO2 >97%
  - Severe cases
    - Respiratory distress (≧30 breaths/ min);
    - Oxygen saturation≤93% at rest in ambient air; or Oxygen saturation ≤97 % with
    - O2 > 5L/min.
    - PaO2/FiO2≦300mmHg
  - Adult ≥ 18 years of age at time of enrolment (no age upper limit)
- **Patient Enrolment : 200 patients, 100 per arm**
  - Masitinib + IsoQ + Best Supportive Care (no HCQ, CQ, and antiviral)
  - Best supportive care (Oxygen, antibiotics, anti-thrombotic, analgesic, antiviral, immunomodulator, HCQ, CQ)

AB20001 Phase 2 study design

Study AB20001 will assess efficacy, safety, and PK parameters of the combination masitinib + Isoquerceting

- **Primary endpoint** :
  - Clinical status of patients at day15 using the 7-point ordinal scale

  The 7-point ordinal scale for clinical status is: 1. Not hospitalized, no limitations on activities; 2.Not hospitalized, limitation on activities; 3. Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6. Hospitalized, on invasive mechanical ventilation or ECMO; 7. Death.

- **Secondary endpoints :**
  - Clinical status of patients at day08 and day29 using the 7-point ordinal scale
  - Time to improvement of two categories in clinical status of patients or discharge
- **Safety assessment :**
- **PK analysis on the first 6 patients**
  - Assess Drug-Drug Interaction

AB20001 Phase 2 study design

Study AB20001 plans to enroll patients in France and potentially in other countries and will last 2 to 6 months depending on intensity and number of waive of contaminations.

- **Coordinating investigator**
  - Pascal Chanez
  - Hôpital Nord, AP-HM, Marseille - France

- **Study timelines**
  - Initiation: May 2020
  - Enrolment: 2 to 6 months depending on waives of hospitalization
  - Time point: 1 month
  - Study results: August to Dec 2020